

Transient neonatal diabetes with fanconi bickel syndrome

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Abstract

Fanconi-Bickel Syndrome (FBS) is a rare glycogen storage disease (GSD) characterized by hepatomegaly, proximal renal tubular acidosis (RTA), hepatorenal glucogen accumulation and marked growth retardation. Transient diabetes is rarely reported with FBS. We describe a patient with FBS diagnosed by diabetes findings and identification of a mutation in Glucose transporter-2 (GLUT2). A male infant, from a consanguineous marriage, presented with hyperglycemia and urinary system infections at 59 days and was given insulin therapy. At age 3 months, insulin was discontinued. In conclusion, neonatal diabetes may be the first presentation of infants with FBS.

Keywords: Monogenic diabetes, GLUT-2, glucosuria

Introduction

Fanconi-Bickel glycogenosis (FBG) is a rare glycogen storage disease manifested by postprandial hyperglycemia, with fasting hypoglycemia, hypergalactosemia, proximal tubular acidosis and hepatorenal glucose accumulation [1,2]. Fewer than 200 cases have been documented in the literature. During the first few months of life initial findings include failure to thrive, polyuria and rickets related to proximal tubular leakage. FBG has an autosomal recessive trait and is caused by homozygous or compound heterozygous mutations in the *SLC2A2* gene (3q26.2-q27) [2]. Several cases of FBG have been detected through neonatal screening of galactose levels [3]. Diagnosis can be confirmed by identification of a mutation in the *SLC2A2* gene. A molecular defect has been identified in the GLUT-2 gene which encodes the facilitative glucose transporter expressed in liver, kidney, intestine and pancreatic islet cells. Neonatal diabetes is a rare presentation of FBS [1-3].

Case Report A 59-day-old male patient was hospitalized with a diagnosis of urinary tract infection. During hospitalization, he was monitored by the endocrinology department because of his elevated glucose levels. The patient was the second child of closely-related parents and was born by cesarean section at 41 weeks, his birth weight being 3340 g. There were no characteristic findings in his history, except for jaundice. Family history revealed that the mother had undergone six pregnancies and had miscarried four times, and that a 4-

year-old brother had mental motor retardation and seizures from the age of 2 years. At the time of hospitalization, our patient's weight was 4920 g and height 54 cm. There were no dysmorphic findings, and he was not dehydrated. He had good feeding and active reflexes. Mild hepatomegaly was detected. Laboratory findings are shown in Table 1. Urinary tract infection was detected. Blood glucose levels increased to 418 mg/dl during monitoring. C-peptide levels investigated when his blood glucose level was 307 mg/dl were 0.476 (IU/ml) and insulin was 3.54 (MU/L). The patient was diagnosed with neonatal diabetes and was started on NPH insulin therapy at a dose of 0.5 U/kg per day. The parents' glucose metabolisms were assessed, and no pathological finding was determined. On the 8th day of therapy, the patient's blood glucose levels decreased to 20 mg/dl, and insulin was discontinued. No further insulin requirement was observed during follow-up. Despite blood glucose levels being normal, glucosuria persisted at urine tests. Hepatic enzymes, which were moderately elevated on admission, had gradually increased to higher levels (Table 1). There was no direct hyperbilirubinemia. Alpha-1 antitrypsin levels were normal, and viral serology was negative.

Based on the clinical and laboratory findings, including transient neonatal diabetes, persistent renal glycosuria and elevated liver enzymes, a presumptive diagnosis of FBS was made. Sequence analysis of the *SLC2A2* gene revealed homozygous p E 279fs mutation, confirming a diagnosis of FBS.

The patient's mother and father were identified as carriers of the same mutation. Reducing substances in urine were positive, and massive dibasic aminoaciduria was determined. Blood galactose levels were also very high.

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Sufficient weight gain was not achieved following discharge. Compensated acidosis was determined in blood gas, and the patient was started on Scholl solution. Before treatment, calcium was measured at 10 mg/dl, phosphorus at 3.78 mg/dl, alkaline phosphatase at 476 U/L and tubular P reabsorption at 93%. The patient was placed on a galactose-free diet.

At 2-month follow-up at the age of 2 years, weight gain was good but height was short. The patient received Scholl solution and phosphate replacement, but compensated metabolic acidosis persisted.

Table 1. Laboratory parameters

	16.5.2014	20.9.2014	20.4.2016
AST(U/L)(0-50)	189	130	50
ALT(U/L)(0-50)	37	238	64
Blood sugar (mg/dl) (65-100)	230-340	120	68
C peptide(iu/ml) (0.8-3.8)	0.4	-	-
Insulin (mU/L) (3-25)	3.54	<2	-
TIT	+3 glucose +2 protein Ketone negative	+4 glucose +1 protein Ketone +positive	+4 glucose +1 protein Ketone +positive
Ca (mg/dl)(8.2-10.5)	9	10	10.3
P(mg/dl)(2.4-5.8)	-	5.2	3.54
ALP(U/L)(0-300)	-	620	
Blood gas pH (7.35-7.45)	7.42	7.40	7.40
HCO ₃ (mmol/l) (22-26)	22	18	17
HbA1c (%)	0.2 (due to fetal Hemoglobin)	5.7	5

Discussion

FBS is a rare cause of neonatal diabetes and must be investigated in cases of transient neonatal diabetes with persistent glucosuria after other causes have been excluded [2]. Our patient had been diagnosed with neonatal diabetes at the age of 2 months, and this syndrome was suspected due to persistent glucosuria while blood sugar levels were normal. The relevant molecular defect was detected in GLUT-2.

GLUT-2 is a glucose transporter protein first described in 1998. The encoding gene, SLC2A2 is located in the 3q26.1-q26.3 locus. GLUT-2 is localized in the pancreas, kidneys, liver, neurons and enterocytes [2,4]. It is responsible for glucose transport to glucose-sensitive beta cells in rats.

Genome-wide association studies have reported that GLUT-2 variants increase the risks of fasting hyperglycemia, transition to type 2 diabetes, hypercholesterolemia and cardiovascular diseases. GLUT-2 (also known as Slc2a2)-expressing neurons can be activated by hypoglycemia to stimulate glucagon secretion [5].

GLUT-1 and GLUT3 may play an important role in facilitating glucose transportation into human beta cells. More than 40 mutations have been identified to date in SLC2A2. The type of diabetes occurring with homozygous recessive inactive mutations is milder than that occurring with biallelic inactivation in SLC2A2 [2].

GLUT-1 receptors are present in beta cells at a level of up to 90% after the 20th week of gestation, while GLUT-2 receptors are present at a level of 10-20%. However,

GLUT-2 is less effective in glucose-sensitive insulin release in humans. Neonatal diabetes does not occur in association with GLUT-1 mutations [3]. Since GLUT-2 is responsible for glucose and galactose transport, elevation may be observed in blood sugar and galactose in this syndrome. Hyperglycemia is also associated with insulin secretion defect.

GLUT-2 facilitates insulin secretion, although the mechanism involved is unclear. In the absence of functional GLUT-2, failure of an as yet unclear signalling cascade may cause impaired insulin secretion and a structural defect in GLUT-2 protein. This all helps explain the particularly transient nature of neonatal diabetes.

As our case shows, GLUT-2 plays an important role in insulin secretion and in human beta cells through interaction with other transporters. There are defects in the hepatic galactose transporter, not only glucose. Impaired utilization of glucose and galactose is another mechanism for explaining FBS pathological findings [6]. Blood galactose levels in our case were considerably above normal, while GALT activity was normal and increased amino acid (dibasic aminoaciduria) expulsion was present in urine. The patient was therefore started on lactose-free baby food.

Neonatal diabetes is observed in only 4% of cases of FBS, not in all. No genotype-phenotype relation has been determined to date. GLUT-1 and -3 being expressed at greater levels than GLUT-2. This condition may perhaps compensate for the rise blood glucose [2]. The rate-limiting step in insulin secretion is not glucose transport, but glucose phosphorylation. Gradual resolution of diabetes may be attributed to an increase in insulin

solution. Indeed, diabetes can be masked with non-pancreatic mechanisms in such a way that intense glucosuria is effective in reducing blood glucose levels [3-6].

What is rare and makes our case of particular interest is that it is the first pathology neonatal diabetes with a pathology of high blood sugar and low c-peptide levels without FBS symptoms and a clinical picture GLUT2 mutations have been shown to be a determinant of insulin secretion. Indeed, in cases of the transcription factor disorder HNF1A-related MODY, mutation in this gene leads to changes in GLUT-2 protein expression. GLUT-2 protein defects can lead to diabetes in the neonatal period and are also responsible for the appearance of clinical manifestations of MODY [7].

To date, six cases of FBS manifesting with neonatal diabetes have been reported. One was reported in 2002 by Yoo et al. [3] and five in 2012 by Sansbury et al [2]. This glycogen storage disease caused by mutations in SLC2A associated with neonatal diabetes has been determined in several cases of FBS to date, the condition generally resolving spontaneously after 18 months [3]. Identification of genetic etiology guides physicians in terms of prognosis, family screening and choice of drugs.

This case is reported since the syndrome, which exhibits a broad clinical and prognostic spectrum, presented as neonatal diabetes. FBS should be considered as a cause of neonatal diabetes, particularly when the parents are consanguineous, diabetes is transient and glucosuria is

persistent. Diagnosis of mutations leading to monogenic diabetes will increase with advanced genetic analyses, and more information will be elicited concerning the pancreatic beta cell and its functions and insulin secretion.

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