The Prevalence and Clinical Study of Galactosemia Disease in a Pilot Screening Program of Neonates, Southern Iran

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Abstract

Background: The aim of the study was to research concerning the epidemiology of newborns' galactosemia during 2007-2008 to find out whether screening was necessary for Iranian newborns or not and also what the symptoms of this disease before or after diet were.

Methods: The data were collected from 24000 newborn babies from Fars Province, southern Iran. The enzymatic calorimetric test was done on their blood and Red questions from the children's parents. For treatment, free lactose milk or soya milk have been used for the feeding of the newborns.

Results: The prevalence of galactosemia in Fars Province was 5:24000 in neonates, being more than those reported among the white race are and Asians are. The maximum clinical symptoms before diet in 10 days after birth were vomiting and jaundice and those after using diet were sepsis, full fontanels, and hepatic failure.

Conclusion: Consanguineous marriage is a major cause of inheritance of the disease in Iran. The number of familial marriage in children's parents was very high. Screening should be executed for all of the families with a history of Galactosemia in Iran. To the best of our knowledge, this is the first large study report on the prevalence of Galactosemia in Iran.

Keywords: Galactosemia, Screening, Infant, Metabolism, Disorder

Introduction

Newborn screening (NBS)(public health funded system) has a new technique for distinguish genetic disorders and congenital metabolic disorder such as galactosemia (1). Galactosemia is an autosomal recessive inherited disorder of carbohydrate metabolism(2). Three enzymes are involved in the utilization of dietary glucose, galactokinase (Ec 2.7.1.6) (OMIM database No. 230200), Galactosemia -1- phosphate uridyl transferase (Ec 2.7.7.12) (OMIM database No.230200) and [uridine diphosphate galactose 4-epimerase (Ec 5.1.3.2) (OMIM database No.230350)] (3, 4). One hundred thirty mutations have been identified in the Alt (galactose -1- phosphate uridyl transferase) gene

on chromosome 9q 13 (5, 6). "Both parents must carry the defective genes" (7). The two main types of galactosemia are called classic and Duarte variant (7-9). Classic galactosemia has two common mutations are associated with, Q 188R and K 285 N, accounting for more than 70% of galactosemia in Caucasian populations (8).

Biochemically, three enzyme deficiencies in the conversion of galactose to glucose (GALK, GALT, and GALE) can lead to galactosemia. Galacto kinase deficiency is the mildest symptom, the main one being cataract formation as elevated galactose is reduced to galactitol in the lens. Galactose -4- epimerase deficiency as the

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rarest and is in most severe form of this disorder has been reported to presenting symptoms similar to those of classical galactosemia (8). Most neonates patient referred to hospital with severe symptoms (jaundice, hepatosplenomegaly, hepatocellular insufficiency sepsis, cataract ,etc) after ingestion of galactose.

The gold standard for diagnosis of classical galactosemia is measurement of GALT activity in the erythrocytes.

In diagnostic laboratories, gas-chromatographic determination of urinary sugars and sugar alcohols demonstrates elevated concentration of galactose and galactitol , is used for detection of galactosemia (9).

Incidence of galactosemia disorder is 1:78000 in New York State and approximately 30 cases per 100,000 live births (10)(11). The incidences of classic transferase – deficient galactosemia in the countries which have pilot programs about galactosemia are is different for example, among the White Americans it is around l in 47000 in UK 1 in 70000, and in Ireland 1 in 23000 and it is increased among itinerants to 1:700 while it is highly frequent in the traveller community as 1 in 480(12) (13).In the United States, 1% of the North American people are carriers; suggestive of a disease frequency of 1 in 40000. The incidence seems to be rather lower among people of African and Asian descent (14). In the west European people, the percents of galactosemia are from 1: 23000 to 1: 44000 (15). The prevalence rate for galactosemia in different countries is displayed in Table -1.

The disorder is thought to be much less common among the Asian people. Galactosemia occurs in all races; however, its variants are based on the exact gene defect. The variants are most notable among African – Americans.

GALT deficiency will result in the rapid development of clinical symptoms following lactose ingestion. Although the infant may be normal at birth, symptoms develop in a few days to two weeks after initiating feedings with so that the infant is often discharged from the hospital prior to the onset of the illness (8). The other symptom that is important to examination for these patients is cataract(16).

Neonates with sever galactosemia (without rapid diagnosis) may lead to *E. coli* septicemia or coagulopathy (14, 17). Chronic or Long-term of this disease are supreme to learning problems, and speech and language deficits are common .Language acquisition might be delayed (18, 19). "Cognitive impairment is present in the majority of patients" (20).

For screening the baby, we receipt blood from a baby who is two to three days old for high levels for detect galactose and galactose -1- phosphate. Rapid and in timely diagnosis in the neonatal period with restriction of dietary galactose is effective in reducing the clinical severity of the disease and limits efficacy in the prevention of long-term complications (21,22). Galactosemia is treated by removing galactose from the diet (a galactose-free formula). Since galactose is a break – down product of lactose, the primary sugar constituent of milk, this means all milk and foods like legumes, organ meats, and processed meats contain considerable amount of galactose and must be avoided. Pills that use lactose, as filler must also be avoided. Soy-based and casein hydrolyzed-based formulas are recommended for infants with Galactosemia (23).

"Over the long term, funding comprehensive newborn screening programs is likely to save money *for* society" (24).

There was an attempt in this study to research about the epidemiology of newborns´ galactosemia during 2007-2008 to find out whether screening is necessary for Iranian newborns or not and also what the symptoms of this disease before or after diet are.

Materials and Methods

This cross-sectional study was carried out from December 2007 to July 2008 for all newborns of Fars Province whose samples were referred to Newborn Laboratory of Paramedical School,

Shiraz University of Medical Sciences, Shiraz, Iran. The questionnaires were completed by asking the children's parents. All the parents signed the medical Ethnics paper of Ethical committee of ACECR paper. Ethics Committee of ACECR approved the study's design.

The family history and clinical and paraclinical findings were taken into account. Blood samples were collected from the heel on the Guthrie Paper and then calorimetric test with enzyme was performed to determine the level of serum galactose -1- phosphate and galactose. The kit was purchased from Roche Company. The cases lower than 5 mg/dl were considered normal while the test was repeated whenever the galactose and galactose -1- phosphate levels were higher than 5 mg/dl. The level of G-I-P was measured .

The patients receiving soy-based milk (galactose- free formula) were examined by a physician for evaluation of physical, emotional and social growth and loco- motor development. The patients were followed these patients for 19 months.

Results

For the analysis of data, descriptive statistics were used. During the study, among 24000 babies born in Fars Province, five babies (one of whom was from Afghanistan) were proved positive for galactosemia with calorimetric test (enzymatic test). One of them died and four survived. Therefore, the frequency of galactosemia in Southern Iran is 1:6000. The patients' fathers were under 35 and their mothers were less than 30 years of age.

Familial marriage among the patients' parents was four out of five and all of them had third degree consanguinity. None of the patients' parents had used chemical drugs, cigarettes and had not been expose to X-ray.

The level of serum galactose-1-phosphate among galactosemia was 5-10 mg/dl (three out of five neonates), 10-100mg/dl (one out of five), and over 100mg/dl (one out of five).

The main clinical symptoms before feeding in 10 days the birth were vomit (three out of five neonates), and jaundice (three out of five neonates).Those after diet were sepsis (one out of five), full fontanel (two out of five), but they did no have other symptoms that other patient neonates who didn't use this diet is low (Table 2).

Table 1: The prevalence of galactosemia in different countries

Country	Extrapolated prevalence	Population estimated
USA	9.788	293.665.405
Turkey	2.296	68.893.918
Afghanistan	950	28.513.677
India	35502	1065070607
Pakistan	5306	104.196.336
Gaza strip	44	1.324.991
Iran	2250	67.503.205
Iraq	845	25.374.691
Israel	206	6.199.008
Jordan	187	5.611.202
Kuwait	75	2.257.549
Lebanon	125	3.777.218
Saudi Arabia	859	25.795.938
Syria	600	18.016.874
United Arab Emirates	84	2.523.915
West Bank	77	2.311.204
Yemen	667	20.024.867

Table 2: The main clinical symptoms before and after feeding

Sympt. / Diet	Vomiting	Jaundice	Sepsis	Full fontanel
Before Galactosemia diet	3	3	1	2
After Galactosemia diet	1	1	1	2

Discussion

The primary objective of the present study was to find the proportion of the babies born afflicted with galactosemia in all those who have been born alive in Fars province. The prevalence of galactosemia in Southern Iran is 5:24000, being higher than that in other nations. This might be because the number of consanguineous marriages in Iran is higher than other populations.

Of course, some studies in Iran indicated that the prevalence of consanguineous marriage is very high. Consanguineous marriage is a main feature of family systems in Iran. "For example in one study in Iran, a multistage sampling design was used with a representative total sample of 306343 couples" (25). In this study, the overall rate of consanguineous marriage was 38.6%. Galactosemia is inherited as the recessive autosomal disease. Hence, in consanguineous marriage, mainly because of the presence of the higher inbreeding coefficient, the probability of the emergence of galactosemia might be increased. To avoid the occurrence of this disease, it is recommended that the families with at least one case of the disease should have genetic counseling prior to their marriage, and also before and during the pregnancy.

Such consultation is required not only for the prospective couples whose family has such a patient but also for their relatives. In other words, continuous genetic counseling complements the relatives.

Concerning the age of the parents, the mothers were all under 30 and fathers under 35 years of age. Moreover, none of the mothers was exposed to the mutagen agents such as X-ray, drug, chemical agents, etc. During pregnancy, indicating no correlation between the parents' age and the presence of the disease. One of five patients with the average of 10 mg/dl galactose 1- phosphate died during their infancy.

Concerning the level of serum galactose-1-phosphate, it was noticed that three of the affected children had classic galactosemia between 5 to 10 mg/dl, one patient had GALT average 10-100 mg/dl and one of the newborns over 100 mg/dl.

It seems that the most reported clinical symptoms before feeding were vomit and jaundice but when they used galactose; the symptoms were sepsis, and full fontanel. Moreover, it seems that after being fed (lactose free milk), the patients revealed a better outcome. The common symptoms typically initiated about the third of life. "Most are asymptomatic and variant galactosemia are not at risk of sepsis or metabolic decompensate" (26).

Moreover, the patient after being screened and identified, the patient should be closely observed to receive appropriate treatment as well as lactose – free milk and special diet. Hence, it seems necessary to find some institutions supporting patients with galactosemia in Iran.

In conclusion, the prevalence of galactosemia in Iran is 5: 24000, being more than that among European and Asian populations. It could be due to high consanguineous marriages in Iran but more studies are required to know how much consanguineous marriages are affected. The early diagnosis and treatment lead to a better outcome and it is cost-effective for the society but more studies should be done to reach statistical amount.

Novel therapeutic strategies, aiming at the prevention of galactose 1- phosphate production, should be developed. Moreover, the follow – up protocol for patients with GALT deficiency should focus on early detection, evaluation and, if possible, early intervention for problems of motor, speech and cognitive development.

Ethical Considerations

Ethical issue principles including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or sub-

mission, redundancy, etc. have been completely observed by the authors.

References

1. Krotoski D, Engelson G, Hanson J, Namaste S, Howell R (2007). Strengthening Newborn Screening in the Middle East and North Africa. 2nd Pan Arab Human Genetics Conference (10.30 – 11.00), Al Bustan Rotana Hotel, Dubai, United Arab Emirates.

2. Goppert F(1917). Galaktosurie nach Michzuck ergabe bei angeborenem, familiaerem chronischem leberleiden. *Klin Wschr* , 54, pp:473-77.

3. Charlwood J, Claylon P, Keir G, Mian N, Winchester B (1997). Defective galactosylation of serum transferrin in galactosemia. *Glycobiology*, 8(4) , pp:351-7.

4. National Center for Biotechnology Information (2006). OMIM:online Mendelian Inheritance in Man[database]. Available at: www.ncbi.nlm.nih.gov/entrez/query.fcgi?db= OMIM.

5. Elsas LJ , Lai K (1998). The molecular biology of galactosemia. *Genet Med* 1,pp; 40-8.

6. Nonymous . *Handbook of Genetic Counselling / Galactosemia.* From Wikibooks, the open-content textbooks collection.

7. Cuatrecasas P, Segal S (1966). Galactose conversion to D-xylulose: an alternate route of galactose metabolism. *Science* ,153 (735) , pp; 549-51.

8. Segal S, Berry GT (1995). Disorders of galactose metabolism. *In the Metabolic and Molecular Bases of Inherited Disease*, 7 th edition. Scriver CR, Beaudet AL, Sly WS , Valle D (ed). McGraw Hill, P: 967-1000.

9. Bosh AM (2006). Classic galactosaemia revisited. *J Inherit metab Dis,* 29; pp:516-25.

10. Nussbaum RL, McInnes RR, Willard HF (2001). *Thompson & Thompson Genetics in Medicine*, Revised Reprint, 6th Edition RL .Chapter 4

11. Applegarth DA, Toone JR, Lowry RB (2000*).* Incidence of inborn errors of metabolism in british Columbia, 1*969-1996. Pediatrics,* 105(1). e10 ISSN: 1098-4275.

12. Suzuki M, West C, Beutler E (2001). Large - scale molecular screening for galactosemia alleles in a pan- ethnic population. *Hum Genet*, 109 (2);pp: 210-5.

13. www.healthatoz. Com/healthatoz/Atoz/common/standard/transf orm

14. Ruiz M, Jover S, Armas M, Duque MR, Santana C, Giros ML, Boleda MD (1999). Galactosemia presenting as congenital pseudoafibrinogenaemia. *J Inherit Metab Dis* ,22;pp:943-44.

15. Bosch AM, Bakker HD, van Gennip AH, van Kempen JV, Wanders RJ, Wijburg FA (2002). Clinical features of galactokinase deficiency; a review of the literature. *J Inherit Metab Dis*,25;pp: 629-34.

16. Celia I.Kaye and committee on genetics (2006). Newborn Screening Fact Sheets. *Pediatrice* 118; e 934-e 963.DOI:10.1542/peds.2006-1783.

17. Levy HL, Sepc SJ. Shih VE, Vawter GF, Klein JO (1997). Sepsis due to Escherichia coli in neonates with galactosemia. *New Eng J Med* ,297, pp; 823-25.

18. Potter NL, Lazarus JA, Johnson JM, Steiner RD, Shriberg LD (2008). Correlates of language impairment in children with galactosemia. *J Inherit Metab Dis* ,31(4),pp; 524-32.

19. Webb AL, Singh RH, Kennedy MJ, Elsas LJ (2003). Verbal dyspraxia and galactosemia. *Pediatr Res*, 53,pp; 396-402.

20. Schadewaldt P , Kamalanathan L, Hammen HW , Wendel U. (2010). Longitudinal assessment of intellectual achievement in patients with classical galactosemia. *Pediatrics* ,125,pp ; 374-81.

21. Gitzelmann R, Steinmann B (1984). Galactosemia: how does long – term treatment change the outcome? *Enzyme,* 32 (1),pp; 37-46.

22. Berry G T, Nissim I, Gibson J B , Lin Z, Elsas L J, Singh R H , Klein P D , Segal S (1997).Quantitative assessment of whole body galactose metabolism in galactosemia patients . *Eur J Pediatr*, 156:S43-S49.

23. Wolf B, Heard GS (1989). *World wide experience in newborn screening for biotinidase deficiency.* In Proceedings of the seventh National neonatal Screening Symposium, ASTPHL, Washington, DC.

24. Carroll AE, Downs SM (2006). Comprehensive Cost-Utility Analysis of Newborn Screening. Strategies. *Pediatrics,* 117 (5) : S287-S295.

25. Saadat M, Ansari- Lari M, Farhnd DD (2004). Consanguineous marriage in Iran. *Ann Hum Biol*, 31,pp; 263-69.

26. Holton JB, Walter JH, Tyfield LA (2001). Galactosemia In: Scriver CR, Kaufman S, Elsensmith E, Woo SLC, Vogelstein B, Childs B (eds). *The metabolic and molecular Bases of inherited disease.* 8th ed. McGraw- Hill, New York, Ch. 72.