A NOVEL MUTATION IN A NEWBORN BABY LEADING TO GLYCOGEN STORAGE DISEASE TYPE IA

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ABSTRACT

Glycogen storage disease type Ia (GSD1A) is caused by mutations in the G6PC gene. The G6PC gene was first cloned in 1993. Since then, many different mutations have been identified leading to this disease. Hepatomegaly is one of the important clinical manifestations of the disease. A 23-day-old girl was admitted to the hospital due to respiratory distress. Her physical examination was normal except for tachypnea. She had hypoglycemia, lactic academia, hyperlipidemia and hyperuricemia. With these clinical findings, GSD1A was considered in the patient and the diagnosis was genetically confirmed. By direct sequencing of the G6PC gene, we identified a novel homozygous variation (c.137T>G/p.Leu46Arg) in the patient and the healthy mother and father were heterozygotes for the variant. Here we present a case with a novel homozygous missense mutation c.137T>G/p.Leu46Arg in the G6PC gene leading to GSD1A clinical findings.

Keywords: Glycogen storage disease type Ia (GSD1A); Novel mutation; von Gierke disease.

INTRODUCTION

Glycogen storage disease type Ia (GSD1A; MIM: 232200) is an autosomal recessive disorder that is caused by deficient glucose-6-phosphatase (G6Pase) activity [1]. Hypoglycemia, lactatemia, hyperuricemia, hyperlipidemia, and marked hepatomegaly are the leading features of this inborn error of metabolism [2]. Up to now, over 100 mutations have been identified in the G6PC gene [3]. Here we present a case with a novel homozygous missense mutation c.137T>G/p.Leu46Arg in the G6PC gene leading to GSD1A clinical findings.

CASE REPORT

A 23-day-old girl was admitted to the emergency room because of respiratory distress. On physical examination, there was no abnormality except tachypnea, and there was no hepatomegaly. She had hypoglycemia (32.0 mg/dL), lactatemia (8.0 mmol/L) and hyperuricemia (9.2 mg/dL). Other routine blood tests, urinalysis, and chest X-ray were normal. She was the first child of consanguineous parents. She was born at 38 weeks’ gestation and weighed 2300 g. Blood samples were obtained for metabolic tests. After hospitalization, hypertriglyceridemia (569.0 mg/dL) was determined. The size of the liver was normal on the ultra-sonographic (USG) examination. Metabolic tests [tandem-mass spectrometry (MS), blood amino acid chromatography, urine organic acids] determined normally. With these findings, the patient was thought to carry GSD1A disease. Her daily diet was planned for 65.0% of total energy intake from carbohydrates, 15.0% from protein and the remainder from fat (with high linoleic acid content). Informed written consent was obtained from parents.

To confirm the diagnosis, mutational analysis of the G6PC gene was performed by direct DNA sequencing. Genomic DNA was isolated from peripheral blood of the proband and her family using a DNA isolation kit (RTA Laboratories, Kocaeli, Turkey). To identify any mutations the proband might be carrying, exons of the G6PC gene including exon/intron flanking regions, were amplified.
by polymerase chain reaction (PCR) with specific prim-
ers that were designed using Primer 3 software (http://
hg.gsf.de/ihg/Exon Primer.html) and H Taq polymerase
(Zeydanlı, Ankara, Turkey). Standard PCR conditions
with 35 cycles were used and performed on a 9700 Thermal
Cycler (Applied Biosystems, Foster City, CA, USA).
The amplified products were purified by using Zymo Re-
search Sequencing Clean-up Kit (Epigenetic Companies,
Irvine, CA, USA). Cycle sequencing was performed with
the BigDye Terminator v3.1 Cycle Sequencing Kit (Ap-
plied Biosystems) on an Applied Biosystems® 3130 Ge-
ettic Analyzer. The sequence data were analyzed using
sequencing analysis v5.3.1 software program (Applied
Biosystems) and compared to the reference sequence
(GenBank Accession Nos. NG_011808.1, NM_000151.3,
NP_000142.2).

Lactatemia and hypertriglyceridemia have continued
in the follow-up examinations. At 9 months of age, USG
revealed mild hepatomegaly (craniocaudal length = 100
mm) for the first time, but there was no hepatomegaly on
physical examination. Liver functions were normal.

**DISCUSSION**

Glycogen storage disease type Ia is a rare disease
that primarily affects the kidneys and liver. There is an
excessive accumulation of glycogen in the liver and kid-
neys due to G6Pase enzyme deficiency [2]. Patients with
GSD1A have various clinical manifestations according to
the patient’s age, including fasting hypoglycemia, hepatome-

galy, hyperlipidemia, lactacidemia, hyperuricemia, poor
growth and short stature [1,2]. In the neonatal period,
patients may present with symptoms of lactic acidosis and
hypoglycemia [4,5]. Our patient presented with hypoglyce-
mia and lactacidemia in the neonatal period. Glycogen
storage disease type Ia was considered in our patient with
other clinical findings and the diagnosis was genetically
confirmed. By direct sequencing of the *G6PC* gene, we
identified a novel homozygous variation (c.137T>G/p.
Leu 46Arg in exon1) in the patient and the healthy moth-
er and father were heterozygotes for the variant (Figure
1). This variant has not been previously reported in the
Human Gene Mutation Database (HGMD; http://www.
hgmd.cf.ac.uk/ac/index.php) and in population studies
(ExAC: Exome Aggregation Consortium and 1000 Gen-
omes Project; http://exac.broadinstitute.org/). *In silico*
analysis program (VarSome; DANN Score: 0.9967; https://
varsome.com/) showed that this change could be the cause
of the disease.

Hepatomegaly is one of the main findings of GSD1A
and it is seen in all patients but proper diagnosis can be
difficult in infants with GSD1A who do not have not se-
vere hepatomegaly. Infants who have not been diagnosed
before are presenting with hepatomegaly at 3 to 6 months
of age [2]. In these patients, hepatomegaly occurs due to
glycogen and fat storage [7].

However, hepatomegaly was not detected either in
the examination or in the USG in the follow-up of our
patient during the first 9 months. First, at the end of the
9th month, USG examination revealed mild hepatomegaly
and an increase of liver echogenicity.

In these patients, liver functions are normal except for

glucose homeostasis, cirrhosis is not expected. Adenoma
may develop in the second decade of life. Liver functions
were normal in our patient. Dietary treatment improves
the quality of life of the patients and may prevent compli-
cations [6]. Our patient’s diet was regulated according to
the European Study on Glycogen Storage Disease Type I
recommendations [7].

We present a patient with GSD1A and a novel mutation
in the *G6PC* gene. Our findings have expanded the
spectrum of causative mutations, and clinical findings in
GSD1A. This novel mutation, which was not previously
described, appears to be a mutation associated with milder
hepatomegaly.

**Declaration of Interest.** The authors report no con-

flicts of interest. The authors alone are responsible for the
content and writing of this article.
REFERENCES


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