A Rare Galactosemia Complication: Vitreous Hemorrhage

Sahin Takci • Sibel Kadayifcilar • Turgay Coskun •
Sule Yigit • Burcu Hismi

Received: 12 August 2011 / Revised: 20 September 2011 / Accepted: 12 October 2011 / Published online: 11 December 2011
© SSIEM and Springer-Verlag Berlin Heidelberg 2011

Abstract Galactosemia is a secondary glycosylation disorder characterized by galactose deficiency of glycoproteins and glycolipids. Abnormal glycosylation of coagulation factors and evidence of liver disease are associated with coagulopathy in galactosemic infants. We report a case of a neonate with galactosemia presenting with bilateral vitreous hemorrhage (VH). During the follow-up, hemorrhage in the right eye resolved; however, it persisted in the left eye. Vitrectomy was planned for the left eye. In addition to cataract, VH is another ophthalmic finding in galactosemia with serious sequelae such as amblyopia. Serious complications of coagulopathy in galactosemic infants can be prevented with early diagnosis and prompt treatment. Inclusion of galactosemia in the neonatal screening program offers an opportunity to prevent early severe symptoms.

Communicated by: Gerard T. Berry

Competing interests: None declared.

S. Takci (✉) • S. Yigit
Neonatology Unit, Hacettepe University Ihsan Dogramaci
Children's Hospital, 06100, Ankara, Turkey
e-mail: stakci@gmail.com

S. Kadayifcilar
Department of Ophthalmology, Hacettepe University Faculty
of Medicine, Ankara, Turkey

T. Coskun
Pediatric Metabolism, Hacettepe University Ihsan Dogramaci
Children's Hospital, Ankara, Turkey

B. Hismi
Department of Pediatric Metabolism, Hacettepe University Ihsan
Dogramaci Children's Hospital 06100, Ankara, Turkey

Abbreviations

GALE	UDP-galactose 4'epimerase
GALK	Galactokinase
GALT	Galactose 1-phosphate uridylyltransferase
VH	Vitreous hemorrhage

Introduction

Galactose is metabolized by a series of sequential reactions collectively known as the Leloir pathway (Fig. 1). The three enzymes that catalyze these reactions are galactokinase (GALK), galactose 1-phosphate uridylyltransferase (GALT), and UDP-galactose 4'epimerase (GALE). Galactosemia is caused by deficiency of any one of these enzymes, resulting in accumulation of galactose 1-phosphate and galactose in breast-fed or regular infant milk formula-fed infants (Fridovich-Keil 2006). The most common and clinically severe form is due to GALT deficiency, which is known as classic galactosemia, affecting about 1:30,000 to 60,000 live-births in the Caucasian population. It is an autosomal recessive disorder caused by a mutation in the *GALT* gene on the short arm of chromosome 9, with more than 150 disease-causing mutations (Bosch 2006; Item et al. 2002).

Compared to GALT deficiency, GALE and GALK deficiencies are rare. The incidence of GALK deficiency is less than 1:100,000 (Fridovich-Keil 2006).

Galactosemia usually presents as a life-threatening disease within the first weeks of life after ingestion of galactose. The initial clinical symptoms are generally nonspecific, like feeding difficulties, vomiting and diarrhea, lethargy, and hypotonia. Clotting abnormalities secondary to liver disease and predominantly *Escherichia*

Fig. 1 The Leloir pathway of galactose metabolism

coli sepsis can lead to early death in untreated infants (Holtan et al. 2001). Affected infants are also at increased risk of delayed development, speech difficulties, and intellectual disability. Females with classic galactosemia may experience reproductive problems caused by ovarian failure (Bosch 2006). Diagnosis and treatment of galactosemia should be performed as early as possible in order to prevent neonatal death and to minimize the complications (Bosch 2006).

Cataract has been reported as the main ophthalmic finding of galactosemia (Burke et al. 1989). Apart from cataract, there are also reports on another ophthalmic complication, vitreous hemorrhage (VH), which is rarely observed (Levy et al. 1996). Here, we present bilateral VH, with spontaneous resolution in one eye, in an infant diagnosed with classic galactosemia.

Case Report

A 12-day-old female infant who was sent from a local hospital was admitted to the neonatal intensive care unit because of poor feeding, jaundice, and hepatomegaly. She was born at 40 weeks' gestation by spontaneous vaginal delivery to a 30-year-old gravida 6, para 3 mother, with a 3,500 g birth weight. The Apgar scores were 8 and 9 at 1 and 5 min, respectively. On the seventh day of life, she was hospitalized because of indirect hyperbilirubinemia and given intensive phototherapy for 2 days. Her parents were first cousins. The mother had two early abortions and a

female baby who had died at 7 days of age with indirect hyperbilirubinemia requiring exchange transfusion.

On admission, the infant was hypoactive with poor sucking. She had been receiving breast-milk exclusively. The vital signs were normal. Physical examination revealed insufficient weight gain (body weight 3,450 g), jaundice and palpable liver 4 cm below the right costal margin. No bleeding was noted from the mucosal membranes or venipuncture sites. Ophthalmologic examination revealed icteric scleras, reactive pupils, and the absence of bilateral red reflexes.

Hemoglobin was 14.9 g/dL, leukocytes $13.4 \times 10^9/L$, and platelets $47 \times 10^9/L$, and immature/total neutrophil ratio was 0.11 in total blood count on admission. The biochemical markers were as follows: glucose 56 mg/dL, serum aspartate aminotransferase 171 IU/L, alanine aminotransferase 96 IU/L, alkaline phosphatase 255 IU/L, gamma-glutamyl transferase 29.9 IU/L, total bilirubin/direct bilirubin: 19.4/13.7 mg/dL, albumin 2.7 g/dL, blood urea nitrogen 12.9 mg/dL, and creatinine 0.23 mg/dL. Activated partial thromboplastin time was 34.2 s, international normalized ratio was 0.95, and fibrinogen level was 280 mg/dL (219–403) on the 18th day of life. Serum C-reactive protein (5.4 mg/dL) and serum procalcitonin levels (8.1 ng/ml) were high. Urine culture was sterile; however, the blood culture was positive for *E. coli*. The treatment with ampicillin and gentamicin, which was started on the first day of admission, was continued. Follow-up blood culture was sterile after 5 days of the antibiotic treatment. Ursodeoxycholic acid was given for cholestasis. Arterial blood gases were normal. Plasma and

urinary amino acid analyses showed mild elevation of tyrosine and phenylalanine. The clinical suspicion of galactosemia was strengthened by positive reducing substance test in the urine and by the detection of galactose spot on urinary sugar chromatography. Low GALT activity in erythrocytes (2.7 U/dL; normal value: 21.2 U/dL) and a homozygous Q188R mutation on molecular genetic testing confirmed the diagnosis of classic galactosemia. Galactose-free formula was started on the 13th day of life and the infant's health status improved gradually. The patient was discharged on the 22nd day of life.

In addition to the metabolic workup, the patient was evaluated on the 13th day of life by a retina specialist, who performed a handheld slit-lamp biomicroscopy and fundus examination, revealing the absence of bilateral red reflexes, bilateral pupillary tunica vasculosa lentis, and bilateral VH. Repeated ophthalmic examination disclosed posterior synechia in the left eye and bilateral VH. There was no evidence of cataract, and intraocular pressures were normal. Ocular ultrasonography showed bilateral VH on the 30th day of life. The left globe was noted to be slightly smaller in size than the right. The last ocular examination revealed diffuse retinal pigment epithelial changes and resolving VH in the right eye on the 39th day of life. Visual evoked potentials for the right and left globe were normal. Vitrectomy was planned for the left eye. Follow-up visits were scheduled under the purview of a team composed of a metabolic physician, dietician, neonatologist, and pediatric ophthalmologist.

Discussion

Galactosemia is an autosomal recessive disorder caused by deficient or absent activities of any of the three enzymes involved in the galactose metabolic pathway. The predominant form is classic-type galactosemia, which is due to a diminished activity or absence of the GALT enzyme. This enzyme deficiency leads to accumulation of galactose and its metabolites, galactose-1 P and galactitol, in body tissues and fluids, and leads to a secondary glycosylation defect. Glycosylation is a post-translational modification that mediates the form and function of many proteins as coagulation factors. Hypoglycosylation of coagulation factors causes the abnormal coagulation function in galactosemia as well as the mechanism of congenital disorders of glycosylation type 1 in untreated patients (Sturiale et al. 2005).

Galactosemic infants often present with jaundice after initiation of lactose-containing formulas. On admission,

indirect hyperbilirubinemia was prominent, and the patient required phototherapy. After the second week of life, direct bilirubin dominated. Woo et al. (2010) reported a case with early indirect hyperbilirubinemia requiring exchange transfusion diagnosed with galactosemia. In our case, the sibling who died (presumably due to undiagnosed galactosemia) also had indirect hyperbilirubinemia requiring exchange transfusion. It should be recognized that the early hyperbilirubinemia in untreated galactosemia is of the indirect type, and that direct hyperbilirubinemia – or less than indirect type – does not appear until about one week of age.

Galactose is converted to galactitol in cells and produces osmotic effects such as swelling of lens fibers, which may result in cataracts (Elsas 2000). Cataract is the main ocular sign associated with classic galactosemia. In an international survey study including 314 galactosemic patients, cataracts were reported in 30%. Only 8 patients diagnosed with galactosemic cataract required surgery; the remaining were mild or transient (Waggoner et al. 1990). It has been suggested in early reports that cataracts appeared with noncompliance with the diet; however, in the retrospective study of Widger et al. (2010), no direct relation between the degree of dietary compliance and cataract formation could be demonstrated. Current guidelines recommend a lifelong regular ophthalmic monitoring for cataract in galactosemic patients, but the period of ophthalmic examination is controversial.

VH is another ophthalmic complication of galactosemia, although its prevalence is unknown (Levy et al. 1996). The retinal vessel changes in galactose-fed dogs have been shown with a wide histopathologic spectrum in a number of animal studies. These retinal changes were associated with the occlusion of capillary beds and subsequent ischemia of the retina, including endothelial cell proliferation, soft exudates, intraretinal microvascular abnormalities and their subsequent degeneration, preretinal–intraretinal hemorrhages, and new vessel growth into the vitreous (Takahashi et al. 1992; Kador et al. 1995; Kobayashi et al. 1998). Galactosemic infants are susceptible to retinal changes probably leading to VH because of galactose and its metabolites.

Retinal hemorrhages are seen in nearly one-third of infants born by vaginal delivery. The incidence of retinal hemorrhage increases to 75% among infants delivered by vacuum extraction. Most retinal hemorrhages due to birth trauma usually resolve by 2 weeks of life (Emerson et al. 2001). Although retinal hemorrhage is frequent, VH is very rare in infants. It results from perinatal complications, disseminated intravascular coagulation, protein C defi-

ciency, retinopathy of prematurity, Terson's syndrome, and shaken-baby syndrome (Ferrone and de Juan 1994).

VH as an ophthalmic complication in galactosemic infants is reported very rarely in the literature. Laumonier et al. (2005) reported a galactosemic infant with unilateral VH who was free from cataract. Levy et al. (1996) reported five galactosemic neonates with VH. Coagulopathy was demonstrated in two neonates, and one infant was noted to have small bruises and bleeding in venous access sites. They suggested that coagulopathy contributed to the retinal vessel fragility of the neonate, exacerbated by galactosemia. The obstetric history revealed no risk for VH in this case. The presence of intravascular coagulopathy could not be ascertained in this case, since the prothrombin and partial thromboplastin times were not determined until 5 days after the baby had been started on a galactose-free formula. VH in infants can have very serious sequelae, such as axial myopia, severe amblyopia, and tractional retinal detachment. These potential sequelae could occur within 5 weeks after dense hemorrhage. In infants, early surgical intervention with vitrectomy is recommended – after waiting 3 to 4 weeks for spontaneous clearance of a dense hemorrhage – because of the severity of the sequelae (Ferrone and de Juan 1994).

In addition to cataract, one has to consider VH in the ophthalmic examination of infants with galactosemia. Presence of coagulopathy may exacerbate retinal hemorrhage progressing to VH in these infants. Q188R is the most common mutation among Turkish classic galactosemia patients as well as all Caucasian populations (Coskun et al. 1995). This mutation is generally associated with a severe biochemical phenotype, with nearly undetectable residual erythrocyte GALT activity in homozygotes. Screening of galactosemia in Turkey will provide an opportunity to prevent early severe symptoms of coagulopathy with early dietary and supportive interventions (Tyfield et al. 1999).

Concise Summary

Cataract has been reported as the main ophthalmic finding of galactosemia. However, there are also reports on another ophthalmic complication, vitreous hemorrhage (VH), which is rarely observed. Here, we present bilateral VH, with spontaneous resolution in one eye, in an infant diagnosed with classic galactosemia.

Details of the Contributions of Individual Authors

Sahin Takci is the corresponding author and the guarantor for this paper.

Sibel Kadayifciler was responsible for the ophthalmic examination.

Turgay Coskun was responsible for the metabolic and genetic workup for galactosemia.

Sule Yigit followed the patient in the neonatal intensive care unit and helped in the writing of the manuscript.

Competing Interest

All authors declare that the answers to all questions on the *JIMD* competing interest questionnaire are “No.”

Details of Funding

The authors confirm independence from the sponsors the content of the article has not been influenced by the sponsors.

Patient Consent Form

A patient consent statement about the patient proof that informed consent was obtained.

References

- Bosch AM (2006) Classical galactosaemia revisited. *J Inherit Metab Dis* 29:516–525
- Burke JP, O'Keefe M, Howell R, Naughton ER (1989) Ophthalmic findings in classical galactosemia-a screened population. *J Pediatr Ophthalmol Strabismus* 26:165–168
- Coskun T, Erkul E, Seyrantepe V, Özgüç M, Tokatli A, Özalp I (1995) Mutational analysis of Turkish galactosaemia patients. *J Inherit Metab Dis* 18:368–369
- Elsas LJ (2000) Galactosemia. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=galactosemia>
- Emerson MV, Pieramici DJ, Stoessel KM, Berreen JP, Gariano RF (2001) Incidence and rate of disappearance of retinal hemorrhage in newborns. *Ophthalmology* 108:36–39
- Ferrone PJ, de Juan E Jr (1994) Vitreous hemorrhage in infants. *Arch Ophthalmol* 112:1185–1189
- Fridovich-Keil JL (2006) Galactosemia: the good, the bad, and the unknown. *J Cell Physiol* 209:701–705
- Holtan JB, Walter JH, Tyfield LA (2001) Galactosemia. In: *The metabolic and molecular bases of inherited disease*, 8th edn. The McGraw-Hill Companies, New York
- Item C, Hagerty BP, Mühl A, Greber-Platzner S, Stöckler-Ipsiroglu S, Strobl W (2002) Mutations at the galactose-1-p-uridylyltransferase gene in infants with a positive galactosemia newborn screening test. *Pediatr Res* 51:511–516
- Kador PF, Takahashi Y, Wyman M, Ferris F (1995) Diabetes like proliferative retinal changes in galactose-fed dogs. *Arch Ophthalmol* 113:352–354
- Kobayashi T, Kubo E, Takahashi Y, Kasahara T, Yonezawa H, Akagi Y (1998) Retinal vessel changes in galactose-fed dogs. *Arch Ophthalmol* 116:785–789

- Laumonier E, Labalette P, Morisot C, Mouriaux F, Dobbelaere D, Rouland JF (2005) Vitreous hemorrhage in a neonate with galactosemia. A case report. *J Fr Ophtalmol* 28:490–496
- Levy HL, Brown AE, Williams SE, de Juan E Jr (1996) Vitreous hemorrhage as an ophthalmic complication of galactosemia. *J Pediatr* 129:922–925
- Sturiale L, Barone R, Fiumara A et al (2005) Hypoglycosylation with increased fucosylation and branching of serum transferrin N-glycans in untreated galactosemia. *Glycobiology* 15: 1268–1276
- Takahashi Y, Wyman M, Ferris F, Kador PF (1992) Diabetes like preproliferative retinal changes in galactose-fed dogs. *Arch Ophthalmol* 110:1295–1302
- Tyfield L, Reichardt J, Fridovich-Keil J et al (1999) Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (GALT) gene. *Hum Mutat* 13:417–430
- Waggoner DD, Buist NR, Donnell GN (1990) Long-term prognosis in galactosaemia: results of a survey of 350 cases. *J Inherit Metab Dis* 13:802–818
- Widger J, O'Toole J, Geoghegan O, O'Keefe M, Manning R (2010) Diet and visually significant cataracts in galactosaemia: is regular follow up necessary? *J Inherit Metab Dis* 33:129–132
- Woo HC, Phornphutkul C, Lupton AR (2010) Early and severe indirect hyperbilirubinemia as a manifestation of galactosemia. *J Perinatol* 30:295–297