Case Report

Galactosemia in Thai Patient at Phramongkutklao Hospital: A Case Report

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Galactosemia is a rare autosomal recessive disorder of galactose metabolism, which occurs as a consequence of a deficiency of one of these three enzymes: galactokinase, galactose-1-phosphate uridyltransferase, and uridine diphosphate galactose-4-epimerase, leading to elevated level of galactose and its metabolites in blood.

The presented case was a 2-month-old, Thai female infant with persistent cholestatic jaundice, bilateral posterior subcapsular cataracts, and hepatomegaly. Laboratory investigations showed slightly elevated serum aminotransferase, and increased urinary excretion of galactose, galactitol and galactonate (by urine gas chromatography/mass spectrometry). These findings indicated an error in galactose metabolism. Soy-based formula was introduced to the patient. Clinical and laboratory results were improved after a few months of treatment. Genetic counseling was provided to the family for 25% of recurrence risk. Prenatal diagnosis is not established in Thailand.

Keywords: *Cataract, Jaundice, Galactosemia, Uridyltransferase deficiency*

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Galactosemia is a rare autosomal recessive disorder of galactose metabolism, which occurs as a consequence of a deficiency of one of these three principal enzymes involved in the metabolism of galactose[1]. These enzymes are galactokinase, galactose-1-phosphate uridyltransferase, and uridine diphosphate galactose-4-epimerase which leads to an elevated level of galactose and its metabolites in blood[1,2]. It can manifest with subtle symptoms to fatal complications. Galactose-1-phosphate uridyltransferase deficiency is the most severe and common form of galactosemia and often referred to as "classic galactosemia"[3].

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The incidence in Canada and USA was reported to be in the range of 1:35,000-73,296 and 1:30,000-191,000, respectively[4]. Cheung et al (1996) reported that the incidence in a Chinese population was approximately 1:400,000. Newborn screening and other surveillance programmes in Europe and North America have established newborn rates of 1:30,000-50,000 in white Caucasians[5-7].

Galactosemia was first described by Groppet in 1917[8], presented with hepatomegaly, jaundice, failure to thrive, and urinary excretion of albumin and sugar. After exclusion of galactose from the diet, these signs and symptoms normalized. The patient was also mentally retarded (development quotient of 14 months at 36 months of age).

The presented case was an infant with clinical, and laboratory findings suspected of galactosemia in Phramongkutklao Hospital in 2005.

Case Report

A 2-month-old female, Thai infant presented with persistent jaundice at 2 weeks of age. At that time, liver function test showed cholestatic jaundice with slightly elevated serum aminotransferase: total serum bilirubin 9.1 mg/dL, direct serum bilirubin 4.3 mg/dL, aspartate aminotransferase (AST, SGOT) 51 IU/L, alanine aminotransferase (ALT, SGPT) 19 IU/L, serum alkaline phosphatase 1,119 IU/L, total serum protein 5.8 g/dL, and serum albumin 3.0 g/dL. Breast milk jaundice was the suspected cause and breast feeding was discontinued for the treatment but clinical jaundice was not improved.

She was the first offspring in the family, born at term by normal labor without any complications. Her birth weight was 2,550 grams. She had been breast-fed for 2 weeks and changed to bottle-fed. Her parents were not consanguineous in marriage (Fig. 1). Both parents were 26 years old and healthy.

Physical examination revealed a 3.9 kg (10-25th percentile) and 51.5 cm long (below 3rd percentile) baby with normal head and chest circumference. She had mild jaundice and hepatomegaly. Her liver was palpated 1-2 cm below the right costal margin with liver span of 8 cm. Bilateral posterior subcapsular cataracts were detected by ophthalmologist. Other physical examination was unremarkable.

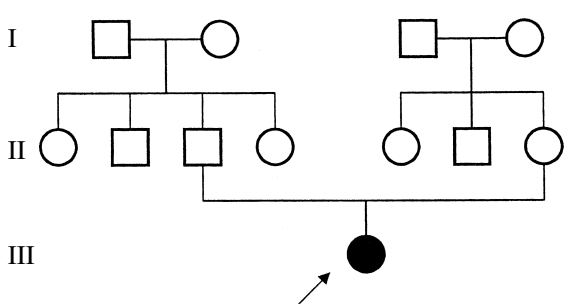

Fig. 1 The pedigree of the patient

Complete blood cell counts, serum electrolytes, blood urea nitrogen and creatinine were normal. Follow up of liver function test showed: total serum bilirubin 147 μmol/L, direct serum bilirubin 97 μmol/L, aspartate aminotransferase (AST, SGOT) 128 IU/L, alanine aminotransferase (ALT, SGPT) 55 IU/L, serum alkaline phosphatase 2,767 IU/L, serum gamma GT 95 IU/L, total serum protein 5.0 g/dL, and serum albumin 2.9 g/dL. Urine analysis was negative for urine glucose by Dip Stix but positive (2+) for urine reducing substance by Clinitest. Ultrasonographic study of hepatobiliary tract revealed normal liver without dilated intrahepatic duct. DISIDA scan demonstrated good biliary drainage into the small intestine. Urine gas chromatography/mass spectrometry (urine GC/MS) showed increased urinary excretion of galactose, galactitol and galactonate (Fig. 2).

Discussion

The authors report a case of 2-month-old female, Thai infant with persistent cholestatic jaundice with slightly elevated serum aminotransferase at 2 weeks of age. Various causes of persistent cholestatic jaundice such as congenital hypothyroidism, congenital infection, and inborn error of metabolism were investigated. Thyroid function test and TORCH titer were negative. Bilateral posterior subcapsular cataracts were detected by ophthalmologist. Urine analysis was negative for urine glucose by Dip Stix but positive (2+) for urine reducing substance by Clinitest, which indicated the presence of reducing substances other than glucose such as galactose or fructose in the urine. Dip stix tests rely on the action of glucose

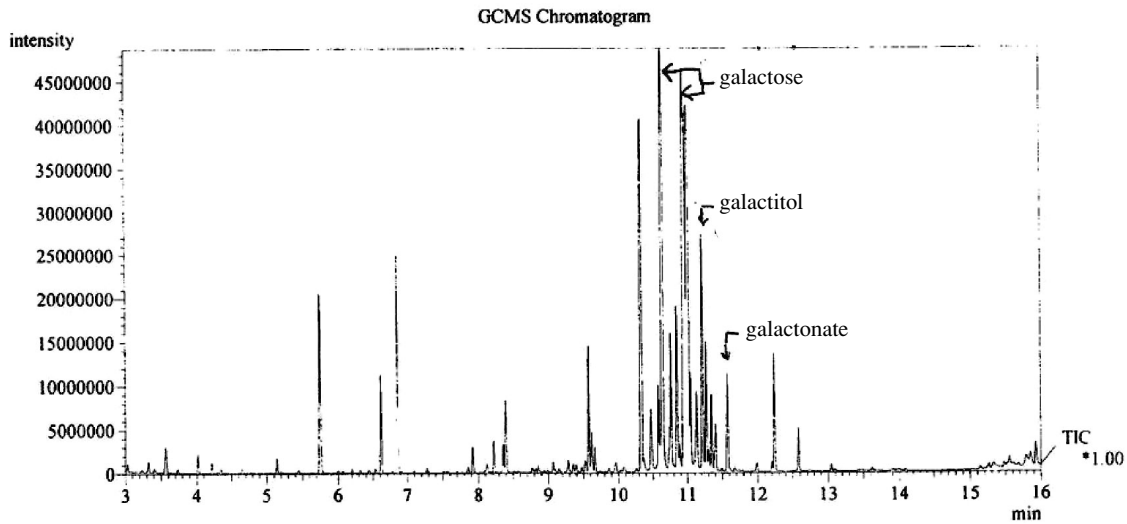

Fig. 2 Urine gas chromatography/mass spectrometry (urine GC/MS) showed increase urinary excretion of galactose, galactitol and galactonate

oxidase, which is specific for glucose and is non-reactive with galactose or fructose. Urine gas chromatography/mass spectrometry (urine GC/MS) was done and showed increased urinary excretion of galactose, galactitol and galactonate. All clinical and laboratory findings indicated an error of galactose metabolism or galactosemia.

Three inborn errors of galactose metabolism are known. Galactokinase deficiency is the most insidious. It results in the formation of cataracts without provoking symptoms of intolerance. Galactose-1-phosphate uridyltransferase deficiency is the most severe and common form of galactosemia and often referred to "classic galactosemia"[3]. It exists in two forms, complete or partial deficiency. The complete or near complete deficiency of this enzyme is life-threatening and affects not only the eye lens but also the liver, kidney and brain. Partial deficiency is usually benign. Uridine diphosphate galactose-4-epimerase deficiency also exists in two forms. The very rare complete generalized deficiency clinically resembles classic galactosemia. The more frequent partial deficiency is benign which is limited to erythrocytes and leukocytes[9].

Classic galactosemia is most often present in the newborn period with a life threatening illness if a galactose restricted diet is not introduced. Symptoms and signs may include: poor feeding, failure to thrive, vomiting and diarrhea which usually begins within a few days of milk ingestion, persistent cholestatic jaundice, cataracts which have been observed within a few days of birth, hypoglycemia, convulsions, lethargy, irritability, hypotonia, hepatomegaly[2,10]. It also present in older infants and children with hepatic cirrhosis, cataracts, ataxia, speech defects, mental retardation and premature ovarian failure[11]. Death from liver and kidney failure and sepsis may follow within days. There appears to be a high frequency of neonatal death

due to *E. coli* sepsis, with a fulminant course[12]. This proneness to sepsis is due to inhibition of leukocyte bactericidal activity[13].

Laboratory diagnosis in classic galactosemia usually proceeds through a demonstration of an elevated level of galactose and its metabolites in blood, an elevated erythrocyte galactose-1-phosphate concentration, and reduced or absence of galactose-1-phosphate uridyltransferase activity in heparinized whole blood, erythrocyte lysates, liver biopsy samples or cultured skin fibroblasts. In partial deficiency, the enzyme activities of 10-50% of the normal activity are measured while in heterozygotes, the enzyme activity is about 50% of the normal activity. In the presented case, activity of galactose-1-phosphate uridyltransferase or uridine diphosphate galactose-4-epimerase could not be done for further characterization of galactosemia because of the unavailability of this test in Thailand.

Another method for definite diagnosis of galactosemia is to perform mutation analysis. The structural gene for galactokinase, galactose-1-phosphate uridyltransferase, and uridine diphosphate galactose-4-epimerase are assigned to the long arm of chromosome 17 (17q24), the short arm of chromosome 9 (9p13), and the short arm of chromosome 1 (1p36), respectively[2,13-16]. In classic galactosemia, in African-Americans, 62% of alleles are presented by S135L mutation, a mutation that may be responsible for the milder disease and is associated with good outcome[17]. In the Caucasian population, 70% of alleles are represented by homozygous for Q188R missense mutation and is associated with classic galactosemia[18,19]. Prenatal diagnosis can be performed by direct enzyme analysis of cultured amniotic fluid cells, or chorionic villi or mutation analysis[20].

Metabolic consequence in classic galactosemia is failure to metabolize galactose-1-phosphate. Galactose-1-phosphate and galactose are accumulated leading for galactitol formation. As in galactokinase deficiency, cataract is formed by galactitol accumulation in the lens causing osmotic swelling of lens fibers and denaturation of proteins. The pathogenesis of hepatic, renal and cerebral disturbances is probably related to the accumulation of galactose-1-phosphate and (probable) galactitol[1,3].

Galactose-free diet will cause striking regression of all the acute symptoms and signs, nausea and vomiting cease and weight gain ensues[3]. Almost all patients with classic galactosemia have a very good response to treatment with elimination of galactose from their diet which will reverse growth failure, renal and hepatic dysfunctions if dietary restriction is initiated early. Liver cirrhosis may be prevented. The cataract can also regress fully and most patients have no impairment of eyesight[21]. Exclusion of all galactose from the diet must be started at once, even before the results of diagnostic tests are available. Early diagnosis and treatment have improved the prognosis of galactosemia.

Summary

Based on the clinical manifestations and laboratory findings, galactosemia was the most likely diagnosis in the presented patient. Definite diagnosis by enzyme assay or molecular diagnosis could not be done for further characterization of galactosemia due to unavailability of these tests in Thailand. Treatment in the presented case was started with soy-based formula which is lactose-free. After 2-3 months of treatment, cholestatic jaundice with slightly elevated serum aminotransferase, and hepatomegaly were improved. The infant had better weight gain. Ophthalmologist also found regression of bilateral posterior subcapsular cataracts, which helped us to confirm the diagnosis of galactosemia in the presented patient. Genetic counseling was provided to the family with the recurrence risk of 25%, due to its autosomal recessive inheritance.

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โรคกาแลกโตสีเมียในโรงพยาบาลพระมงกุฎเกล้า: รายงานผู้ป่วย

บุญชัย บุญวัฒน์, มหัทธนา กมลศิลป์, นภอร ภาวิจิตร

โรคกาแลกโตสีเมีย เป็นโรคที่มีการถ่ายทอดทางพันธุกรรมแบบจีนด้อยที่พบได้ไม่บ่อย และเกี่ยวข้องกับเมตาบอลิสมของน้ำตาลกาแลกโตส เกิดจากการลดหรือขาดการทำงานของเอนไซม์ 1 ใน 3 ชนิดนี้ ได้แก่ galactokinase, galactose-1-phosphate uridyltransferase และ uridine diphosphate galactose-4-epimerase เป็นผลให้มีการคั่งของน้ำตาลกาแลกโตสและเมตาบอไลต์ของน้ำตาลกาแลกโตสในเลือด

รายงานผู้ป่วยเด็กหญิงไทย 1 ราย อายุ 2 เดือน มาด้วยอาการตัวเหลือง ตรวจพบต้อกระจกที่ตาทั้ง 2 ข้างและมีตับโต การตรวจทางห้องปฏิบัติการพบว่า มีการเพิ่มสูงขึ้นของเอนไซม์ในตับเล็กน้อย และมีการเพิ่มการขับของน้ำตาลกาแลกโตส กาแลกไตตอล และกาแลกโตเนตในปัสสาวะโดยวิธี urine gas chromatography/mass spectrometry (urine GC/MS) ซึ่งบ่งชี้ถึงความผิดปกติในเมตาบอลิสมของน้ำตาลกาแลกโตส ผู้ป่วยรายนี้ได้รับการรักษาด้วยนมถั่วเหลือง อาการทางคลินิกและผลการตรวจทางห้องปฏิบัติการของผู้ป่วยดีขึ้นหลังจากได้รับการรักษาในระยะเวลา 2-3 เดือน ครอบครัวของผู้ป่วยได้รับการให้คำปรึกษาทางพันธุศาสตร์ โอกาสเกิดซ้ำในบุตรคนต่อไปร้อยละ 25 การวินิจฉัยก่อนคลอดยังไม่สามารถทำได้ในประเทศไทย