Transient Neonatal Diabetes as a Presentation of Fanconi- Bickel Syndrome

Aria Setoodeh1,2 and Ali Rabbani1,2

1 Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran
2 Department of Pediatric Endocrinology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

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Abstract- Fanconi- Bickel Syndrome (FBS) is a rare type of glycogen storage disease (GSD) characterized by hepatomegaly, proximal renal tubular acidosis (RTA) and marked growth retardation. We report a case of FBS presenting with diabetic ketoacidosis and transient neonatal diabetes. A female infant, product of consanguineous marriage presented with diabetic ketoacidosis at age 33 days, and was treated as neonatal diabetes with insulin. At age 14 months, insulin was discontinued. She presented with short stature, hepatomegaly, RTA and hypophosphatemic rickets at age 4 and (FBS) was diagnosed. Diagnosis was confirmed by mutation analysis, showing mutation in SLC2A2 gene. In conclusion: neonatal diabetes or diabetic ketoacidosis may be the first presentation of infants with FBS.

Keywords: Fanconi Bickel syndrome; Hypophosphatemic rickets; Neonatal diabetes; Severe short stature

Introduction

FBS also classified as glycogen storage disease type X1, is an autosomal recessive disease, identified by a mutation in Glut-2 gene of hepatocyte, B cell of pancreas and renal tubules, with now more than 110 cases has been published in literature (1). These patients mostly present with hepatomegaly, severe growth retardation, fasting ketotic hypoglycemia, post prandial hyperglycemia and hypophosphatemic rickets.

Case Report

The patient is an 8.5 years old girl, product of a consanguineous marriage, full term, was delivered by elective cesarean section with birth weight: 2050 g, length: 45 cm and H.C:33cm. she presented with poor feeding, fever, and irritability in 33 days of life. At the time of admission growth parameters were as follows: weight: 2700gr length: 46cm and head circumference: 34 cm. patients was ill, dehydrated, and tachypnic. Lab data was as follows: blood sugar: 519 mg/dl, VBG: PH 7.24, CO3H 5.2, PCO2 12.4, Urine ketone 2⁺. She was treated with the impression of neonatal diabetes, and was discharged in good condition on 3 units of NPH daily divided in 2 doses. In her follow up, developed few episodes of hypoglycemia and insulin was titrated and eventually discontinued at age of 14 months.

With normal sugars and normal development, she presented with severe short stature (SDS: -5.5) at age 4 years, and was put on growth hormone injections 0.1 unit/kg/day.

After 3 months of injection, hepatomegaly was detected, and she was referred to hospital for further work up. At her second admission growth parameters were as follows: weight 12.5kg, height 81cm, head circumference 46.5cm, BMI 19.5. She had hepatomegaly 5 cm below right costal margin (BMR), No splenomegaly. At the time of admission, lab data were as follows: blood sugar 131mg/dl, ALT 182 IU/L (NL:upto49), AST 70 IU/L(upto46), lactate 19mg/dl (NL2-20), cholesterol 170 mg/dl(120-220), Triglyceride 268 mg/dl (40-140), albumin 4.3 g (3.5-5.2), Calcium 9.7 mg/dl, P 3 mg/dl, alkaline phosphatase 2203 IU/l (180-1200), tyrosine 1.4 mg/dl (up to 2), VBG: pH 7.34, CO2H 16.1, PCO2 29.9, PT 13 sec(13), INR 1, PTT 30, sec (30-40),

Urine

Specific gravity 1035, PH 7, Prot 2+, sugars 3+, fractional excretion of phosphate 30%. In sonography: she had normal kidneys, and spleen, liver span 118mm with normal echo.
Bone age was 18 months, and signs of rickets were seen in hand X-ray. Liver biopsy was suggestive of glycogen storage disease. With the clinical impression of FBS, she was treated with phosphate Sandoz® tablets, At 10 drops and Schohl’s solution. Now at 8 years of age she has had complete recovery of rickets, size of liver decreased to 4 cm BRCM, she has NL AST, ALT and height SDS has improved to -3. For confirmation of diagnosis, molecular study was done, and sequencing analysis, showed her to be homozygous for a splicing mutation C.963+1 G>A, in intron 7 of the SLC2A2 gene, resulting in aberrant splicing.

**Discussion**

Fanconi–Bickel syndrome, (OMIM, 227810) is a rare inherited disease. FBS was first described by Guido Fanconi and Horst Bickel in 1949 (2). The first patient,
Transient neonatal diabetes

Claudio presented with failure to thrive, polydipsia, and constipation at 6 months of age. At age 2.8 years he had severe short stature (-6 SDS), also rickets and hepatomegaly and liver histology showed steatosis and increased amount of glycogen.

But fasting hypoglycemia and post prandial hyperglycemia was detected. He has been alive till (1997), at 52 years of age with severe short stature (140cm) hepatomegaly 10 cm below right costal margin (3).

In 1988, Fokumoto et al. (4) isolated glucose. Transporter 2 from adult human liver and kidney and localized the gene to chromosome 3q26.1-q26.3 and suggested a role for this glucose transported in glucose sensing by β-cells. The pathophysiological model of the disease was described by Santer et al. (3) molecular gene as assay was first done.

Molecular genetic assay was first done in 1997, by Santer et al, who described the basic defect was homozygous mutations in glucose transporter 2 (GLUT 2) (3). This gene is located in hepatocytes, renal tubules, enterocytes and B cells of pancreas, accounting for the involvement of these organs. All causative genetic defects reported to date have been within the SLC2A2 (GLUT2) gene on chromosome 3q26. About 40 likely causative mutations in this gene have been reported to date (4).

Since then, more than 110 cases from 88 families have been described world wide (3).

Most of the patient presented with growth retardation hepatomegaly, RTA and hypophostaeemic rickets (6-10).

Though postprandial hypoglycemia has been reported in several cases (5-6), our case is very interesting in her presentation with DKA and neonatal diabetes, followed by hepatome galy and rickets at age 4 and FBS was diagnosed at that time and molecular study showed mutation in SLC2A2gene.

She is being treated with phosphate supplement, AT 10 drops, and Schohl's solution. Because of severe short stature she has been one growth hormone injection since 4 years of age, improving the height SDS from -5.5 to -3 (Figure 1).

The prognosis for this disease is not grave, with adequate medical management they can live in to adulthood, and hepatomegaly regresses after puberty.

Recently a case report of successful pregnancy was published in 31 years old case of FBS delivering a healthy boy (11). In conclusion, neonatal diabetes and DKA in new born or infancy period may be a rare manifestation of FBS and these patients must be under close observation for growth velocity, hepatomegaly, and hypophosphatemic rickets which may be detected later in the course of the disease.

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References