Review Article

PREVALENCE, EPIDEMIOLOGY AND CLINICAL STUDY OF GALACTOSEMIA

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ABSTRACT

Galactosemia is an autosomal carbohydrate metabolic disorder caused by the deficiency of galactose 1-phosphate uridyltransferase (GALT). Frequency of occurrence of this disorder varies, more common in Irish population and very less in Asians. There are three types of galactosemia but GALT is most common. The prominent sign and symptoms include hypoglycemia, hepatomegaly, ascities, jaundice, poor feeding and vomiting. Cataracts, premature ovarian failure, decreases in bone mineral density, mental retardation are few of the long term complications. Symptoms appear within first few days of galactosemic infants. Strict dietary control (i.e. galactose free diet) can prevent acute toxicity but it does not guarantee the prevention of long term complications. The only treatment is complete elimination of galactose/lactose free diet and calcium supplements are used as supportive therapy.

***Keywords*:** Galactosemia, carbohydrate metabolic disorder, GALT

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Galactosemia is an inborn carbohydrate metabolic disorder and can be fatal and life-threatening during the newborn period [1, 2, 3]. Galactosemia is a rare genetic and an autosomal recessive disorder (meaning a child must inherit one defective gene from each parent to show the disease), caused by the deficiency of galactose 1-phosphate uridyltransferase (GALT) [4, 5, 6].

Galactosemia was first described in Germany by von Reuss as cited by George in 1908 and by Göppert in 1917, and first in the United States by Mason and Turner in 1935 [7, 8, 9]. Kalckar et al. identified in 1956 that galactosemia is due to defect in galactose metabolism [5].

The synonymous of galactosemia are galactose diabetes, essential galactosuria, congenital galactosemia, congenital galactosuria, galactosis, and galactemia [7].

Incidence Rate

The incidence rate varies in different populations i.e. 1 case per 40,000-60,000 persons (unites states) [3], 1 case in 70,000 people (UK) but 1 case in 20,000 people in Ireland. Galactosemia is very common within the Irish Traveller population. In Asians, this disorder is less common [10].

Types of Galactosemia

There are three types

1. Type 1, Classic Galactosemia, the most common and most severe form. This is due to Galactose-1 phosphate uridyl transferase (GALT) deficiency.
2. Type 2, Deficiency of galactose kinase (GALK/GALK1)
3. Type 3, Deficiency of galactose-6-phosphate epimerase (GALE) [3, 11]

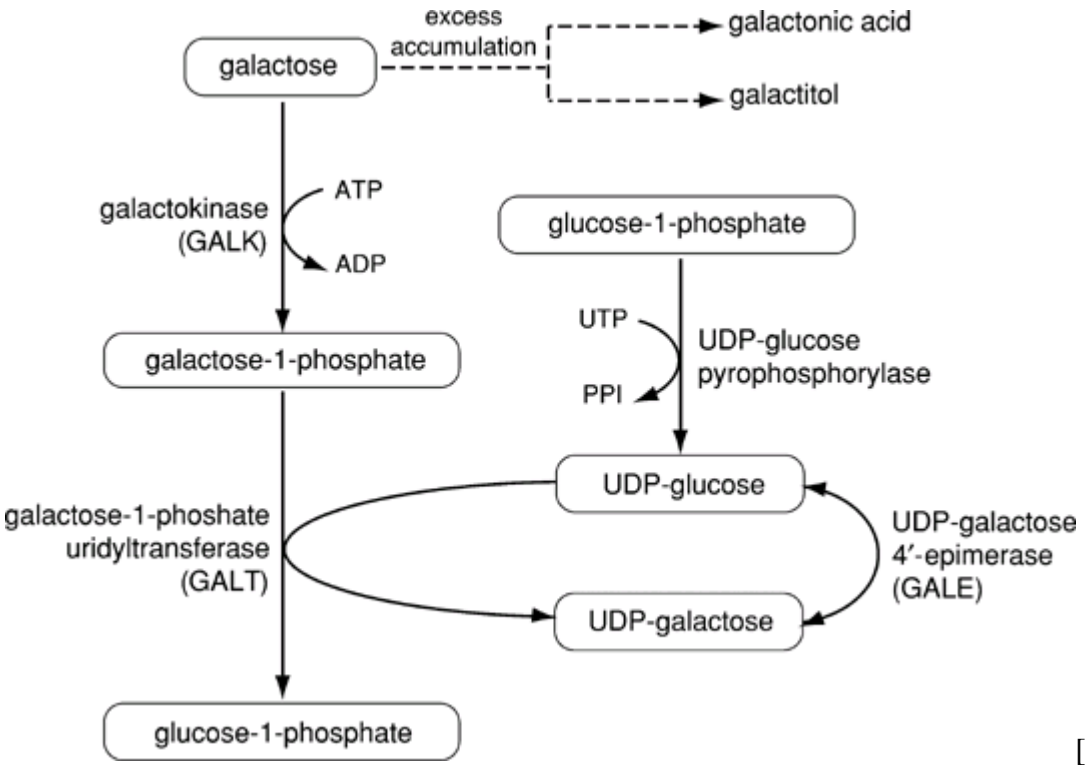
Clinical Signs & Symptoms

Aminoaciduria ,Hepatomegaly, Ascites ,Hypoglycemia are prominent signs of this disorder.. Symptoms include Convulsions, Irritability, Lethargy, Poor feeding, Poor weight gain, jaundice, Vomiting. Septicemia (blood infection with *E. coli*) may be responsible for these symptoms. Galactosemic infants whom galactose containing diet was not stopped e.g. breast milk, can develop symptoms within the first few days of life [1, 3].

LONG TERM COMPLICATIONS

They include premature ovarian failure and neuropsychiatric features, including cognitive problems, learning difficulties, behavioral changes, such as withdrawn personality, and speech difficulties, Cataracts, liver cirrhosis, Mental retardation, septicemia with *E. coli*, Tremors and uncontrollable motor functions, ataxia, decrease in bone mineral density [1, 12, 13, 14, 15].

Normal Galactose Metabolism



[16]

Toxic Metabolites of Galactose

Galactitol and Galactose-1-phosphate are two toxic galactose metabolites. Galactitol is responsible for the cataracts, and Galactose-1-phosphate induces the rest of the clinical symptoms. To distinguish galactosemic patients from normal subjects urine and plasma levels of Galactitol should be measured. Early diagnosis and strict use of milk free products can help the patient to live a relatively normal life. However, mild intellectual impairment may develop, even in people who avoid galactose [1, 17].

What genes are related to galactosemia?

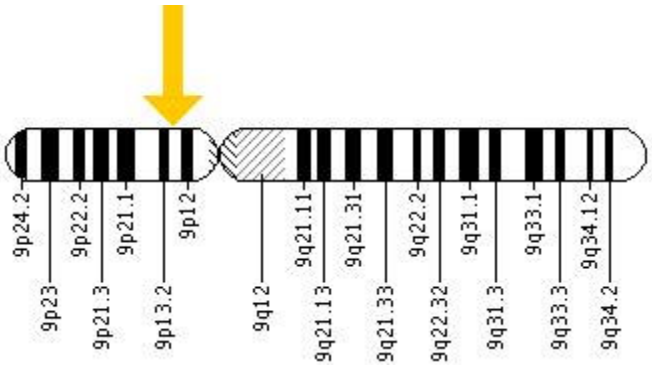
Mutations in the GALE, GALK1, and GALT genes cause galactosemia.

Type of Galactosemia	**Gene Mutation**
Classic Galactosemia, type I	GALT gene
Galactosemia type II	GALK1 gene
Galactosemia type III	GALE gene

These genes provide all the necessary instructions required for making enzymes that are essential for galactose metabolism. Galactose is broken down into glucose, another simple sugar and other molecules in the presence of these enzymes and body can store easily these break down products or use them for energy. There are two types of mutations in GALT gene: In one type there is complete elimination of activity of enzyme produced by GALT, this is called classic Galactosemia and in 2nd type of GALT gene mutation, there is reduction in activity of enzyme rather than complete elimination and this is called Duarte Galactosemia variant. The Duarte

Galactosemia variant is caused by N314D. Homozygosity for N314D reduces GALT activity to 50%. People with the Duarte variant tend to have much milder features of Galactosemia [4, 18, 19, 20].

Exact Location of Galt Gene



The GALT gene is located on the short (p) arm of chromosome 9 at position 13 (9p13).

More precisely, the GALT gene is located from base pair 34,646,634 to base pair 34,650,573 on chromosome 9 [6, 19, 21, 22, 23].

Diagnosis

Following Laboratory tests help in diagnosis of this autosomal disorder:

1. Prenatal diagnosis by directly measuring the enzyme galactose-1-phosphate uridyl transferase [1].

2. A Galt isoelectric-focusing electrophoresis test for specific molecular diagnosis. The most common Galt allele in caucasians is the *Q188r* mutation. The *S135l* mutation is common in blacks [23].

3. Blood culture for bacterial infection (E. COLI sepsis) [1].

4. Measurement of galactose-1-phosphate uridyl transferase activity in RBC [1, 24].

5. Detection of reducing substances in urine by using tube test [1, 24.]

6. Detection of ketones in the urine [1].

7. Multiplex enzyme assay for galactosemia in erythrocytes using ultra-performance liquid chromatography-tandem mass spectrometry [25].

Brain Imaging of Galactosemic Patients

Brain MR Imaging and proton MR spectroscopy studies showed cerebral and cerebellar atrophy, multiple small hyper intense lesions in the cerebral white matter on T2-weighted images [1, 26, 27, 28, 29, 30].

Treatment

a) Complete elimination of dietary lactose/galactose, use Soy formula, Meat-based formula or Nutramigen (a protein hydrolysate formula), anyother lactose-free formula b) supportive therapy with calcium supplements c) use antibiotic also in case of septicemic patient

This treatment can reverse growth failure, Hepatomegaly, formation of cataract and also reduce the death reports due to septicemia but long term complications can not be prevented [1].

Medical Care

Acute toxicity symptoms of this inborn disorder can be prevented in infants by immediate dietary galactose restriction (do not give mother feed) but it does not ensure absence of all symptoms and long-term complications routinely occur [4, 33, 34]. Long term complications of Galactosemia are independent of diet [35].

CONCLUSION

Galactosemia is a rare genetic autosomal recessive disorder. It is linked with mutations in GALT, GALE, GALK1 genes. When galactosemic infants feed breast milk, symptoms start appearing soon after birth. Galactose/ Lactose free diet is pre-requisite condition for galactosemic persons to pass normal life, though long term complications can not be prevented because they are independent of diet.

REFERENCES

1. Berry GT, Segal S, Gitzelmann R. (2006). Disorders of Galactose Metabolism. In: Fernandes J, Saudubray JM, van den Berghe G, Walter JH, eds. Inborn Metabolic Diseases: Diagnosis and Treatment. 4th ed. New York, NY: Springer; chap 7.
2. Segal S. (1995). Galactosemia unsolved. Eur J Pediatr. 154(7 Suppl 2), 97-102.
3. Fridovich-Keil J, Walter. (2008). Galactosemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York, NY: McGraw-Hill Medical Publishing Division; 72.
4. Elsas LJ 2nd, Lai K. (1998). The molecular biology of galactosemia, Genet Med. 1(1): 40-48.
5. Herman M, Kalckar, Elizabeth P, Anderson, Kurt J, Isselbacher. (1956). Galactosemia, a congenital defect in a nucleotide transferase, Biochimica et Biophysica Acta. 20: 262-268.
6. Coffee B, Hjelm LN, DeLorenzo A, Courtney EM., Yu C, Muralidharan K. (2006). Characterization of an unusual deletion of the galactose-1-phosphate uridyl transferase (*GALT*) gene. Genet Med. 8: 635–40.
7. George M Guest. (1958). Hereditary galactose disease, JAMA. *168(*15): 2015-2019.
8. Goppert F. (1917). Galaktosurie nach Milchzuckergabe bei angeborenem, familiaerem chronischem Leberleiden. Klin Wschr. 54: 473-477.
9. Mason HH., Turner ME. (1935). Chronic galactosemia: report of case with studies on carbohydrates. Am J Dis Child. 50: 359-74.
10. Miriam Murphy, Brian McHugh, Orna Tighe, Philip Mayne, Charles O'Neill, Eileen Naughten, David T Croke. (1999). Genetic basis of transferase-deficient galactosaemia in Ireland and the population history of the Irish Travellers. European journal of Human Genetics. 7(5): 549-554.

11. Galactosemia. Genetics Home Reference. January 2008 Available athttp://www.ghr.nlm.nih.gov/condition=galactosemia. Accessed June 9, 2011.
12. Dr. Rubio-Agusti., Movement Disorder Society (MDS) 15th International Congress of Parkinson's Disease and Movement Disorders: Abstract 166. Presented June 6, 2011.
13. Keith R, Ridel BS, Nancy D, Leslie MD, Donald L, Gilbert MD MS. (2005). An Updated Review of the Long-Term Neurological Effects of Galactosemia, Pediatric Neurology. 33 (3): 153-161.
14. Kaufman, Francine Ratne., Devgan, Sunita. (1995). Classical Galactosemia: A Review., Endocrinologist. 5(3): 189-197.
15. Waggoner D, Buist N, Donnell G. (1990). Long-term prognosis in galactosemia: Results of a survey of 350 cases. J Inherit Metab Dis .13: 802-818.
16. www.google images.com
17. Palmieri M, Mazur A, Berry GT. (1999). Urine and plasma galactitol in patients with galactose-1-phosphate uridyltransferase deficiency galactosemia. Metabolism. 48: 1294–1302.
18. Elsas LJ, Dembure PP, Langley S, Paulk EM, Hjelm LN, Fridovich-Keil J. (1994). A common mutation associated with the Duarte galactosemia allele. Am J Hum Genet. 54: 1030–6.
19. Bosch AM, Ijlst L, Oostheim W, Mulders J, Bakker HD, Wijburg FA, Wanders RJ, Waterham HR. (2005). Identification of novel mutations in classical galactosemia. Hum Mutat. 25: 502.
20. Cuthbert C, Klapper H, Elsas L. (2008). Diagnosis of inherited disorders of galactose metabolism. Curr Protoc Hum Genet. Chapter 17, Unit 17.5.
21. Calderon FR, Phansalker A, Crockett D, Miller M, Mao R. (2007). Mutation database for the galactose-1-phosphate uridyltransferase (GALT) gene. Hum Mutat. 28: 939–943.
22. Elsas L, Fridovich-Keil J, Leslie N. (1993). Galactosemia: a molecular approach to the enigma. In: International Pediatrics. PP 101-109.
23. Elsas LJ 2nd, Langley S, Paulk EM. (1995). A molecular approach to galactosemia. Eur J Pediatr. 154(7): 21-27.
24. Fishler K, Koch R, Donnell GN, Wenz E. (1980). Developmental aspects of galactosemia from infancy to childhood. Clin Pediatr. 19: 38–44.
25. Ko DH, Jun SH, Park KU, Song SH, Kim JQ, Song J. (2011). Newborn screening for galactosemia by a second-tier multiplex enzyme assay using UPLC-MS/MS in dried blood spots. J Inherit Metab Dis. 34(2): 409-14.
26. Leslie N. (2003). Insights into the pathogenesis of galactosemia. Annu Rev Nutr. 23: 59–80.
27. Wang ZJ, Berry GT, Dreha SF. (2001). Proton magnetic resonance spectroscopy of brain metabolites in galactosemia. Ann Neurol. 50: 266–269.

28. Wehrli SL, Berry GT, Palmieri M. (1997). Urinary galactonate in patients with galactosemia: quantitation by NMR spectroscopy**.** Pediatric Res. 42: 855–61.

29. Krabbi K*,* Uudelepp ML, Joost K, Zordania R, Ounap K. (2011). Long-term complications in Estonian galactosemia patients with a less strict lactose-free diet and metabolic control, Molecular Genetics and Metabolism. 103(3): 249-253.

30. Otaduy MCG, Leite CC, Lacerda MTC, Costa MOR, Arita F, Prado E, Rosemberg S. (2006). Proton MR Spectroscopy and Imaging of a Galactosemic Patient before and after Dietary Treatment (case report, Pediatrics),American Journal of Neuroradiology. 27: 204-207.

31. Waisbren SE, Norman TR, Schnell RR, Levy HL. (1983). Speech and language deficits in early-treated children with galactosemia**.** J Pediatr. 102**:**75-77.

32. Guerrero NV, Singh RH, Manatunga A, Berry GT, Steiner RD, Elsas LJ. (2000). Risk factors for premature ovarian failure in females with galactosemia**.** J Pediatr. 137: 833-841.

33. Komrower GM, Lee DH. (1970). Long-term follow-up of galactosaemia. Arch Dis Child. 45(241): 367-73.

34. Gitzelmann R, Steinmann B. (1984). Galactosemia: how does long-term treatment change the outcome? Enzyme. 32: 37–46.

35. Nelson MD, Wolff JA, Cross CA. (1992). Galactosemia: evaluation with MR imaging. Radiology. 184: 255–61.