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A Rare Homozygous Variant in the GALT Gene is Consistent with the Diagnosis of Duarte Type of Galactosemia: A Case Report

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Abstract

Background: Galactosemia is a rare metabolic genetic disorder due to a deficiency of Galactose -1-Phosphate Uridyltransferase (GALT). The disorder usually affects many systems with acute as well as long-term consequences. Galactosemia is inherited as an autosomal recessive pattern. More than one hundred mutations have been identified, some associated with the severe clinical picture and others with benign or maybe asymptomatic. Here we presented a clinically normal infant with abnormal newborn screening and positive mutation most likely causing Duarte type of galactosemia. The prognosis of classical Galactosemia is poor with high morbidity and mortality rate while it is benign with Duarte type of galactosemia, which is related to complete or partial enzyme deficiency.

Material and methods: We report a female infant of Saudi origin product of consanguineous marriage (double consanguinity) With abnormal low (GALT) in repeated newborn screening tests through Dried Blood Spot (DBS) which is consistence with a genetics variant discovered by Whole Exome Sequence (WES).

Result: The constellation of clinical presentation and biochemical findings confirmed by Molecular genetics investigations showed a rare homozygous variant c.940A>G p.(Asn314Asp) in the GALT gene (OMIM:606999) which is consistence with Duarte galactosemia.

Keywords: Galactosemia • Duarte type of galactosemia • Deficiency of Galactose -1-Phosphate Uridyltransferase (GALT) • GALT gene • Homozygous variant c.940A>G p. (Asn314Asp)

Introduction

Galactosemia (OMIM: 230400) is a rare metabolic genetic disorder. Clinical presentation varies depending on the level of enzyme deficiency. Complete or near complete deficiency in the galactose 1 phosphate uridyltransferase (classical galactosemia) usually presented with severe clinical presentation. Symptoms start after newborn feeding either breastfeed or regular milk formula since both contain disaccharide lactose, which is the principal carbohydrate in the milk, providing 40% of its total energy for newborns (lactose is a disaccharide carbohydrate hydrolyzed in the small intestine into galactose and glucose). The symptom appears in the second half of the first week with poor feeding, persistent vomiting, hypoglycemia, and hypoactivity. Jaundice, hepatomegaly, decrease in liver function, and elevation of liver enzymes may follow. Nuclear cataracts may occur in the neonatal period. Death may follow due to sepsis usually by gram-negative bacteria (*E. coli*) in untreated neonates. long term complications of classical galactosemia include mental retardation, verbal dyspraxia, motor abnormalities, ovarian failure, and hypogonadism [1].

Symptoms are milder with partial transferase deficiency associated with residual GALT activity 25% are usually asymptomatic. In partial deficiency with only 10% of GALT activity, there may be long-term consequences such as failure to thrive, liver impairment, and developmental delay. Duarte variant due to N314D GALT gene mutation is usually benign and symptomatic. usually discovered through newborn screening and followed by identified specific mutations.

The incidence of galactosemia, more than 167 mutations in the GALT gene (OMIM: 606999) have been identified [2-4]. The mode of inheritance is autosomal recessive. A prevalent mutation (Q188R) and many common variants in the GALT gene have been identified including (K285N) and (S135L) is known to cause classical galactosemia (G/G). Duarte type duo to homozygous mutation (D/D) in which an A-to-G transition at base pair 2744 of exon 10 in the GALT gene, the transition that produces a codon change converting asparagine to aspartic acid at position 314 (N314D). The proposed Duarte biochemical phenotypes of GALT are as follows 75% for heterozygous mutation (D/N), 50% for homozygous mutation (D/D), and 25% for compound heterozygous mutation (D/G) of enzyme activity [5,6].

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Classical galactosemia is associated with high morbidity and mortality even with diet restriction with long-term complications. Most of the affected infants developed multisystem failure and deaths may follow. However, the Duarte type is usually benign and asymptomatic and required no dietary restriction and no sequel since the enzyme activity is above 25% of enzyme activity [7,8]. Here, we report a new case, an infant (asymptomatic) which showed an abnormal GALT level in the newborn screening test and the genetic testing supporting a diagnosis of Duarte galactosemia with rare mutation.

Methods

Human subject: In the present study, we clinically investigated a single affected individual (proband) from a Saudi-origin family. The proband underwent a comprehensive clinical evaluation by a general pediatrician, clinical geneticist, and metabolic consultant.

Biochemical test: Newborn screening tests by Tandem Mass Spectrometry (TMS) through Dried Blood Spot (DBS) have been done which include the common metabolic, endocrine, and hereditary blood disease disorders. One of the diseases including in this screening program is galactosemia.

Molecular genetic test: Genomic DNA is enzymatically fragmented, and target regions are enriched using DNA capture probes, these regions include approximately 41 Mb of human coding exome (targeting >98% of coding RefSeq from human genome build GRCh37/hg19), as well as the mitochondrial genome. The generated library is sequenced on an Illumina platform to obtain at least 20x coverage depth for 98% of the targeted bas of es. An in-house bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly and revised Cambridge Reference Sequence (rCRS) of Human Mitochondrial DNA (NC_012920), variant calling, annotation, and comprehensive variant filtering is applied. All variants with Minor Allele Frequency (MAF) of less than 1% in the gnomAD database, and disease-causing variants reported in HGMD, in ClinVar, or centoMD are evaluated. The investigation for relevant variants is focused on coding exons and flanking =/-10 intronic nucleotides of genes with clear gene-phenotype evidence (based on OMIM information). All potential patterns for the mode of inheritance are considered. In addition, providing family history and clinical information are used to evaluate identified variants concerning their pathogenicity and disease causality. Variants are categorized into five classes (pathogenic, likely pathogenic, VUN, likely benign, benign) along ACMG guidelines for the classification of variants. All relevant Variants related to the phenotype of the patient are reported

Results

The tandem mass spectrometry showed low GALT levels of 2.986 u/dl, 3.3 u/dl, 2.6 u/d in the first week, 3ed week, and 4 weeks of the newborn compared to normal values>3.4 u/dl. Molecular genetic testing through Whole Exome Sequence (WES) detects a homozygous variant at GALT gene c.940A>G p.(Asn314Asp) causing an amino acid change from asparagine to aspartic acid at 314 positions. These constellations of clinical, biochemical, and genetic tests support the diagnosis of Duarte galactosemia.

Case Presentation

KFGH case report

We presented a female infant born in a private hospital of healthy consanguineous Saudi parents from Eastern province. This is the first baby for the young couple. The mother reported no medical problems and no exposure to teratogens or alcohol. The mother was on regular follow-up antenatally and it was reassuring.

AT 38 weeks of gestation the fetus is delivered by normal vaginal delivery. Apgar score was 9, 10 at 1 and 5 minutes respectively. The newborn weighed 2,850 g (50th centile) with a length of 52 cm (75th centile) and a head circumference of 33 cm (50th centile) vital signs were within normal limits and the newborn showed no dysmorphism. The newborn started on breastfeeding the first day of life and was discharged with the mother on the 3ed day with good feeding and activity. Initial newborn screening has been sent.

The result of the first newborn screening test showed a low GALT level of 2.896 u/dl where the cut level is > 3.4 u/dl. the family was called to evaluate the baby in the ER by the metabolic team, by that time the age of the baby is 3 weeks, and had a normal baby examination. GALT levels have been requested again through Dried Blood Spot (DBS) and since the baby was well and had no symptoms or signs suggestive of the disease and kept on breastfeeding, the family was educated about the manifestation of the disease and another Tandem Mass Spectrometry (TMS) sample have been sent. Unfortunately, the 2ed sample showed low GALT and the result is 3.3 u/dl (near normal GALT level).

The family was very worried and not convinced about the result since the baby was active, feeding well, and had no abnormal symptoms. At this time 3ed samples of Tandem Mass Spectrometry (TMS) have been sent, the baby started on a galactose restriction diet (lactose-free formula) and a gene test through Whole Exome Sequence (WES) was requested as an additional test to support the diagnosis, and to figure the mutation related to this presentation of galactosemia. 5 days later the result of the 3ed sample of TMS again showed a low GALT level, which was 2.6 u/dl. We advise the family to continue with lactose-free formula till the result of the gene test. at the age of 6 weeks, the gene test showed homozygous variant c.940A>G p.(Asn314Asp) at the GALT gene which was described by HGMD Professional 2022, as a risk factor with additional supporting functional evidence for galactosemia, Duarte variant by Elsas LJ, et al. [5] (PMID: 8198125), Podskarbi, et al. (PMID: 8892021), Greber-Platzer, et al. (PMID: 9222760). Hence, the family was contacted and advised to resume breastfeeding as tolerated and hold a galactose-free diet, regular follow-up for the baby on monthly bases showed no abnormal symptoms with normal examination. Currently, he is 9 months old with normal development for his age.

Discussion

In 2005, the national newborn screening program was initiated in Saudi Arabia, the program aiming to screen common metabolic and endocrine disorders in the kingdom. According to the Saudi Ministry of Health the program aimed to screen all newborns within 24-72 hours of delivery. Currently, the program is performed in more than 183 hospitals all over the kingdom in addition to many private hospitals [9,10].

Newborn screening program the screening test is performed by drying blood samples on filter paper (Figure 1). Usually, the result will take about three working days to be reported. The national newborn screening program in Saudi Arabia recently includes all the following disorders: Galactosemia, Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD), Homocystinuria (HCU), Citrullinemia (CIT), Argininosuccinic Aciduria (ASA), 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG), Methylmalonic Acidemia/Propionic Acidemia (MMA/PA), Betaketothiolase Deficiency (BKT), Glutaric Acidemia1 (GA1), Isocaloric Acidemia (IVA), Medium chain acyl-CoA-dehydrogenase deficiency (MCAD), 3-Methylcrotonyle Carboxylase deficiency (3MCC), Very Long Chain Acyle-CoA-Dehydrogenase Deficiency (VLCAD) and Biotindase Deficiency (BTN). In addition to two endocrine disorders including congenital hypothyroidism (TSH) and congenital adrenal hyperplasia (N17H). Recently some inherited blood diseases have been included, including glucose 6 phosphate dehydrogenase deficiency (G6PD), sickle cell disease, and thalassemia (Table 1).

The current patient is the first case to be reported from Saudi Arabia in the eastern region. The proband has no clinical presentation suggesting galactosemia. Since birth, the baby doing well with normal breastfeeding, the only abnormality was a low GALT level in repeated TMS. The difficulty was

Figure 1. Dry blood sample for newborn screening.

Table 1. List of diseases screened within the national newborn screening program in Saudi Arabia.

Aminoacidopathies	Phenylketonuria
	Argininosuccinate lyase deficiency
	Maple syrup urine disease
	Citrullinemia
	Homocystinuria
Organic acid disorder	Methylmalonic acidemia
	Propionic acidemia
	Glutaric acidemia
	3-methylcrotonyl-CoA carboxylase deficiency
	Isovaloric acidemia
Fatty acid oxidation disorder	Medium-chain acyl CoA dehydrogenase deficiency
	Very long-chain acyl CoA dehydrogenase deficiency
Ketogenesis and ketolysis disorders	3-hydroxy-3-methylgluteryl-CoA lyase deficiency
	Beta-ketothiolase
Carbohydrate disorders	Galactosemia
Endocrine disorder	Congenital hypothyroidism
	Congenital adrenal hyperplasia
Vitamin responsive disorders	Biotinidase deficiency
Inherited blood diseases	Glucose-6-phosphate dehydrogenase deficiency
	Sickle cell anemia
	Thalassemia

which decision the be taken during the management of this baby. Shall we keep him on a galactose-free diet while he is having no abnormal symptoms or shall we advise the mother to continue breastfeeding? And the decision to go more advanced to find the explanation for this low GALT level by doing genetic testing. WES performed by detecting this mutation variant (N134D) which goes with the diagnosis of benign type of galactosemia (Durate type). Articles have been reviewed regarding the false positive and false negative results regarding GALT, and this issue is a common problem regarding the screening of galactosemia [11]. However some times difficult to have an explanation for the result, further workup including molecular genetics can be very helpful.

Conclusion

Galactosemia (Durate type) is a rare entity metabolic disease and one of the interesting diseases to work on till finalizing the definitive diagnosis. We alert clinicians to consider the possibility of Durate type whenever there are asymptomatic newborns or infants with abnormal GALT in newborn screening. Molecular genetics test specifically Whole Exome Sequence (WES) is very helpful to reach a definitive diagnosis and to rule out other differential diagnoses.

Finally, we emphasize the need for longitudinal data, as such information will provide a profile encompassing care recommendations, Future research is needed to elucidate. The long-term outcome of these patients.

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Consent for Publication

Not applicable.

Ethical Approval

Ethical approval is not required at our institute to publish an anonymous case report.

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Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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