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CASE REPORT

BCS1L gene mutation causing GRACILE syndrome: case report

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Abstract

GRACILE syndrome is a rare autosomal recessive disease characterized by fetal growth retardation, Fanconi type aminoaciduria, cholestasis, iron overload, profound lactic acidosis, and early death. It is caused by homozygosity for a missense mutation in the BCS1L gene. The BCS1L gene encodes a chaperone responsible for assembly of respiratory chain complex III. Here we report that a homozygous mutation c.296C > T (p.P99L), in the first exon of BCS1L gene found in an affected 2-month-old boy of asymptomatic consanguineous parents results in GRACILE syndrome. This genotype is associated with a severe clinical presentation. So far no available treatments have changed the fatal course of the disease, and the metabolic disturbance responsible is still not clearly identified. Therefore, providing prenatal diagnosis in families with previous affected infants is of major importance. Mitochondrial disorders are an extremely heterogeneous group of diseases sharing, in common, the fact that they all ultimately impair the function of the mitochondrial respiratory chain. A clinical picture with fetal growth restriction, postnatal lactacidosis, aminoaciduria, hypoglycemia, coagulopathy, elevated liver enzymes, and cholestasis should direct investigations on mitochondrial disorder.

Keywords

Cholestasis, Fanconi type aminoaciduria, growth retardation, iron overload, profound lactic acidosis

History

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Introduction

GRACILE syndrome is a rare autosomal recessive disease characterized by fetal growth retardation, Fanconi type aminoaciduria, cholestasis, iron overload, profound lactic acidosis, and early death.[1] It is caused by homozygosity for a missense mutation in the BCS1L gene.[2] The BCS1L gene encodes a chaperone responsible for an assembly of respiratory chain complex III.[3] Here, we report that a homozygous mutation c.296C > T (p.P99L), in the first exon of BCS1L gene found in an affected 2-month-old boy of asymptomatic consanguineous parents results in GRACILE syndrome. This genotype is associated with a severe clinical presentation.

So far no available treatments have changed the fatal course of the disease, and the metabolic disturbance responsible is still not clearly identified. Therefore, providing prenatal diagnosis in families with previous affected infants is of major importance.[4]

Case report

A 2-month-old boy was referred to our department for growth retardation and elevated liver enzymes. This index case, the sixth child of consanguineous Turkish parents, was born at term following an uncomplicated pregnancy. He was born by normal vaginal delivery with a birth weight of 1985 g. He was presented with intrauterine growth restriction and transient tachypnea of the newborn. He had developed hypoglycemia and severe metabolic acidosis on the first days of life. Physical examination at the time of admission revealed failure to thrive (2140 g < 3 p), microcephaly (33 cm < 3p), and jaundice. Abdominal ultrasonography was normal and blood testing showed conjugated hyperbilirubinemia, treatment resistant metabolic acidosis, and elevated liver enzymes. His aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubins, and alkaline phosphatase (ALP) levels were elevated (AST 340 IU/L, ALT 118 IU/L, ALP 1833 IU/L, total bilirubin 8.6 mg/dL, and direct bilirubin 4.8 mg/dL). Tandem mass spectroscopy revealed elevations of alanine and tyrosine. Urinary organic acid profile showed non-specific mild elevation of dicarboxylic acids. Urinary succinylacetone was not detected and plasma amino acid analysis was remarkable for elevations of tyrosine suggestive of liver dysfunction. Transferrin isoelectric focusing was normal. His venous blood lactate level was elevated (3.8 mmol/L normal level < 2 mmol/L). Magnetic resonance imaging of the brain was normal. An elevated serum concentration of ferritin (1288 ng/mL; nv < 150 ng/mL) was detected. Urine amino acid analysis showed generalized amino aciduria and urine glucotest was positive. Cardiologic examination showed patent foramen ovale. We used formulae enriched with medium-chain triglyceride content and fractional meals with enteral nutrition at night for an adequate nutrition and to prevent hypoglycemia. Subsequently, a homozygous mutation c.296C > T (p.P99L) has been found as the genetic etiology for growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death (GRACILE) syndrome.

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The exons and immediately adjacent intronic regions of the BCS1L gene are PCR amplified and then sequenced in the forward and reverse directions using automated fluorescent dideoxy sequencing methods. This analysis will not detect large heterozygous deletions or duplications, inversions, or mutations within the promoter or deep intronic regions. GenBank (NCBI) NM_004328.4 is used as the reference sequence. An apparently homozygous mutation, c.296C > T (p.P99L), at the first exon of BCS1L gene was detected. The homozygous c.296C > T (p.P99L) mutation has been reported in two unrelated consanguineous families with Complex III deficiency and pathogenicity is supported by functional studies.[5] These molecular results confirmed the clinical diagnosis.

Discussion

We report the clinical and genetic findings of a 2-month-old male of Turkish descent with a homozygous mutation, c.296C > T (p.P99L), in the BCS1L gene. Mitochondrial disorders are an extremely heterogeneous group of diseases sharing in common the fact that they all ultimately impair the function of the mitochondrial respiratory chain. A clinical picture with fetal growth restriction, postnatal lactacidosis, aminoaciduria, hypoglycemia, coagulopathy, elevated liver enzymes, and cholestasis should direct investigations on mitochondrial disorder.[6] The other noticeable laboratory abnormality in this patient was hyperferritinemia. The mitochondrion plays a prominent role in iron metabolism and mitochondrial dysfunction can lead to pathological iron overload.[7]

GRACILE syndrome is a metabolic disorder with an autosomal recessive mode of inheritance. The disease is dominated by growth retardation, tubulopathy, cholestasis, iron overload, lactacidosis, early death, and there are no dysmorphic or neurological signs. More than 20 pathogenic human mutations have been reported in BCS1L. All mutations of BCS1L disrupt the assembly of Complex III.[8] So far it has been described mostly in newborn infants with parents of Finnish origin, and the incidence is approximately 1:50,000 in Finland.[9] Awareness of this disease is important and suspected cases should be studied using chromosomal markers flanking the critical region. Despite intensive care and alkali therapy, about half of the infants die during the first days of life, and the remainder within four months of life.[3,4,6] In conclusion, diagnostic work-up of neonatal liver disorder should include assessment of function and structure of the complexes as well as mutation screening for known genes.[2–4]

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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