A Study of Galactosemia from a Tertiary Care Centre

Author
Sujay Chaudhuri
Division of Pediatric Gastroenterology, Department of Gastroenterology, PGIMER Chandigarh
ADDRESS: Akshaytara Apartment, Flat No. 1/7, 2nd Mile Sevoke Road, Siliguri-734001, Near Don Bosco Mobile – 7797931687, Email: drsujoychowdhury@gmail.com

Abstract
Objectives: Galactosemia is an inborn error of carbohydrate metabolism manifesting in neonatal period. It causes early cirrhosis in infancy, hence early detection and management are of great importance. In the present study we observed various clinical and investigational profile of galactosemia in a tertiary care centre.

Methods: Various clinical manifestations and investigational profile and outcome of galactosemic children admitted in pediatric Gastroenterology at PGIMER, Chandigarh were recorded and analysed. Ultrasound of abdomen and HIDA scan were done to rule out EHBA. Hemogram, blood culture, LFT, coagulogram, work up for intrauterine infections were carried out. Urinary examination for reducing substrabces, eye checkup, liver biopsy and enzyme assay were done in all cases.

Results: Nineteen children of galactosemia were seen from June 1993 to June 2003. Age of onset of symptoms was 3-25 days of life. Males were 12 (63%) and females were 7 (36%). Cholestatic jaundice was present in all 19 infants manifesting as clay colored stool and high colored urine staining diaper. Hepatomegaly was present in 5/19 (26%), hepatosplenomegaly in 14/19 (74%), ascites in 9/19 (47%), seizure in 3/19 (15%), sepsis in 1/19 (05%) , renal tubular acidosis in 2/19 (10%) and hypoglycemia in 5/19 (26%) infants. Five infants died. Conjugated bilirubin was raised in all infants, transaminitis was present in 11/19 (57%) and coagulopathy in 9/19 (47%) infants. Liver biopsy was suggestive of galactosemia in all. Urinary reducing substance was positive in 15/19 (79%), cataract was present in 7/19 (36%) cases. Galactose 1-phosphate uridy1 transferase enzyme deficiency was detected in all 19 cases. Urine analysis for renal tubular acidosis was positive in 2 infants. 14 infants were put on galactose free diet and all improved.

Conclusion: Galactosemia is an uncommon but important cause of metabolic liver disease in early infancy. High degree of suspicion and early detection are mandatory for better outcome, since these children require galactose free diet.

Introduction
Galactosemia is a rare genetic metabolic disorder which affects an individual’s ability to metabolise sugar galactose properly. It is due to deficiency in an enzyme responsible for galactose degredation.

Friedrich Goppert (1870-1927), a German physician first describe the disease in 1917.(1)
Isselbacher KJ et al observed that defect in galactose metabolism was due to enzymatic defect and this defect was identified by a group led by Herman Kalcker in 1956.(2)
Murphy M et al observed that the incidence of galactosemia is one in 60,000 birth of European ancestry. It is more common in the Irish population.\(^{(3)}\)

Lactose in food (such as milk and dairy products) is broken down by lactase enzyme into glucose and galactose. In individuals with galactosemia, the enzymes needed for further metabolism of galactose (galactose-1 phosphate uridylyl transferase) are severely diminished or missing entirely, leading to toxic levels of galactose – 1 phosphate in various tissues as in case of classic galactosemia resulting in hepatomegaly, cirrhosis, renal failure, cataract, vomiting, seizure, hypoglycemia, lethargy, brain damage, sepsis and ovarian failure. Galactosemia is inherited as autosomal recessive manner. The child must be homozygous and received one defective gene from each parent. Heterozygous are carrier because they inherit one normal gene and one defective gene.\(^{(4)}\)

Narendra Rathi et al observed that three congenital disorders are related to galactose metabolism – a) type one galactosemia (classic galactosemia) – deficiency of GALT (galactose-1 phosphate uridylyl transferase) b) type two galactosemia – deficiency of galactokinase. It solely presents with cataract c) type three galactosemia – deficiency of UDP – galactose – G – epimerase. It has two forms – Benign and severe. Benign is asymptomatic and does not require treatment. Severe is classic galactosemia– it presents with deafness and hypotonia. It is suspected in children with features of classic galactosemia with normal GALT activity.\(^{(5)}\)

we got one case of sepsis out of 19 patients (5%), ascites in 9/19(47%), hepatosplenomegaly in 14/19(74%), seizure in 3/19(15%), renal tubular acidosis in 2/19(10%), hypoglycemia in 5/19(26). Cuthbert C et al observed that GALT is one in ten thousand to one in thirty thousands. GALE is rarest.\(^{(6)}\)

Some researchers observed that potential causes of galactosemia include deficiency of three enzymes of galactose metabolism (GALT/GALE/GALK), porto systemic shunting, fanconi syndrome.\(^{(7)}\)

Hughes J et al observed that galactose restriction is only treatment of galactosemia. But galactose restricted diet from early new born period showed speech disorder, language delay, neurological abnormality (MRI brain showed evidence of progressive cerebellar degenerative changes). There is no significant difference in outcome between early treatment or late treatment group or any correlation with mean serum galactose-1 phosphate or galactitol level.\(^{(8)}\)

Stambolian D et al observed that any of three enzyme deficiency can cause cataract. Cataract is detected by slit lamp examination and missed by ophthalmoscope. Heterozygous galactokinase deficiency can cause cataract. Galactitol in lens causes cataract. Early introduction of galactose free diet can cause clearing of lens.\(^{(9)}\)

Van Erven et al observed that despite diatery treatment from new born period, more than 90% of women with classic galactosemia develops primary ovarian insufficiency. But pregnancy rate in women with classic galactosemia and primary ovarian insufficiency is higher than women with primary ovarian insufficiency of any other cause.\(^{(10)}\)

Sanders RD et al observed that FSH levels are significantly higher and antimullerian hormone (AMH) are significantly lower in galactosemia cases relative to control. FSH and AMH are biomarkers of ovarian functions. In classic galactosemia, primary ovarian insufficiency is detected by biomarkers shortly after birth.\(^{(11)}\)

Fritovich Keil JL et al observed that Duarte variety of galactosemic babies are typically asymptomatic on breast milk or lactose containing formula but not always. When they develop jaundice, they rapidly recover soon after shifting to galactose free diet. Their RBC GALT activity is 14 – 25 % of control activity. Duarte (D2) GALT allelic variant is in either heterozygous or homozygous state.\(^{(12)}\)
In Duarte variant of galactosemia- there is structural and functional abnormality leading to instability of GALT.

Using D for Duarte and N for normal allele, and G for galactosemia allele, D/N is 75% of normal GALT Activity, d/d is 50% of normal GALT Activity, D/G is 25% off normal GALT Activity. Some observers noticed that Duarte variant galactosemia (DG) does not cause clinical disease either with or without intervention. Neuro developmental outcome of DG children are conflicting and further studies are required. Duarte (D2) GALT allelic variant is in heterozygous or homozygous state. There is no consensus whether infants with DG benefit from dietary galactose restriction during infancy or early child hood. Parents or health care workers may choose either to restrict dietary galactose in infancy or not. When galactose is restricted at infancy – galactose challenge is done at one year of age followed by measurement of RBC galactose 1 – phosphate level. If level is within normal limit (less than 1mg%)- no dietary restriction is done. If RBC galactose 1 – phosphate level is more than 1mg% at 1 year after galactose challenge test – galactose restriction is done.

Galactose 1 phosphate level is changed every 4-6 months until it is less than 1 miligram percent. Sibling of DG patients are evaluated by genetic testing of GALT variant.

DG is auto somal recessive in inheritance.

If one of patients is D2 / normal allele and other parent is GALT pathogenic /normal allele then 25% chance of D2 galactosemia, 25% chance of asymptomatic chance of pathogenic variant, 25% chance of no affection/ not crier of either variant.

We have to suspect Duarte variant of galactosemia when newborn is positive for galactosemia screening test (elevated galactose or its metabolites galactose 1 phosphate but baby has little clinical findings). Duarte variant may be homo or heterozygous. They may be combined with GALT pathogenic variant.

RBC galactose 1 phosphate is considered high when it is more than 30 mg % and normal when it is less than 1 mg %\(^{(13)}\).

Measurement of RBC galactitol and galactonate presents a new method of characterizing patients and their level monitored over time may provide new insight in development of longterm complication in affected children\(^{(14)}\).

Some observers noticed that galactose -1-phosphate along with galactitol and galactonate are accumulated in cells. Surplus galactose is reduced to galactitol and oxidized to galactonate. By mass spectrometry, galactitol, galactonate and free galactose are measured in plasma and blood. Galactose restricted diet can reverse hepatic – renal immune dysfunction with reduced accumulation of galactose metabolites.

But chronic and progressive neurological impairment can occur when galactose restriction starts from newborn period\(^{(15)}\).

Galactosemia presents in first week of life with liver dysfunction, cerebral edema, sepsis, cataract, Fanconi syndrome. After galactose restriction within first week of life, 80 % children at 6 years of age have developmental delay, learning difficulties, 13% have impaired motor function and balance. 80% female have premature ovarian failure. 60 % have speech disorders. 20% have growth retardation, difficulty in running, handwriting. There is severe personality like timidity, lack of inner drive. Since metabolic disturbance is expressed in galactosemic fetus, these abnormalities may have a prenatal origin. There is rationalities to restrict milk in pregnancy at risk but these strategy doesn't show much benefit.

It is postulated that there is over stimulation of galactose production (endogenously produced or derived from non dairy food) which causes accumulation of toxic substances (galactose-1-phosphate)\(^{(16)}\).

Electron microscopy shows extreme fatty change and delicate fibrosis, cholestasis, lipid droplets, increased endoplasmic reticulum, abnormal mitrochondria\(^{(17)}\).
Methods

Various clinical manifestations and investigational profile and outcome of galactosemic children admitted in pediatric Gastroenterology at PGIMER, Chandigarh were recorded and analysed. Ultrasound of abdomen and HIDA scan were done to rule out EHBA. Hemogram, blood culture, LFT, coagulogram, work up for intrauterine infections were carried out. Urinary examination for reducing substabces, eye checkup, liver biopsy and enzyme assay were done in all cases.

Results

Nineteen children of galactosemia were seen from June 1993 to June 2003. Age of onset of symptoms was 3-25 days of life. Males were 12 (63%) and females were 7 (36%). Cholestatic jaundice was present in all 19 infants manifesting as clay colored stool and high colored urine staining diaper. Hepatomegaly was present in 5/19 (26%), hepatosplenomegaly in 14/19 (74%), ascites in 9/19 (47%), seizure in 3/19 (15%), sepsis in 1/19 (05%), renal tubular acidosis in 2/19 (10%) and hypoglycemia in 5/19 (26%) infants. Five infants died. Conjugated bilirubin was raised in all infants, transaminitis was present in 11/19 (57%) and coagulopathy in 9/19 (47%) infants. Liver biopsy was suggestive of galactosemia in all. Urinary reducing substance was positive in 15/19 (79%), cataract was present in 7/19 (36%) cases. Galactose 1-phosphate uridyl transferase enzyme deficiency was detected in all 19 cases. Urine analysis for renal tubular acidosis was positive in 2 infants. 14 infants were put on galactose free diet and all improved.

Discussion

From gene to disease studies, Bosch AM et al noticed that gene encoding for GALT is located on choromosome 9p13. It is related to hepatomegaly, hypotomia, liver failure, hypoglycemia, sepsis, cataract etc. Mental developmental problem, disordered motor function , disoriented speech, hypergonadotropic hypogonadism can present even on galactose free diet from early new born period.\(^{(18)}\)

F Steril et al noticed that girls with DG (Duarte galactosemia) develop no apparent decrease in AMH (anti mullerian hormone) level or increasing FSH levels suggesting that these girls are not at increased risk for premature ovarian insufficiency.\(^{(19)}\)

Spencer JB et al noticed that more than 80% of girls and women with classic galactosemia expressed primary or premature ovarian insufficiency despite neonatal diagnosis and rigorous lifelong dietary galactose restriction. Plasma anti mullerian hormone (AMH) and FSH levels, antral follicle counts are ascertained by USG and ovarian function. Ovarian function is ascertained by spontaneous or augmented menarche. Both pre and post pubertal girls and women with classic galactosemia demonstrated low antral folilcle counts related to age related control. More than 73% of pre and post pubertal girls and women with classic galactosemia (age 3months to 30years) demonstrate AMH less than 95 % confidence interval for AMH compared to control of same age.\(^{(20)}\)

Steven F Dobrowolski et al described that Q188R mutation of galactose-1-phosphate uridyl transferase gene was found in 72% of allele. Cognitive score for homozygous for Q188R was 75 which was not statistically different from outcome of heterozygous group. Tremor, ataxia have not been associated with Q188R mutation. Variables of outcome for patients with classic galactosemia cannot be expressed by Q188R status alone, at least with regard to cognitive function, presence of neurological symptom and timing of onset of ovarian failure.\(^{(21)}\)

Narandra Rathi et al observed that Ecoli infection is common in galactosemic patients but klebsiella, enterobacter, staphylococcus, beta streptococcus, streptococcus feacalis are also seen. Galactosemic infants are more prone to sepsis due to inhibition of leucocyte bactericidal activity.
secondary to impairment of cellular release of super oxide ion by galactosemia. Sepsis is more common at the end of first week or second week. Galactosemia is suspected with Ecoli sepsis in infancy even when other features of galactosemia is absent. It is important in developing country where new born screening is absent. Galactosemic children should undergo periodic check up for ophthalmological problems, developmental assessment, speech assessment, accumulation of toxic substances (RBC, galactitol, galactose-1-phosphate, galactonate) abnormal motor function, premature ovarian failure. It is debated as to how stringent the diet control should be after first year of life, endogenous galactose production is in order of magnitude higher than that form ingested food other than milk.\(^5\)

Winder AF et al noticed that assessment of galactose tolerance may be useful investigation in patients with an incidents of cataract. Partial deficiency of enzyme (GALK or GALT) associated with galactose intolerance (as determine by oral test) was notice in females who have incidence of cataract in childhood.\(^22\)

Winder AF et al noticed that partial deficiency of enzyme of galactose metabolism can be associated with cataract both directly and through maternal affects during pregnancy on enzymatically normal children. This association is modest. Manifestation of cataract is due to heterozygousity or severe deficiency of enzyme galactose metabolism – anenable to early diet control of children or mothers at risk.\(^23\)

Universal neonatal galactosemia screening is debateable. Radomysha B et al observed that result of mass screening for galactosemia is poor because mental retardation is common like other babies without screening. Now screening is stopped in Poland. Diagnosis of new case is made on basis of symptoms. Selective screening for high risk families are advised. Prophylactic lactose free diet of pregnant mother during pregnancy are done. This prevents clinical manifestation in new born.\(^24\)

Karadag N et al observed that early diagnosis of galactosemia and its treatment can partially prevent and recover complication but not all of them. Cataract can develop even in first week of life. Early intervention can prevent severe cataract. New born screening can improve mortality.\(^25\)

Stambolian D et al noticed that galactosemia is caused by deficiency of any one of the three possible enzymes (galactokinase/ transferase /epimerase). Any single enzyme can cause cataract by accumulation of galactitol in lens. Early recognition of cataract followed by diet restriction can cause complete clearance of lens. Even heterozygous galactokinase deficiency may be associated with cataract.\(^26\)

We got seven cases of cataract out of 19 patients(36%). Molecular cloning and characterization of all three human galactose metabolic genes– cause galactosemia (galactokinase or GALK/transferase or GALT/ epimerase or GALE).\(^27\)

Palmieri M et al noticed that patients who are homozygous for Q188R mutation has urinary galactitol five to ten times of normal persons of comparable age. Plasma galactitol is elevated in galactosemic patients. Plasma galactitol is undetectable in normal individual. Urine and plasma galactitol distinguish galactosemic patient from normal. Urinary galactitol excretion is an important parameter for assessment of steady state galactose metabolism in galactosemia. Most patients with Duarte Allele and G allele excrete normal amount of galactitol.\(^28\)

C Ficicioglu et al noticed that DG children on restricted diet have RBC galactose-1-phosphate concentration with reference value. Increased concentration of RBC galactitol and RBC galactose have been seen in DG children. This increased concentration of galactose metabolites correlate with galactose intake and
neither cause any developmental and clinical problem during childhood nor oblige on lactose restricted diet.\textsuperscript{(29)}

Geurrero NV et al noticed that primary ovarian failure in future with galactosemia is more likely if patients genotype is: a) Q188R/Q188R (b) if mean RBC Gal-1-phosphate is more than 3.5 mg\% during therapy and( c) if recovery of 13 CO\textsubscript{2} from whole body 13 C – galactose oxidation is reduced below 5\% to administered 13C-galactose.\textsuperscript{(30)}

The author postulated that abnormal signal intensity in MRI imaging of galactose is due to altered myelin formation secondary to inability to metabolise galactose.\textsuperscript{(31)}

Homzygous Duarte form (D/D) of galactosemia have 50 reduction of galactose-1-phosphate uridyl transferase (GALT). It has molecular genotype of N314D/N314D. There is also a “Los Angeles” variant of galactosemia – which has higher (150\%) GALT activity.

In LA biochemical phenotype – all had a 1721C\rightarrow T transition in exon 7 in cis with N314D misense mutation. This Los Angeles variant presents as a combination of (LA/N), (LA/G) and (LA/D).\textsuperscript{(32)}

\textbf{Conclusion}

Galactosemia is an uncommon but important cause of metabolic liver disease in early infancy. High degree of suspicion and early detection are mandatory for better outcome, since these children require galactose free diet. Early detection can prevent mortality and morbidity.

\textbf{Conflict of interest:} Nil

\textbf{Reference}

1. Goopert F (1917) Kalinische worchenschrift (German) 54:473-7
2. Isselbacher KJ et al Congenital galactosemia, a single enzymatic block in galactose metabolism. Science 123 635-6
3. Murphy M et al Genetic basis of transferase deficient galactosemia in Ireland and population history Irish travelers Euro J Human Genetics 1999
4. Henderson H et al The clinical and molecular spectrum of galactosemia in patients from capetown region of south Africa. BMC pediatr 2002
5. Galactosemia presence as recurrent sepsis Journal of tropical pediatrics Vol.57 no.6 2011 by Narandra Rathi
6. Diagnosis of inherited disorder of galactose metabolism Cuthberth C et al Curr . protoc Hum. Genet. 2008
7. Sweat and sour – an update on classic galactosemia Review article Coelho AL et al J inherit metab. Disease 2017
8. Outcome of sibling with classical galactosemia Hughes J et al J pediatr. 2009
9. Cataracts in galactosemia Jerry Johnson et al American journal of ophthalmology 1953
10. Fertility in adult women with classic galactosemia and primary ovarian insufficiency Fertile steril 2017 July 108(1) 108-174 By Van Erven B et al
11. Biomarker of ovarian function in girls and women with classic galactosemia Fertile steril 2009 July 92(1) By Sanders RD et al
12. Duarte variant of galactosemia By Fritovich Keil JT Publisher-> University of Washington Seattle (WA)
13. A common mutation associated with duarte galactosemia allele American J Hum. Genet.1994 By Elias LJ et al
14. Galactitol and galactonate in red blood cells of galactosemic patients Mol. Genet.metab.2003 By Yager CT et al
15. Early diagnosis of inherited metabolic disorders towards improving outcome – the controversial issue of galactosemia Eur. J Pediatr 2003, By Schweitzer- Kratz S et al
16. An updated review of long term neurological effects of galactosemia Ridel KR et al Pediatr.neoral.2005
17. Editorial – clouds over galactosemia
Lancet 1984 1379-80
18. From gene to disease galactosemia and
galactose-1-phosphate uridyl transferase
deficiency By Bosh AM et al Ned Tijdschr
geneeski 2004 Feb.
19. Ovarian function in Duarte galactosemia
Fertile steril 2011 By Badik JR et al
20. Modifier of ovarian function in girls and
women with classic galactosemia J Clin.
Endocrinl. Metab. 2013 By Spencer JB et al
21. Analysis of common mutation in
galactose-1phosphate uridyl transferase
gene By Steven F Dobrowolski J Mol.
Dign.2003
22. Galactose intolerance and risk of cataract
Winder AF et al Br.J .opthalmol.1982
23. Direct and maternal aspects of risk of
cataract with partial disorder of galactose
metabolism Winder AF et al Clin.
Genet.1985
24. Effectiveness of screening program of
galactosemia, New strategy in Poland,
Med. Wieku Roz woj 2001, By Radomysha B et al
25. Literature review and outcome of classic
galactosemia diagnosed in neonatal period
Clin. lab.2013, By Karadag N et al
26. Galactose and cataract, Stambolian D et al,
Surv.opthalmol.1988
27. Molecular basis of disorders of human
galactose metabolism past present and
future, Novelli G et al, Mol. Genet.
Metabol.2000
28. Urine and plasma galactitol in patients
with galactose- 1- phosphate uridyl
transferase deficiency galactosemia.
Metabolism 1999, By Palmieri M et al
29. Monitoring of biochemical status in
children with Duarte galactosemia Utility
of galactonate, galactitol, galactose-1-
phosphate uridyl transferase, By C
Ficicioglu et al Clinical chemistry 2010
30. Risk factor premature ovarian function in
female with galactosemia, J pediatr 2000
Dec. 137(6), 833-41, By Guerrero NV et al
31. Galactosemia– evaluation with MR
imaging, Radiology 1992, By MD Nelson
Jr. et al
32. Molecular basis of Duarte and Los
Angeles variant of galactosemia, By SD
Langley, Am. J. Human genet. 1997.