JIMD Reports
DOI 10.1007/8904_2013_259

CASE REPORT

Pregnancy and Lactation Outcomes in a Turkish Patient with Lysinuric Protein Intolerance

Özlem Ünal · Turgay Coşkun · Diclehan Orhan · Ayşegül Tokatl · Ali Dursun · Burcu Hişmi · Özgür Özyüncü · Serap Hatice Kalkanoğlu Sivri

Received: 20 July 2013 / Revised: 20 August 2013 / Accepted: 29 August 2013 / Published online: 20 October 2013

Abstract Maternal lysinuric protein intolerance (LPI) is associated with increased risk of anemia, toxemia, and retarded growth in fetus during pregnancy, and bleeding complications during delivery. There has been limited number of reports about pregnancy and outcomes of lactation in LPI. Here we present pregnancy and lactation outcomes in a Turkish patient with LPI. In the pregnancy and delivery period, her metabolic status was stable with protein-restricted diet and citrulline. Pathological examination of the placenta revealed multifocal placental infarcts. A successful outcome was achieved with well-controlled anemia, thrombocytopenia despite hemophagocytosis in bone marrow, and placental infarcts during pregnancy. The baby was exclusively breastfed for 6 months. His growth and development was normal. Mild proteinuria started at the fourth month of the delivery. Our case report showed the importance of follow-up of these patients in terms of placental pathologies during pregnancy and for other complications during lactation period.

Communicated by: Eva Morava, MD PhD

Competing interests: None declared

Ö. Ünal · T. Coşkun · A. Tokatl · A. Dursun · B. Hişmi · S.H.K. Sivri
Division of Metabolism, Department of Pediatrics, Hacettepe University, İhsan Doğramacı Children's Hospital, Ankara, Turkey

D. Orhan
Division of Pediatric Pathology, Department of Pediatrics, Hacettepe University, İhsan Doğramacı Children's Hospital, Ankara, Turkey

Ö. Özyüncü
Department of Obstetrics and Gynecology, Hacettepe University, Ankara, Turkey

Ö. Ünal (✉)
Eserköy Sitesi 3A-1 06530, Ümitköy/Ankara, Turkey
e-mail: unalozlem@gmail.com

Introduction

Lysinuric protein intolerance (LPI) is an autosomal recessively inherited, rare, multisystem disorder affecting cationic amino acid transport including ornithine, arginine, and lysine in the kidney and intestine. *SLC7A7* (MIM#603593) named solute carrier family 7A member 7 is the only gene which is known to cause LPI and it was identified in 1997 (Borsani et al. 1999; Torrents et al. 1999). The gene encodes the y(+)LAT−1 protein, the catalytic light chain subunit of a complex belonging to the heterodimeric amino acid transporter family (Sebastio et al. 2011). Main clinical findings are severe failure to thrive, aversion to protein-rich foods, periodic vomiting and diarrhea, hepatomegaly, and tendency to mild leukopenia. Episodes of hyperammonemia that is caused by impaired urea cycle accompany the disease. Interstitial changes, progressing into severe pulmonary alveolar proteinosis in the lung, glomerular and tubular involvement of the kidney, bone marrow anomalies resembling hemophagocytic lymphohistiocytosis/macrophage activation syndrome, lipid abnormalities including hypercholesterolemia and hypertriglyceridemia, autoimmunity and immunologic abnormalities, growth retardation and growth hormone deficiency, pancreatitis, and increased risk of pregnancy complications are the major complications of the disease (Sebastio and Nunes 2006; Sebastio et al. 2011).

Increasing number of patients with inborn errors of metabolism (IEMs) including LPI, are now reaching adulthood, and childbearing age. Therefore, pregnancy complications of IEMs are becoming more important. Maternal LPI is associated with increased risk of anemia, toxemia, and retarded growth in fetus during pregnancy and bleeding complications during delivery (Tanner et al. 2006). There has been limited number of reports about pregnancy

and outcomes of lactation in LPI. Here we present pregnancy and lactation outcomes in a Turkish patient with LPI.

Case Report

The patient was admitted to our center when she was15 years old with the complaints of aversion to protein-rich foods from the infancy, growth failure, and delayed puberty. Her parents were second cousins. On physical examination, her weight was 33.400 kg (<3rd percentile), height was 136 cm (<3rd percentile); she had hepatomegaly (6–7 cm) and muscle wasting. She was prepubertal according to Tanner staging. Serum amino acid analysis showed decreased levels of lysine (93 μmol/L N: 108–223) and arginine (30 μmol/L N: 44–130), and urine amino acid analysis showed highly elevated levels of lysine (6895 μmol/24 h N: 48–328), ornithine (137 μmol/24 h N: 0–53), and arginine (115 μmol/24 h N: <57). Ammonia level was elevated after protein loading (409 μg/dL N ≤120). Abdominal USG revealed hepatomegaly and nephrolithiasis. Molecular genetic analysis revealed c.283insTGG/-(p.Glu95_Thr96insTrp) in the SLC7A7 gene.

She was diagnosed with LPI and treated with citrulline and protein-restricted diet. Pulmonary function tests and HRCT were normal. Complete blood count revealed hemoglobin: 10.5 g/dL; leukocyte count: 3.8 × 10^9/L; and platelet: 313×10^9/L and it was consistent with mild bicytopenia. Serum biochemical investigations showed elevated levels of total cholesterol (250 mg/dL N: <200), triglyceride (1076 mg/dL N: <140 mg/dL), lactate dehydrogenase (699 U/L N: 240–480), and hypofibrinogenemia (107 mg/dL N: 144–430). She had no renal involvement and proteinuria. Liver enzymes were within normal limits. Light microscopic evaluation of bone marrow aspirate yielded increased histiocytes and prominent hemophagocytosis. Specific treatment for hemophagocytic syndrome was not given. Her bone mineral density Z score was −5.4 and calcium and 1,25-dihydroxyvitamin D3 were added to the treatment. Her menstrual cycle started at 19 years of age. In addition, she was treated with hormone replacement therapy for menstrual cycle irregularities.

When she was 25 years old, conception occurred after 10 weeks from ceasing of hormone replacement therapy. She continued to be treated with protein-restricted diet (1 g/kg/day) and citrulline 5 g/day. Hemoglobin, blood pressure, urinary protein, and serum ammonia levels were checked on every visit during pregnancy. Biochemical parameters, lipid profile, and thyroid testing was checked every 4 months. In the pregnancy and delivery period, her metabolic status was stable. Arterial blood pressure was normal. Serum transaminase levels and renal functions were

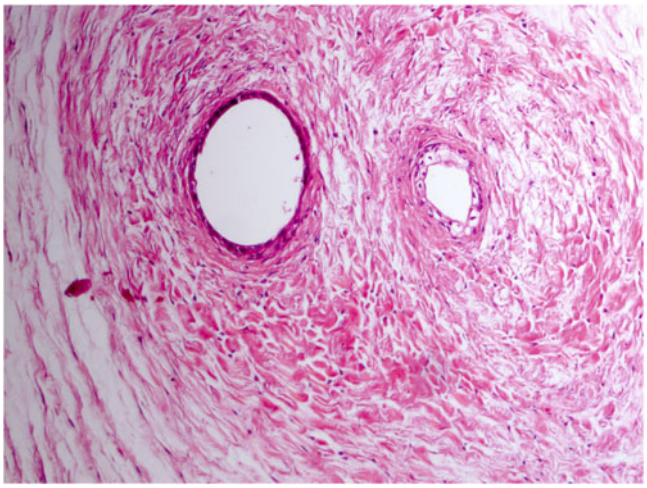

Fig. 1 Omphalomesenteric duct remnants in umblical cord section (Hematoxylin & Eosin, original magnification x100)

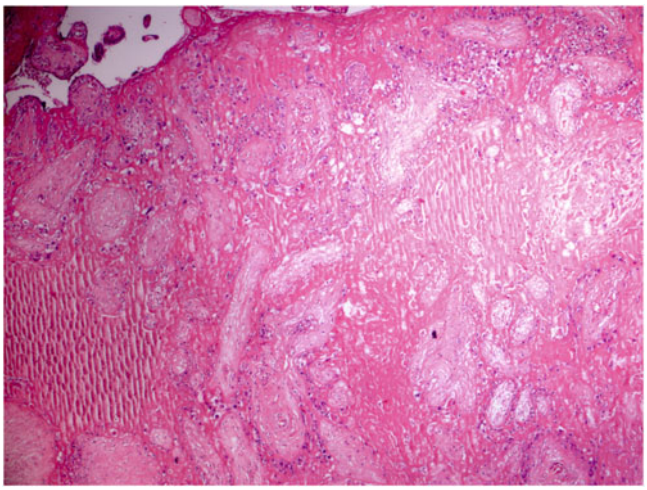

Fig. 2 Ischemic infarct area under the membrane (Hematoxylin & Eosin, original magnification x40)

normal. Total cholesterol and triglyceride levels did not increase when compared to prepregnancy levels. No complications occurred except for mild thrombocytopenia (73,000/mm^3) and severe anemia that fell to 6 g/dL, requiring erythrocyte suspension transfusion before delivery. Thrombocyte transfusion was given during delivery. Her serum ammonia levels were within normal levels both before and after delivery. The baby was born full-term and healthy with a birth weight of 3,200 g. Head circumference was 35.5 cm.

Pathological examination of the placenta revealed multifocal placental infarcts (Figs. 1 and 2). Prothrombotic risk factors other than metabolic disorder were searched for. Molecular genetic analysis for Factor V Leiden, prothrombin 20210A, methylenetetrahydrofolate reductase (MTHFR) A1298C mutations were normal. She was found heterozygous for

PAI-I 4G/5G and homozygous for MTHFR C677T. Serum homocystein and folic acid levels were normal [11.83 μmol/L (N: 4.44–13.56), 4.03 ng/mL (N: 3.1–19.9), respectively]. Anti-cardiolipin and antiphospholipid antibodies were negative. Complement 3 and 4 levels were normal. INR, activated prothrombin time, antithrombin activity, protein C activity, and activated protein C resistance were normal. Free protein S was 48% and mildly low (N: 60–130).

The baby was exclusively breastfed for 6 months. His growth and development was normal. Because lactating women have increased nutrient demands, dietary protein was increased. The mother received 1.3 g/kg/day protein in the lactation period. Metabolic status was stable also in the lactation period as in pregnancy. But mild proteinuria started at the fourth month of the delivery. Total urine protein and microprotein was 154 mg/gün (N: 0–80) and microprotein was 17.06 mg/dL (N<12), respectively.

Discussion

Lysinuric protein intolerance (LPI) is an autosomal recessively inherited disorder affecting the basolateral transporter for cationic amino acids including ornithine, arginine, and lysine in the kidney and intestine. Mutant form of *SLC7A7* gene causes lysinuric protein intolerance. Product of the gene, y^+ LAT–1 protein, is a light chain of the heterodimeric amino acid transporter. Highest prevalence of LPI was reported in Finland. Southern Italy and Japan have relatively high prevalence (Sperandeo et al. 2005; Koizumi et al. 2003). LPI cases were also reported from other countries. There are limited reports about pregnancy outcomes in the patients with LPI and no reports about lactation period in the literature. Here we presented pregnancy and lactation outcomes in a Turkish patient with LPI.

Although number of cases are a few, the most comprehensive study about pregnancy and delivery complications in LPI has been reported by Tanner et al. (2006) from Finland. In their study, outcomes of 18 pregnancies of 9 Finnish mothers with LPI and the follow-up of their 19 children showed that maternal LPI is truly associated with increased risk of anemia, toxemia, and intrauterine growth retardation during pregnancy and bleeding complications during delivery. But the children of the mothers with LPI generally had developed normally. They concluded that successful pregnancies and deliveries could be achieved with careful follow-up of blood pressure and laboratory parameters. Special care of maternal protein nutrition and control of blood ammonia levels, anemia, and toxemia during pregnancy are essential. In another case report from Japan, a successful outcome without serious complication of maternal LPI has been reported (Takayama et al. 1995).

In our patient, pregnancy occurred after severe pubertal delay and menstrual irregularity that was treated with hormone replacement therapy for 6 years. There was no severe complication related to pregnancy except for worsening anemia and thrombocytopenia, but multifocal placental infarcts were detected on placental pathological examination. Although etiological investigations showed heterozygosity for PAI-I 4G/5G and homozygosity for MTHFR C677T mutations that could contribute to thrombophilia and placental infarction, homocystein and folic acid levels were within normal limits, suggesting placental infarctions were more likely to be related to LPI. Placental bleeding after amniotic sac puncture, partial retention of the placenta, overweight of placenta for gestational age, altered fetal-placental ratio, and altered vascular development of the placenta that is considered the probable underlying cause for preeclampsia were reported placental abnormalities in patients with LPI in the study of Tanner et al. (2006), but no histological examination has previously been performed on the placentas of mothers with LPI in their study.

There has been no report on outcomes of lactation period in patients with LPI. Breast milk is made from nutrients in the mother's bloodstream and bodily stores. Although maternal nutritional status and amino acid levels may affect the quality of breastfeeding, composition and amount of the breastfeeding changes depending on how often and how effectively the infant sucks and, as well as on the age of the child. Even if the breastfeeding mother is undernourished, breastfeeding is recommended. The child of our patient was exclusively breastfed for 6 months. Normal growth and development of the baby showed that the breastfeeding was safe. But proteinuria started during lactation. Glomerular and tubular involvement is common in LPI. Isolated mild proteinuria is the initial sign of renal disease. The pathogenesis of the renal involvement is unknown. Pregnancy and lactation may have additional physiological stresses, and organs that are already damaged by the underlying metabolic illness may be compromised further. So, theoretically, it was thought that, pregnancy and lactation period might aggravate renal involvement in this patient. Blood pressure was normal during pregnancy and after delivery. Complete urine analysis was normal except for mild proteinuria. The patient was in lactation period, and treatment was not started for microproteinuria. But, follow-up for renal involvement is going on.

In our patient, a successful outcome was achieved with well-controlled anemia, thrombocytopenia despite hemophagocytosis in bone marrow, and placental infarcts during pregnancy. However, it is very important to follow up closely of patients with LPI for pregnancy complications. Our case report showed the importance of follow up of these patients in terms of placental pathologies during pregnancy and for other complications during lactation period.

Take-Home Message

Follow-up of the patients with lysinuric protein intolerance is important in terms of placental pathologies during pregnancy and for other known complications of the disease during lactation period.

Compliance with Ethical Guidelines

- The article has not been and will not be published elsewhere in the same form (Accepted as a poster presentation at ICIEM 2013).
- The submitting author has circulated the article and secured final approval of the version to be peer-reviewed from all coauthors prior to the publication of the article.
- Substantial contribution of coauthors to the work: The report was planned by first, second, and last authors; pathological investigations were performed by third author; obstetrical follow-up of the patient was performed by seventh author. All authors contributed to the conception and interpretation of data. First draft was written by the first author and revised by the second author.
- Özlem Ünal, Turgay Coşkun, Diclehan Orhan, Ayşegül Tokatl, Ali Dursun, Burcu Hişmi, Özgür Özyüncü, and Serap Hatice Kalkanoğlu Sivri declare that they have no conflict of interest.
- 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 the patient for publication.
- This article does not contain any studies with human subjects performed by the any of the authors.

References

Borsani G, Bassi MT, Sperandeo MP et al (1999) SLC7A7, encoding a putative permease related protein, is mutated in patients with lysinuric protein intolerance. Nat Genet 21:297–301

Koizumi A, Matsuura N, Inoue S et al (2003) Mass Screening Group. Evaluation of a mass screening program for lysinuric protein intolerance in the northern part of Japan. Genet Test 7:29–35

Sebastio G, Nunes V (2006) [updated 2011] Lysinuric protein ntolerance. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K (eds) GeneReviews™ [Internet]. University of Washington, Seattle. Available from http://www.ncbi.nlm.nih.gov/books/NBK1361

Sebastio G, Sperandeo MP, Andria G (2011) Lysinuric protein intolerance: reviewing concepts on a multisystem disease. Am J Med Genet C Semin Med Genet 157:54–62

Sperandeo MP, Annunziata P, Ammendola V et al (2005) Lysinuric protein intolerance: identification and functional analysis of mutations of the SLC7A7 gene. Hum Mutat 25:410–416

Takayama N, Hamada H, Kubo T (1995) Lysinuric protein intolerance in pregnancy: case report with successful outcome. Arch Gynecol Obstet 256:49–52

Tanner L, Näntö-Salonen K, Niinikoski H, Erkkola R, Huoponen K, Simell O (2006) Hazards associated with pregnancies and deliveries in lysinuric proteinintolerance. Metabolism 55:224–231

Torrents D, Mykkänen J, Pineda M et al (1999) Identification of SLC7A7, encoding y+LAT-1, as the lysinuric protein intolerance gene. Nat Genet 21:293–296<