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The Incidence and Clinical Study of Galactosemia in Fars Province in South of Iran

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Abstract

Background: In this survey we studied the incidence and clinical presentations of galactosemia in Fars province, in south west of Iran. Galactosemia is a rare genetic metabolic disorder of galactose. Its metabolism can be performed through 3 pathways. Although enzymes deficiency of each of them can lead to galactose accumulation in plasma, the term galactosemia is specifically used for UDP-galactose uridyl transferase (GALT) deficiency. Classical galactosemia (G/G) is mostly manifested by poor growth, irritability, lethargy, vomiting, poor feeding, and jaundice. **Materials and Methods:** 337000 newborns were screened for galactosemia by measuring total galactose level. Blood samples were collected from the heel on the Gauthriepaper, and then calorimetric test with enzyme was performed to determine total galactose level. Blood galactose level below 4mg/dl was considered as normal and it was repeated if it was more than 4mg/dl in the first stage. The test was considered as abnormal if it was more than 5mg/dl, then blood samples were collected on filter paper and dried for 3-4 hours at room temperature and shipped frozen to laboratory for detection of GALT activity and galactose and galactose-1-phosphate. **Results:** From those who were gone for screening, 105 newborns had total galactose level more than 5mg/dl, among them, 37 patients had galactose level more than 15 mg/dl. Overall, 12 cases were considered as classic galactosemia with an incidence rate of 1/28000, in Fars province. **Conclusion:** Although all of our patients were symptomatic and were admitted by hyperbilirubinemia before receiving the results, neonatal screening had an important role in the early diagnosis and management of this disease.**[GMJ. 2014;3(1):39-45]**

Keywords: Galactosemia; Screening; Newborns; Metabolic Disorder; Fars; Iran; UDP-Galactose Uridyl Transferase

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Introduction

Galactosemia is a rare genetic metabolic disorder which affects the metabolism of galactose[1].The three enzymes of the galactose metabolism pathway are galactokinase, galactose-1-phosphate uridyltransfrase (GALT), and uridindiphosphate (UDP) galactose-4-epimerase[2]. Although a deficiency of any of the three enzymes can lead to galactose accumulation in plasma, the term galactosemia is used specifically for GALT deficiency[3]. Profound GALT deficiency which is termed classic galactosemia occurs with a frequency of approximately 1 in 30000 to 1 in 60000 live births[4]. However, this frequency varies over a wide range among geographic population (from 1/16,476 in Ireland to 1/1000,000 in Japan) [5, 6].

Galactosemia is inherited as an autosomal recessive disorder which can be caused by over one hundred mutations. The most common one is Q188R which can induce complete loss of ability to process galactose; yet, other mutations can only diminish the process and the Duarte variant (N314D) has enzyme activity of about 50% of the normal level and usually produces no clinical manifestation.

Classic galactosemia (G/G) is a severe disease which its symptoms are typically seen in second half of the first week of life. The most common initial signs of GALT deficiency are poor growth, irritability, lethargy, vomiting and poor feeding; persistent jaundice may also be seen in the first few weeks of life [7, 8].

By continuing lactose ingestion, multi-organ toxicity syndrome ensues; it is associated with liver disease which can progress to cirrhosis, anemia, brain edema, and kidney damage[9]. Without treatment, mortality and morbidity rate in infants with galactosemia is high [10]. Thus, if lactose/galctose restricted formula is provided during the first ten days of life, the neonatal symptoms quickly resolve and the problems related to the mentioned symptoms usually disappear[11].

Although early diagnosis and treatment have improved the prognosis of galactosemia, patients may still have ovarian failure, mental retardation, speech dyspraxia and ataxia. Yet, mechanisms for these problems are still unknown. Some studies suggest that endogenous production of galactose could be accountable for these long term complications [12].

There are several techniques for the quantitative and qualitative detection of galactose in the blood [13, 14]. One approach of screening is measuring the GALT activity which mostly detects transferase deficiency irrespectively to prior dietary intake of galactose. Yet, it does not evaluate either epimerase deficiency or galactokinase deficiency. Another approach is to measure total galactose (galactose and galactose-1-phosphate) which depends on prior dietary intake, and thus, it evaluates all three enzyme deficiencies [6]. Besides detecting infants with classic galactosemia, infants with other treatable forms of galactosemia as well as those who are carriers of galactosemia or galactosemic variant are identified by newborn screening[15].

In Fars province, newborn screening for galactosemiahas been done since 2007. Senemar et al. reported that the prevalence of this disease in neonates is 5/24000 in Fars Province [16]. This study is an overview of incidence, clinical presentations and complications of this disease from 2007 to 2012in Fars, south west of Iran.

Materials and Methods

From June 2007 to June 2011, 337000 newborns were screened for galactosemia by measuring total galactose level, in the laboratory of Paramedical school of Shiraz university of medical sciences, Shiraz, Iran.

Blood samples were collected from the heel on the Gauthrie paper, then calorimetric test with enzyme was performed by ELISA Reader to determine the total galactose levels. The kit was purchased from Kimia Pejuhan Company, Tehran, Iran.

Blood galactose levels below 4mg/dl was considered as normal and it was repeated if it was more than 4mg/dl in the first stage. The test was considered abnormal if it was more than 5mg/dl, then blood samples were collected on filter paper and dried for 3-4 hours in room temperature and shipped frozen to Wagner laboratory in Germany for detection of GALT activity and galactose and galactose-1-phos-

phate.
This test was performed as a content of the panel for neonatal screening. The result was considered positive if GALT activity was under 20% and if total galactose was more than 18 mg/dl, then free galactose was measured for determining the free galactose and galactose-1-phosphate.

Results and Discussion

From June 2007 to June 2011, 337000 newborns were screened for galactosemia (Table-1, Table-2), among them, 142 newborns had total galactose level more than 5mg/dl, of them 37 patients had galactose level more than 15mg/dl.
GALT activity <5% was found in seven patients with signs and symptoms of galactosemia and considered as classic galactosemia. For three patients, exchange transfusion were done due to high bilirubin level, for one patient exchange transfusion was done two times due to very high level of serum bilirubin [37], blood samples were taken from them after exchange transfusion and showed normal results but they were symptomatic and had high galactose levels while their symptoms were resolved promptly after starting soy based formula.
Furthermore, for one patient, GALT activity was not checked due to high blood galactose,

Table 1. Number of Neonates who were Screened Between 2007-2011

Year	2007	2008	2009	2010	2011
Number of Neonate	37228	76855	72332	74335	76250
Suspected Patients	19	25	29	43	26

Table 2. Lab Data in Patients with Classic Galactosemia

Number	T.BIL	D.BIL	ALT	AST	PT	PTT	ALKP	GAL
1	22	4	78	78			1548	350
2	27				32	>120		38
3	22	4.5	100	150	17.2	107	2487	59
4	37	0.4	85	110			3060	55
5	22	4	169	640	19			103
6	18	10	61	160			2737	71
7	23	4	46	50	19	40	4262	60
8	Hyper Bili	Liver Failure						102
9	22		85	120				122
10	18							215
11	22							118
12	Hyper Bili	Liver Failure						102

family history of classic galactosemia, and also signs and symptoms of galactosemia.

One patient died before checking GALT activity due to liver failure and ascites (blood galactose was 102 mg/dl). Overall, 12 cases were considered as classic galactosemia with an incidence rate of 1/28000 in Fars province. All of the patients were symptomatic before screening. Family history was positive in four patients, two in siblings and two in second degree relatives.

In infantile period, all patients used soya-based formula and their diet were free of lactose which is present in the dairies but not in the vegetables and fruits. Yet, we do not have the ability to measure RBC galactose-1-P regularly for follow-ups.

During the study, the age range of patients were from 12 months to 5.5 years old; 75% of them were from two small towns; 50% of parents were relatives.The patients became symptomatic from 3 days to 10 days after birth.

In this study, the incidence of galactosemia in Fars province was 1/28000 which was slightly more than other reports. In a study by Sen-

Table 3. Clinical Findings in Patients with Classical Galactosemia.

Patient	Jaundice	Vomiting	Poor feeding	Hepatomegaly	Sepsis	Bulged Fontanel	Cataract	Death
1	*		*					
2	*		*				*	
3	*		*	*			*	
4	*	*	*					
5	*	*	*	*	*			
6	*		*	*		*		*
7	*		*			*	*	
8	*	*	*	*			*	
9	*						*	
10	*	*					*	
11	*		*					
12	*	*	*	*				*
Percentage	100%	41%	83%	41%	8.3%	16%	50%	16%

Table 4. Age Distribution

Age	12 month	15 month	2 year	2.5 year	3.5 year	4 year	5 year
Number	2	2	1	1	2	1	1

emar et al. the incidence of galactosemia in Fars province was reported as 1/6000; they used total galactose level for the diagnosis of galactosemia[16]. Galactosemia is inherited as autosomal recessive and has a high incidence in Iranian population which is because of high rate of consanguinity marriages. In one study by Saadat et al. the prevalence of consanguinity marriages in Iran was 38%[17]. Early cataract was detected in 50% of our patients which was higher than other reports. In one study by Pagan et al. the rate of cataract formation was 30% and in two other studies, the prevalnces of cataract were reported as 7% and 10% [18]. Cataracts regressed in all of our patients except one after starting soya-based formula while in those whose soya-based formula was discontinued due to normal GALT activity , cataract became bilateral and needed surgery after 3 years. In Pagan's study, one patient needed surgery although soya-based formula was started early for him [18]. All of our patients became symptomatic before the screening tests, 100% had hyperbilirubinemia and 83% had poor feeding. This underlines the clinical judgment for diagnosis of classical galactosemia. Mean days for diagnosis was 15 days (from 7 to 21 days); in all four patients screening tests were delayed because they were admitted in local hospitals due to hyperbilirubinemia then they developed other signs and symptoms of liver failure , two of them died due to liver failure even after starting soya-based formula.

The early diagnosis was because of screening and clinical vigilance, while in non-screened ones, diagnosis time was reported to be almost 60 days and sometimes even up to 5 months according to two reports[19, 20]. Mortality rate in this study was 16%. It can reach to 75% without early diagnosis and treatment[21], vice versa, it could be 0% if screening had been done in appropriate time.

Of our patients, 33% had positive family history, and as previously mentioned, consanguinity marriages are common in Iran, so it is important to determine gene mutations in this region for familial counseling and prenatal diagnosis.

Sepsis occurs in patients with galactosemia with an incidence of 10%, Ecoli is the leading cause, even though we had one case of sepsis (8.3%) with hemolytic streptococcus [18]. Moreover, speech problem, hypogonadism, and mental retardation could persist in patients with galactosemia even after treatment with galactose restricted diet. Speech problem can be evaluated after three years. Vocabulary and articulation problems occurred in one patient; only four patients in our study had more than three years, so the incidence of speech problem in our patients was 25%. It was reported in 48% [22] of individuals aged three years or older in an study and in another one, it was reported up to 56%. In a recent study by Lawrence et al., the incidence of Childhood apraxia of Speech (CAS) was 24% [23] which is near to our study. Difference in reports could be due to different criteria and specific alleles which involved in galactosemia, in one study by Ander et al. speech problems were much higher in patients with one specific mutation ,Gln188Arg [24]. Weights less than 10% were demonstrated in 3 patients (25%) and height lower than 10% was seen in one patient (8.3%). The same results have been reported in treated galactosemic patients [25]. Our retrospective study group was small and too young to be evaluated for all complications of galactosemia.

Conclusion

In many countries galactosemia is a part of newborn screening program. Screening leads to early diagnosis and could reduce neonatal mortality and morbidity by prevention of many complications such as liver failure and cirrhosis, cataract, kidney failure, and sepsis.

In Iran, neonatal screening for galactosemia only takes place in Fars province which ust be perfomed in other regions as well. Even with early and adequate therapy, some complications such as speech defect, poor growth, poor cognitive function, and premature ovarian failure cannot be completely prevented. It is imperative to prevent this disease by gene study through carrier detection, family counseling, and prenatal diagnosis. It is also important to perform the screening in appropriate time in hospitalized patients.

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Conflict of Interest

None declared

References

1. Wang BB, Xu YK, Ng WG, Wong LJ. Molecular and biochemical basis of galactosemia. Mol Genet Metab. 1998;63(4):263-9.
2. Cuthbert C, Klapper H, Elsas L. Diagnosis of Inherited Disorders of Galactose Metabolism. Curr Protoc Hum Genet. 2008 ;Chapter 17:Unit 17.5.
3. Segal S, Berry GT, editors. Disorders of galactose metabolism. 7th ed. New York: McGraw-Hill; 1995.
4. Fridovich-Keil J, Walter JH. editors. Galactosemia. 8th ed. New York: McGraw-Hill Medical Publishing Division; 2008.
5. Suzuki M, West C, Beutler E. Large –Scale molecular screening for galactosemia alleles in pan-ethnic population. Hum Genet. 2001;109(2):210-5.
6. Fujimoto A, Okano Y, MIAGI T, Isshiki G, Oura T. Quantitative Beulter Test for Newborn Mass Screening of Galactosemia Using a FluorometricMicroplateReader. Clin Chem. 2000;46(6 Pt 1):806-10.
7. Cederbaum S, Berry GT. Inborn Errors of Carbohydrate Metabolism In Christine. 9th ed. Gleason A, Devaskar SU, editors. Philadephia: Elsevier Saunder; 2012.
8. Saudubray JM, Nassogne MC, Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. Semin Neonatol. 2002;7(1):3-15.
9. Health NIo. Galactosemia. [cited 2008 1 September]; Available from: http://ghr.nlm.nih.gov/condition=galactosemia.
10. 10. Shield JP, Wadsworth EJ, MacDonald A, Stephenson A, Tyfield L, Holton JB, et al. The relationship of genotype to cognitive outcome in galactosaemia. Arch Dis Child. 2000;83(3):248-50
11. Novelli G, Reichardt JK. Molecular basis of disorders of human galactose metabolism: past, present, and future. Mol Genet Metab. 2000;71(1-2):62-5.
12. Berry GT, Nissim I, Lin Z, Mazur AT, Gibson JB, Segal S. Endogenous synthesis of galactose in normal men and patients with hereditary galactosaemia. Lancet. 1995;346(8982):1073-4.
13. Jensen UG, Brandt NJ, Christensen E, Skovby F, Nørgaard-Pedersen B, Simonsen H. Neonatal Screening for Galactosemia by Quantitative Analysis of Hexose Monophosphates Using Tandem Mass Spectrometry: A Retrospective Study. Clinl Chem. 2001;47(8):1364-72.
14. Hongl SP, Yoon HR, Kim MK. Development of a New HPLC Diagnostic Method for Galactosemia Using 8-Amino-2- naphthalenesulfonic acid. Chromatographia. 2001;54:83-6.
15. Health UDo. Galactosemia:A Newsletter of the newborn screening program and the newborn screening laboratory; 2004.
16. Senemar S, Ganjekarimi AH, Senemar S, Tarami B, Bazrgar M. The Prevalence and Clinical Study of Galactosemia Disease in a Pilot Screening Program of Neonates, Southern Iran. Iranian J Publ Health. 2011;40(4):99-104.
17. Saadat M, Ansari- Lari M, Farhud DD. Consanguineous marriage in Iran. Ann Hum Biol. 2004;31(2):263-9.
18. Pagon RA, Bird TD, Dolan CR, Adam MP, Stephens Kea. Galactosemia. Seattle: University of Washington; 2000.
19. Henderson H, Leisegang F, Brown R, Eley B. The clinical and molecular spectrum of galactosemia in patient from the cape town region of south Africa. BMC Pediatr. 2002;2:7.

20. Botkin JR. Research for Newborn Screening : Developing a National Framwork. Pediatrics. 2005;116(4):862-71.
21. Bosch AM. Classic galactosemia revisited. J Inherit Metab Dis. 2006;29(4):516-25.
22. Coss KP, Doran PP, Owoeye C, Codd MB, Hamid N, Mayne PD, et al. Classical Galactosaemia in Ireland: incidence, complications and outcomes of treatment. J Inherit Metab Dis. 2013;36(1):21-7.
23. Shriberg LD, Potter NL, A. SE. Prevalence and Phenotyp of Childhood Apraxia of Speech In Youth with Galactosemia. J Speech Lang Hear Res. 2011;54(2):487-519.
24. Robertson A, Singh RH, Guerrero NV, Hundley M, Elsas LJ. Outcomes analysis of verbal dyspraxia in classialactosemia. Genet Med. 2000;2(2):142-8.
25. Panis B, Gerver WM, Rubio-Gozalbo ME. Growth in classical galactosemia patients. Eur J Pediatr. 2007;166(5):443-6.