Galactosemia in Three Filipino Patients - The Importance of Newborn Screening

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ABSTRACT

Disorders of galactose metabolism can be fatal if not treated early. Newborn screening has made it possible to detect and treat this disease. Three cases of galactosemia, one with galactokinase deficiency and two with galactose-1-phosphate uridyltransferase deficiency detected by newborn screening, are presented. Because of early detection and management, the first patient was spared the early complications of galactosemia and continues to grow and develop normally. The two other patients were diagnosed at 1 month, initial presentation included hepatomegaly and failure to thrive. Institution of treatment was able to reverse the acute complications and both are currently doing well. The importance of galactosemia newborn screening in preventing complications resulting from the disease is emphasized.

Key Word: galactosemia, newborn screening, cataracts, liver failure, lactose free milk

Introduction

Galactosemia is a group of disorders of galactose metabolism that can result in life-threatening complications.[1] Infants with galactosemia develop clinical symptoms after ingesting lactose from milk and milk products. Exogenous lactose is hydrolyzed into galactose and glucose by lactase in the small intestine.[2] Complete oxidation of galactose requires activation and conversion into UDP-glucose by galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT) and uridine diphosphate galactose 4-epimerase (GALE) (Figure 1).

Three inborn errors of galactose metabolism are known. Classical galactosemia results from complete or partial deficiency of the GALT enzyme. It can present with feeding problems, failure to thrive, hepatocellular damage, bleeding, and sepsis in untreated infants. In approximately 10% of individuals, cataracts are present.[1,2] GALE deficiency can present with a very rare profound deficiency which clinically resembles classical galactosemia. The more common partial deficiency is benign.[2] Galactokinase (GALK) deficiency presents primarily as cataracts in untreated patients.[1]

Galactosemia is easily diagnosed through newborn screening using a galactosemia spot test to check for total galactose and galactose-1-phosphate metabolites and the Beutler assay[3] to determine the activity of the GALT enzyme. Birth incidence of classic galactosemia is about 1 per 47,000 in the Caucasian population[4] and about 1 per 600,000 in Japanese.[5] Philippine newborn screening data (through December 2008) shows a detection rate of about 1:165,000 for classical galactosemia.

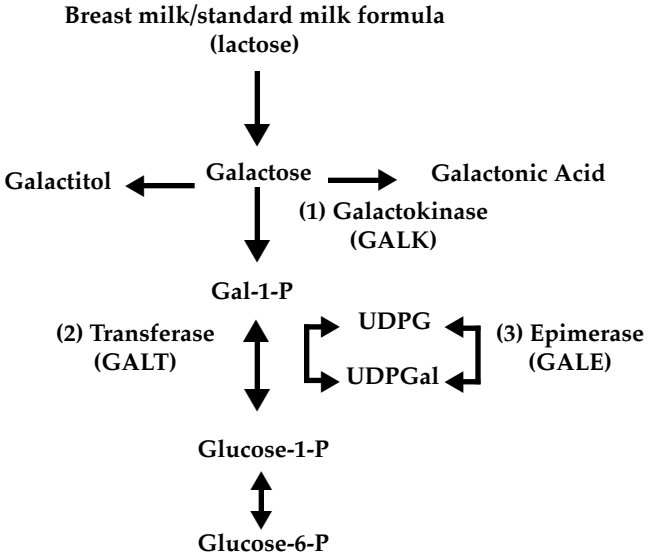

Figure 1. Galactosemia pathway with multiple enzymatic steps is shown. The enzymes allow the subsequent conversion of galactose into galactose-1-phosphate by GALK (1); galactose-1-phosphate and uridine diphosphate glucose (UDP glucose) into glucose-1-phosphate and UDP-galactose by GALT (2) and the interconversion of UDP-glucose and UDP-galactose by GALE (3).

Laboratory Screening for Galactosemia

Laboratory screening for galactosemia, as part of the Philippine Newborn Screening Program, was initially performed as part of the collaborative services of the New South Wales Newborn Screening Laboratory, The Children's Hospital at Westmead, Sydney, Australia. As capabilities became available at the Manila newborn screening laboratory, the services were shared such that initial screening was performed in Manila and any additional second-tier testing was completed on specimens mailed to Sydney. Since April 15, 2008, both first and second tier screening analyses have

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been conducted in Manila. The following paragraphs give an overview of the laboratory screening procedure.

Detection of galactose and galactose-1-phosphate in a dried blood specimen (galactosemia spot test) is done enzymatically in a two-step process. First, alkaline phosphatase, galactose dehydrogenase, and nicotinamide adenine dinucleotide (NAD) are added to a punched blood sample. Any galactose and galactose-1-phosphate in the blood sample reduces NAD^+ to NADH, which is fluorescent. If NADH is formed, it is detected visually by spotting the reaction mixture onto chromatography paper and viewing with ultraviolet light (366nm). The intensity of fluorescence is directly proportional to the combined concentration of the galactose and galactose-1-phosphate. The chromatography spot is manually read and compared to control samples. The presence of fluorescence suggests galactosemia.[6]

Specimens with a 'positive' spot test undergo second tier testing using the Beutler assay. A second punched sample is obtained, and a mixture of the enzymes UDP-glucose, galactose-1-phosphate, and nicotinamide adenine dinucleotide phosphate ($NADP^+$) is added. In the presence of UDP-glucose and galactose-1-phosphate, galactose-1-phosphate uridyl transferase catalyzes a reaction where NADP is reduced to NADPH. This compound also fluoresces at 366 nm and is manually compared to control GALT deficient samples. Absence of fluorescence after 4 hours indicates a deficiency of the GALT enzyme, which corresponds to classical galactosemia. A normal Beutler screening result and a positive galactosemia spot test on the same specimen indicates possible GALK deficiency.[7]

Case reports

Patient 1

Patient 1 is a 1 year 11 month old male born to non-consanguineous parents. Newborn screening at 1 week of life showed elevated galactose metabolites (8 mmol/L; normal value = 1.4 mmol/L) and normal GALT activity (done at The Children's Hospital at Westmead, Sydney Australia). This profile was highly suggestive of GALK deficiency. Lactose-free milk was started on the 12th day of life. His growth and development are currently normal. Ophthalmologic and physical examinations are also normal. Regular monitoring for galactose metabolites continue to show normal results.

Patient 2

Patient 2 is a 1 year 11 month old male born to consanguineous parents. He had a 10 day history of jaundice with onset on the 3rd day of life, which resolved spontaneously. His initial diet consisted of breast milk supplemented with lactose milk formula. He was referred to genetics clinic at age 1 month 10 days after a galactosemia screening test showed elevated galactose metabolites (8 mmol/L) and non-detectable GALT activity (done at The Children's Hospital at Westmead, Sydney Australia). During the consult, hepatomegaly was noted. He was immediately started on lactose-free milk. Presently, he is developmentally at par with age. He has no cataracts and his liver is no longer palpable. Regular monitoring for galactose metabolites continues to give normal levels.

Patient 3

Patient 3 is a 1 year 11 month male born to non-consanguineous parents. He presented with abdominal enlargement and failure to thrive at 1 month of age. When initially seen at the genetics clinic, he was febrile, dehydrated and noted to have hepatomegaly, for which he was admitted and treated for gram negative sepsis. Galactosemia screening results indicated GALT deficiency: elevated galactose metabolites (7 mmol/L) and non-detectable GALT activity (done at The Children's Hospital at Westmead, Sydney Australia). He was started on a galactose free diet; he showed improvements and was discharged after 2 weeks. Currently, his growth and developmental milestones are normal. However, his liver is still enlarged with the edge palpable 3-4 cm below the right costal margin. The initial abdominal ultrasound showed hepatomegaly. Regular monitoring for galactose metabolites continues to show normal levels. Repeat abdominal ultrasound and liver enzyme tests have not yet been done.

Discussion

Galactosemia is an inborn error of carbohydrate metabolism characterized by elevated levels of galactose and its metabolites owing to enzyme deficiencies involved in its metabolism. Diagnosis by newborn screening has allowed the prevention of acute complications with the timely institution of the appropriate management. Dietary elimination of milk and milk products containing lactose is the usual treatment for all types of galactosemia.[1]

GALK deficiency primarily causes cataracts in untreated patients. Cataracts result from the accumulation of galactitol in the lens, because the block increases the conversion of galactose into galactonate and galactitol. The latter can cause osmotic swelling of lens fibers and denaturation of proteins leading to cataracts. When diagnosis is made rapidly and treatment begun within first 2-3 weeks of life, the cataracts can resolve. When treatment is too late and cataracts are too dense, they must be removed surgically.[2] In patient 1, due to early detection and management, cataract complications were prevented.

Patients 2 and 3 have a deficiency of GALT enzyme activity consistent with classical galactosemia. Within days of ingesting breast milk or lactose-containing formula, affected infants develop life-threatening complications, including feeding problems, failure to thrive, hypoglycemia, hepatocellular damage, bleeding diathesis, jaundice, hyperammonemia, Escherichia coli sepsis, shock and/or death. If a lactose-free diet is instituted within the first 10 days of life, symptoms disappear promptly; jaundice resolves within days, cataracts may clear, liver and kidney

functions return to normal and liver cirrhosis may be prevented.[1,2] Untreated infants who survive the neonatal period develop mental retardation and other cortical and cerebellar tract signs.[1] These two patients did not undergo newborn screening hence symptoms were already present at the time of diagnosis. With the institution of dietary management, there was complete resolution of symptoms in patient 2 within 4 months; however, hepatomegaly is still evident in patient 3. Prolonged hepatomegaly after treatment has not been reported in classical galactosemia. Whether the patient's hepatomegaly can be attributed to the delay in treatment during the neonatal period or to some other etiology remains for further study.

The clinical courses of these 3 patients emphasize the need for early detection of galactosemia through newborn screening. The outcome for Patient 1 illustrates how early diagnosis and management can prevent complications such as cataracts. Conversely, the outcomes for Patients 2 and 3 demonstrate the adverse effects of late diagnosis. The latter two cases also demonstrate that appropriate treatment, even when delayed, can reverse some of the acute complications of classic galactosemia.

Despite early and adequate therapy, long-term complications in older children and adults with classic galactosemia can still occur. These include cataracts, speech defects, poor growth, poor intellectual function, neurologic deficits (predominantly extrapyramidal findings with ataxia), and ovarian failure.[8] Possible explanations include the capability of humans for endogenous production of galactose, since the body is able to synthesize galactose from glucose, even in patients with galactosemia.[2] Milligram amounts of galactose cause an appreciable rise of galactose-1-phosphate in erythrocytes, and it is possible that the same happens in sensitive tissues, such as the brain, liver, and kidney.[2] Possible mechanisms for ovarian dysfunction include the production of abnormal FSH, abnormal receptor activity, and a direct toxic effect of galactose, galactose-1-phosphate, or other metabolites on ovarian tissue.[9]

In summary, galactosemia and its acute complications can be prevented by early diagnosis through newborn screening. Consequently, early institution of management following early diagnosis is also achievable. Nonetheless, long term complications from galactosemia can still occur despite early diagnosis and treatment. Thus, regular monitoring and evaluation are necessary.

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