http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **19**(2):215-218
doi: 10.2478/v10255-012-0026-0

GALACTOSEMIA: DIAGNOSIS AND TREATMENT

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received: March 03, 2012 *accepted*: April 20, 2012
available online: May 31, 2012

Abstract

Galactosemia is a hereditary metabolic disease, having autosomal recessive transmission. It can be the result of three distinct enzyme deficits on the path of galactose metabolism: Galactose-1-phosphate uridylyltransferase (GALT), Galactokinase and UDP-glucose 4-epimerase (GALE). The symptoms and signs appear in the first 2-3 days of life and has a poor prognosis: repeated haemorrhages, modified liver tests, hepatosplenomegaly, jaundice, sistemic infections, especially with gram-negative bacteria (usually E coli), liver and renal failure, cataract. The newborn metabolic screening plays a decisive role in early detection of galactosemia.

key words: *galactosemia, newborn genetic screening, diagnostic, treatment*

Introduction

Hereditary metabolic diseases have autosomal recessive transmission and are characterised by an enzyme deficit. Galactosemia is indicated by high levels of seric galactose and can be the result of three distinct enzyme deficits on the path of galactose metabolism: GALT, Galactokinase and GALE.

Clinical forms

Depending on the enzymatic deficit, galactosemia can be classified as classic and incomplete.

Classic galactosemia, also called type 1, is characterised by a GALT activity of less than 1% of normal. The symptoms appear in the first 2-3 days of life and has a poor prognosis.

Signs and symptoms include: deterioration, coma and death.

Liver damage is a constant in the development of the disease and can manifest by repeated haemorrhages, modified liver tests, hepatosplenomegaly and jaundice; these are usually the signs that draw the attention of the parents/physician and lead through more specific tests to the diagnosis. The most common complications of galactosemia are systemic infections, especially with gram-negative bacteria (usually E coli) with an evolution towards sepsis.

The incomplete forms of galactosemia are usually diagnosed later in the course of the

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disease. The organ involvement depends on the degree of metabolic impairment and may include liver and renal failure and cataract.

The newborn metabolic screening plays a decisive role in early detection of galactosemia (and this is also applicable for other hereditary enzymopathies).

Epidemiology

The desease is equally spread between boys and girls.

All forms of galactosemia are inherited in an autosomal recessive manner. In the classical form (G/G) the GALT activity is virtually non-existant (less than 1%). The most common type of galactosemia is found in the heterozygotes where one allele codes the severe type (G) and one allele codes the less severe type (D) and the enzymatic activity is around 50% of normal. There have been described over 190 subtypes of incomplete galactosemia with various degrees of clinical manifestation and organ impairment.

Pathophysiology

In patients with classic galactosemia, galactose and its derivatives (galactoil and galactonate) are cumulating, especially in liver and kidney, leading to growth retardation. Galactose deposits in the crystalline may lead to cataract. Furthermore, galactose deposits are considered to be the cause of ovarian failure and dyspraxia.

Signs and symptoms severity and the degree of organ involvement depend strictly on the remnant enzyme activity; accordingly, the classic form of galactosemia, where the GALT activity is below 5% of normal, is the more severe form. Incomplete types of galactosemia are characterised by higher GALT activity such as 50% for homozygote D/D form, also called Duarte, or heterozygote G/N form, or even 75% for heterozygoute D2/N form, also called Duarte variant.

Case presentation

Pacient N.E.I of masculine sex, born at term, APGAR: 8 (late tonus), 3800 g weight, 53 cm, length, 34 cm cranial perimeter**.**

Family history (non-inbred parents):

– mother*:* 29 years-old, monogesto, monopara, clinically healthy, blood type BIII, Rh: positive
– father: 32 years-old, hepatic steatosis, blood type BIII, Rh: negative
– the mother had a brother deceased as a newborn, cause unknown

At birth: good general condition, pink skin, rhythmic cardiac sounds, heart rate (HR) 128 bpm, vesicular murmur present, supple abdomen, late muscular tonus (APGAR 8), discharged the 3rd day.

Case evolution (diagnostic)

First follow - up (13 days of birth): anterior fontanel was normotensive, somnolent, with low muscular tonus. The patient was thermodynamically stable with HR of 90 bpm, the liver was palpable its lower border 1.5 cm below the costal margin, weight 3.800g, breastfed.

Considering the familly history we made a genetic screening, the results being expected in 2 weeks time.

Second follow - upt (2 weeks after the first one) - persistence of low muscular tonus, and increased jaundice comparing to prior visit.

Blood tests:

– CBC: leukocytes: $9.52*10^3$/µl; erythrocytes: $3.4*10^3$/µl; Hb: 10.81 g/dl; Ht:32.66%; plt: $356*10^3$mii/µl;

lymphocytes 69.6%; monocytes: 7.9%; neutrophils: 19%; eosinophils: 3.3%; bazophils: 0.2%; reticulocytes: 6.2%;
- direct bilirubin 0.4 mg/dl; total bilirubin: 7.74 mg/dl.
- Coombs test: negative.
- Blood type: BIII, Rh negative
- anti IgG (C3d): negative
- the serum presented intense jaundice.

Abdominal ultrasound showed normal sized liver, biliary ducts, spleen and kidneys.

Step diagnosis

1. Prolonged jaundice.

2. Hemolysis, probably due to galactosemia [1].

3. The newborn genetic screening shows a GALT activity lower than normal: 2.1UI/gHb (normal value > 2.3UI/gHb) [2].

A differential diagnosis was made between an incomplete form of galactosemia (probably D/N) and a false positive test. Considering that the patient was born at term, did not receive any prior antibiotics nor glucose, the blood sample had the laboratory confirmation of being correctly harvested and kept in proper conditions, we decided to test the GALT and UDP-Galactose-4-epimerase activity in order to identify the subtype of galactosemia.

The epimerase deficient subtype can account for muscular hypotonia and later can associate neurological deafness and requires exclusion of galactose from diet, whereas the benign form is limited to erytrocytes and leukocytes and requires no treatment.

Treatment

Replacement of breast milk with HUMANA SL.

Positive diagnosis

Twelve days after weaning, the blood test results arrived and a diagnosis of heterozygoute form of galactosemia, Duarte variant (D/N) was made:
- GALT < 15µmol/gHb,
- UDP-Galactose-4-epimerase activity 23 µmol/gHb (normal 19-35)

Differential diagnosis

Depending on the type and severity of symptoms, the differential diagnosis is made between:
- other causes of sepsis
- other causes of liver impairment (infectious, genetics)
- obstruction of bile ducts
- other metabolic impairments (tezaurismoze)
- mitochondrial disease (mitochondrial DNA depletion).

Discussion

Duarte galactosemia is an incomplete galactosemia with a partial GALT enzymatic deficit in erytrocytes due to an affected allele and a normal one. The signs and symptoms are discreet if any. It is a common form of galactosemia (1 in 20 newborns) being 10 times more frequent than the classic form.

Disease management:

Duarte variant galactosemia management is a subject of dispute and most clinicians do not recommend breastfeeding discontinuation and supplement the diet with galactose free formula while monitoring the serum levels of galactose-1-phosphate. Ficiccioglu and col [3] reported that breastfed newborns with Duarte galactosemia (D/G) have a higher serum concentration of galactotil, galactonate (2-6

times higher) and galactose (2 times higher) than those reeving galactose free formula. Galactotil and galactonate serum levels are proportional with galactose intake but they are not toxic and their cumulation does not impair growth, nor does it have any pathological consequences.

Other clinicians recommend glactose free diet for every galactosemia type in course of investigation. This precaution is necessary if GALT activity is less than 10% of normal, due to high risk of organ impairment. The restriction becomes less important at preschool age [4].

In the presented case, the restriction was necessary due to prolonged jaundice and haemolytic anaemia, the latter being caused by a structural deficit in erythrocyte's membrane. Paul, Marks and Ruth [5] (1959) have also shown that hydrolysis and the rest of the symptoms recover with age due to the improvement of alternative galactose metabolism pathway (UDP GAL pyrophosphorylase) whose enzymatic activity grows in time. As such the decision of maintaining a galactose free diet, at least while the reticulocyte number is high (0-2 years) seems a better approach.

Secondary prevention is made with calcium (up to 1200mg/day) and vitamin D3 (up to 1000UI/day) supplements until a galactose diet is progressively reintroduced and while monitoring the serum levels of erythrocytary galactose-1-phosphate.

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