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Case Report Open Access

Cystathionine B -Synthase Deficiency, Turner Syndrome and İmmune Hydrops Fetalis in a Newborn: A Rare Coincidence

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Abstract

Cystathionine β-synthase (CBS) deficiency is a rare inborn error of amino acid metabolism affecting energy supply at the cellular level. Neonatal screening allows early presymptomatic diagnosis and better outcome, by preventing the complications like thrombotic disease. Here we present a female newborn baby with immune hydrops fetalis and mosaic Turner syndrome who has incidentally been early diagnosed with CBS deficiency upon detection of increased methionine on serum amino acid chromatography. The patient was unresponsive to pridoxine treatment which was compatible with p.S349N mutation detected on both alleles of *cystathionine β-synthase* gene. We would like to stress the point that CBS deficiency can be diagnosed by screening even in the setting of exchange transfusions and amino acid paper chromotography is a cheap and valuable metabolic screening tool in experienced hands. Since routine newborn screening for many metabolic diseases is currently not practiced in Turkey, all newborns born to families in which previous siblings had died due to unknown cause should be evaluated by amino acid paper chromotography and by other conventional metabolic tests when necessary.

Keywords: Homocystinuria; Immune hyrops fetalis; Turner syndrome mosaisizm

Introduction

Homocystinuria represents a group of hereditary metabolic disorders characterized by accumulation of homocysteine in the serum and an increased excretion of homocystine in urine. *Cystathionine β-synthase* (CBS) deficiency is the most frequently encountered cause of homocystinuria and may clinically present with developmental delay, mental retardation, ectopia lentis, severe myopia, skeletal abnormalities or thromboembolism. Severity of the untreated disease is determined mostly by the underlying genetic defect, and patients with milder forms of CBS deficiency usually respond to pharmacological doses of pyridoxine by a marked decrease of their total homocysteine plasma levels. B6-responsive homocystinuria usually exhibits milder clinical signs than the non-responsive variant [1,2]. Ectopia lentis occurs in almost all untreated patients by eight years of age [3]. A tall and slender constitution with an asthenic habitus resembling Marfan Syndrome and predisposition to osteoporosis are typical features for CBS deficiency. Seizures, psychiatric problems, extrapyramidal signs such as dystonia, hypopigmentation, pancreatitis, malar flush, and livedo reticularis are the other possible features. The crucial point is that thromboembolism is the primary cause of mortality and morbidity. Neonatal screening for CBS deficiency gives the opportunity of early presymptomatic diagnosis and early treatment, which improves outcome by preventing probable life-threatening complications [4]. Herein, we present a female newborn baby with immune hydrops fetalis and mosaic Turner syndrome who has incidentally been early diagnosed as CBS deficiency upon detection of increased methionine on blood amino acid paper chromatography.

Case Report

A baby girl was born by caesarian section at 35.2 weeks' gestation to a 34-year-old gravida 9, now para 3 mother. Previous six gestations of the mother resulted in intrauterine exitus (all in the second trimester) or postpartum exitus most probably due to Rh hemolytic disease and she was referred to our hospital's gynecology & obstetric department on 24th gestational week. The baby had received intrauterine transfusions five times during pregnancy. Although immune hydrops fetalis was sufficient to explain her reccurent miscarriages, the mother was also investigated for TORCHs and prothrombotic risc factors which were all normal. Serum homocysteine of the mother was not available. The chromosomal analysis from cordocentesis, performed before intrauterine transfusions, revealed that the baby was a case of mosaic Turner syndrome seen on three of 30 metaphases (45 X(3)/46 XX (27)). Neither in fetal life nor postnatally there was not any clinical stigma of Turner syndrome. The labour was uneventful and she was not hydropic at birth. On admission physical examination was normal.

The initial laboratory analysis from cord blood revealed a hematocrit of 18.8%, hemoglobin 6.8 g/dL, WBC 17.200/µl, platelets 173.000/µl, Total/direct bilirubine 5.92/0.01 mg/dL. In addition the direct Coombs test was positive and hemolysis was detected in peripheral blood smear. Following exchange transfusion intravenous immunoglobuline (IVIG) was given and phototherapy was started. Postnatally by the third day the baby improved well and no recurrent exchange transfusion, phototherapy or IVIG were needed.

According to our hospital's policy, urine and blood amino acid paper chromotography is used as a first line metabolic screening tool for every newborn admitted to intensive care unit. Incidentally, hypermethioninemia was detected on serum amino acid chromotography and a serum homocysteine level of 287.02 µmol/L considered the diagnosis of CBS deficiency. Pridoxine treatment was started and a month later the decrease in serum homocysteine level was not satisfactory (186.16 µmol/L) so she was put on a methionine-

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restricted diet with the special formula. On mutation analysis, she was found to carry homozygous c.1046 G>A; p.S349N mutation on CBS gene. The nature of the mutation and the inadequate decrease in homocysteine with pridoxine treatment were compatible with a non-responsive type of homocystinuria.

Eye examination and cranial ultrasound of the baby were normal. We could not perform family screening except the mother, whose serum homocysteine level was normal. The genetic counseling was provided for the family.

Discussion

Homocystinuria is the most common inborn error of methionine metabolism. Along with its first description, newborn screening was proposed for this rare but disabling disorder and is currently available worldwide. There are different methods like Guthrie bacterial inhibition assay, thin layer chromatography or Tandem MS used for screening, but diagnosis should be confirmed with the enzyme activity measurement and/or molecular genetic techniques [5]. National newborn screening programme in Turkey currently includes phenylketonuria, congenital hypothyroidism and biotinidase deficiency, so homocystinuria is not routinely screened. However "urine and blood amino acid paper chromotograhpy screening protocol" of our hospital broadens this screening programme to some extent and give us the chance to early diagnose aminoacidopathies like tyrosinemia, homocytinuria (CBS deficiency), maple syrup urine disease, etc.

Detection of hypermethioninemia is the hallmark in CBS deficiency screening, but it's not unique to it. In case of increased methionine with normal/slightly increased homocysteine levels, further work up for methyladenosyltransferase I/III (MAT I/III), guanidinoacetate methyltransferase (GAMT), and adenosylhomocysteine hydrolase deficiencies are needed. Increased methionine together with increased homocysteine in blood and presence of homocystine in urine brings us to the diagnosis of CBS deficiency. According to this protocol our patient was diagnosed as CBS deficiency.

Cystathionine β-synthase (CBS; EC 4.2.1.22) is pyridoxal phosphate (PLP)-dependent enzyme and catalyzes the condensation of serine and homocysteine to form cystathionine, which is then converted to cysteine. Severity of the untreated enzyme deficiency is determined mostly by the underlying genetic defect. Among 150 mutant alleles described (http://www.uchsc.edu/cbs/cbsdata/cbsmain.htm) missense mutations are the most prevelant ones. It has been proposed that *CBS* mutant enzyme caused by missense mutations may misfold, and this may be responsible for their pathogenicity [6]. We detected homozygous missense mutation c.1046 G>A; p.Ser349Asn for CBS gene in this patient. This mutation was first described in Spanish propands and found to affect evolutionarily conserved residues suggesting that it may impair enzyme function [5]. Further functional assays revealed that p.S349N monomer levels were similar to those of the wild-type, with the absence of any enzyme activity most likely related to the lost tetramerization capacity [7]. Recently in the report of Kozich et al. [8] p.R369C (which was located near to our patient's mutation (p.Ser349Asn), was studied and found to be located in the surface of the active core of CBS tree-dimensional structure, in close interaction with pyridoxal 5-phosphate (PLP).

Turner syndrome is the most common sex chromosome abnormality among females, characterized with total or partial monosomy of the sex chromosome X. It covers a broad spectrum of features, but almost all affected individuals suffer from short stature and ovarian failure. It is mostly discovered in cytogenetic studies performed for advanced maternal age, congenital anomalies, or biochemical screening. Increased nuchal translucency, cystic hygroma, renal and cardiac defects are the typical ultrasonographic findings [9]. 45,X mosaicism almost always results from the loss of a chromosome from a normal disomic fertilization. Prevalence of 45,X mosaicism is greater in live births than in abortuses, suggesting that the prevalence of second line could increase the chances of survival. The presence of congenital defects were found to be statistically lower in 45,X mosaicism (38.1%) than in 45,X cases (63.7%) [10,11]. Furthermore, Hsu et al. [12] reported that the percentage of normal outcome in 45,X mosaicism is low (12.4%) in a series of 265 cases. Prenatal counseling for 45,X mosaicism should take into account the expectation of a milder phenotype. Our patient revealed no sign of Turner syndrome at birth. She was not hydropic but exchange transfusion and IVIG was required for her Rh hemolytic disease.

Both CBS deficiency and Turner syndrome are related with first trimester miscarriages. The miscarriages in the mother of the presented case, were all in the late period of the second trimester. The number of consecutive miscarriages which is not less than 2 occurred within the 16th week of gestation, is determined as recurrent fetal loss. As a result of thrombophilia, the vascular system supporting the placenta comes to harm and this leads to a deficiency of placental functions and development which may cause the loss of the conception product. Also hyperhomocysteinemia damages the vascular endothelium [13]. Probably the miscarriages were a result of Rh hemoltytic disease.

To our knowledge, this is the first case of CBS deficiency together with mosaic Turner Syndrome and immune hydrops fetalis diagnosed by neonatal screening. We would like to mention that CBS deficiency can be diagnosed by screening even in the setting of exchange transfusions and amino acid paper chromotography is a cheap and valuable metabolic screening tool in experienced hands. Since routine newborn screening for many metabolic diseases is currently not practiced in Turkey, all newborns born to families in which previous siblings had died due to unknown cause should be evaluated by amino acid paper chromotography and by other conventional metabolic tests when necessary.

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