

Fanconi-Bickel syndrome in three Turkish patients with different homozygous mutations

İnci Nur Saltık-Temizel¹, Turgay Coşkun², Aysel Yüce¹, Nurten Koçak¹

Sections of ¹Gastroenterology, Hepatology and Nutrition and ²Nutrition and Metabolism, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Saltık-Temizel İN, Coşkun T, Yüce A, Koçak N. Fanconi-Bickel syndrome in three Turkish patients with different homozygous mutations. Turk J Pediatr 2005; 47: 167-169.

Three Turkish patients with Fanconi-Bickel syndrome are presented. Prominent clinical findings of patients included hepatomegaly, growth retardation, hypoglycemia, characteristic tubular nephropathy, and rickets. Each patient had a different homozygous mutation of glucose transporter 2 (GLUT2) gene.

Key words: Fanconi-Bickel syndrome, glycogenosis, mutation analysis.

Fanconi-Bickel syndrome (FBS) is an autosomal recessive disorder of carbohydrate metabolism characterized by hepatorenal glycogen accumulation, Fanconi nephropathy, and impaired utilization of glucose and galactose. Clinical signs as originally described by Fanconi and Bickel are hepatomegaly secondary to glycogen accumulation, fasting hypoglycemia, a characteristic tubular nephropathy, rickets, and markedly stunted growth¹. Santer et al.² described the basic defect of this disease within the gene of glucose transporter 2 (SLC2A2, also referred to as GLUT2), which encodes a facilitative glucose transporter expressed in the liver, kidney, intestine, and pancreatic islet cells. Since then, many mutations have been reported²⁻⁵. Here we report three Turkish children with FBS who had three different homozygous mutations.

Case Reports

Case 1

A first child of consanguineous parents presented with growth retardation and hepatomegaly at the age of 10 months. He was born at term weighing 2,600 g after an uncomplicated pregnancy and delivery. On admission his weight, length and head circumferences were below the 3rd percentile. The liver had a soft consistency, and was palpable 6 cm below the right costal margin. He also had clinical manifestations of rickets. On laboratory investigations, glucosuria and

generalized aminoaciduria were observed. Complete blood count and smear were unremarkable. Serum concentrations of liver aminotransferases were high: aspartate aminotransferase (AST) 80 IU/L; alanine aminotransferase (ALT) 73 IU/L. Serum calcium level was normal (9.2 mg/dl) and phosphorus was below the normal range (2 mg/dl, normal 2.7-4.5). Serum levels of triglycerides (879 mg/dl) and cholesterol (203 mg/dl) were elevated. Skeletal roentgenograms revealed findings typical of rickets. Abdominal ultrasonography showed hepatomegaly and bilateral nephrocalcinosis. Liver biopsy revealed findings compatible with glycogen storage disease. Liver glycogen content was high (18.2% of wet tissue weight, normal <7%) with normal enzyme activity for glucose 6-phosphatase (5 nmol/Pi/h/mg protein, normal 5-7). The clinical diagnosis of FBS was confirmed by DNA analysis showing a homozygous 783del17 mutation of the GLUT2 gene; both parents were heterozygous carriers of this mutation. The patient was treated symptomatically with active vitamin D, phosphorus, oral alkaline solution and uncooked cornstarch. He has been followed to date up to 3.5 years of age and still has growth retardation and other findings of FBS.

Case 2

Clinical findings of patient 2 with the diagnosis of GSD with tubular dysfunction were reported elsewhere⁶. She was admitted to the hospital for evaluation of growth retardation at the age

of four months. She had consanguineous parents. On physical examination, growth retardation, a doll-like face, and clinical manifestations of rickets were observed. The liver was soft on palpation and measured 3 cm below the right costal margin. Laboratory examinations revealed glucosuria, generalized aminoaciduria, hypoglycemia. Metabolic acidosis, and a trace of proteinuria. Serum total lipid (840 mg/dl) and cholesterol (242 mg/dl) levels were elevated. Blood lactate level was high. A liver biopsy revealed palely stained swollen hepatocytes, compatible with glycogenesis. She was given neutral phosphorus solution, oral alkaline solution, vitamin D and uncooked cornstarch. At the age of nine years, glycogen content was found high (13% of wet tissue weight) and enzyme activity for glucose-6-phosphatase was normal (18.4 nmolPi/h/mg protein). Glucosuria, aminoaciduria and proteinuria persisted. Serum calcium was 10.6 mg/dl and phosphorus was 2.3 mg/dl. Serum transaminases were high (ALT 82 IU/L and AST 78 IU/L). DNA analysis revealed a

markedly elevated alkaline phosphatase (8300 IU/L) on laboratory examination. X-ray of the wrist showed active rickets. Galactosemia was ruled out and idiopathic Fanconi syndrome was diagnosed. She has been followed to date up to 4.5 years of age and treated symptomatically. Family history revealed that a sibling died at the age of four years with hepatomegaly, rickets, and metabolic acidosis. A liver biopsy was performed at the age of 4.5 years and revealed swollen and vacuolated hepatocytes consistent with glycogenesis. Glycogen content of the liver was high (11.6% of wet tissue weight) and glucose-6-phosphatase enzyme activity was normal (5 nmolPi/h/mg protein). After clinical diagnosis of FBS, sequencing of the GLUT2 gene was performed. A splice site mutation (IVS 5+1 g>t) at the transition of exon 5 to intron 5 was found. The patient was treated symptomatically with active vitamin D, phosphorus, oral alkaline solution and uncooked cornstarch.

The clinical and laboratory findings and detected mutations of patients are shown in Table I.

Table I. The Clinical and Laboratory Findings and Detected Mutations of Patients

	Patient 1	Patient 2	Patient 3
Age of admission/gender	10 months/M	4 months/F	2 months/F
Hepatomegaly (cm)	+(6)	+(3)	+(3)
Findings of rickets	+	+	+
Liver glycogen content (Normal: <7% of wet tissue weight)	18.2	13	11.6
Glucose-6-phosphatase activity (Normal: 5-7 nmolPi/h/mg protein)	5	18.4	5
Mutation in the GLUT2 gene (all homozygous mutations)	783del17	818C>G	IVS5+1 g>t

homozygous nonsense mutation (818C>G) of the GLUT2 gene and, as expected, both parents were heterozygous carriers of this mutation. She has been followed with uncooked cornstarch, frequent feedings and supplemental therapy with neutral phosphorus solution, oral alkaline solution, and vitamin D.

Cases 3

A four-year-old girl born to consanguineous parents was admitted for evaluation of hepatomegaly and idiopathic Fanconi syndrome. At the age of two months, she had hepatomegaly measured 3 cm below the right costal margin on physical examination and generalized aminoaciduria, galactosuria, hypophosphatemia (1.7 mg/dl) with normal serum calcium level and

Discussion

Fanconi-Bickel syndrome is a rare autosomal recessive disorder of carbohydrate metabolism. Clinical findings of hyperglycemia and hypergalactosemia in the fed state, hypoglycemia during fasting and Fanconi nephropathy with severe glucosuria are compatible with a functional loss of the glucose transporter 2 (GLUT2) protein. This protein is present in the plasma membranes of pancreatic β cells, hepatocytes, and intestinal and renal absorptive epithelial cells¹. Although the GLUT2 gene has been cloned and mapped to chromosome 3q26.1-26.3, the mechanism by which GLUT2 gene mutations lead to FBS is still unclear⁷. Since the first report of mutations in the GLUT2 gene², more than 30 different mutations have been

identified, and most of the reported mutations are private and confined to a single family³⁻⁵. We have reported three patients who have characteristic findings of FBS and have homozygous mutations of the GLUT2 gene. There are also patients reported who have clinical findings of FBS; however, no mutations are detected in the protein-coding region of the GLUT2 gene^{5,8}. Sakamoto et al.³ suggested the possibility that some GLUT2 mutations may cause the dominant form of familial glucosuria. Yoo et al.⁴ described a patient with FBS presenting with neonatal diabetes mellitus and galactosemia, and they suggested that severe clinical presentation and poor prognosis may be correlated with patient's genotype. Further studies are thus needed to identify, a genotype-phenotype correlation in FBS, if one exists. Similar to that seen in our patients, the first symptoms of FBS are fever, vomiting, growth failure, and hypophosphatemic rickets at the age of 3-10 months. Later, patients presented with short stature, hepatomegaly and moon-shaped face¹. These clinical findings of FBS are similar to the glycogen storage disease (GSD) type 1. Tubular dysfunction is also a finding of GSD type 1⁹, and differential diagnosis should be done by glucose-6-phosphatase enzyme study, which is normal in FBS patients. All our patients had normal glucose-6-phosphatase enzyme activity. There is no causal therapy for FBS. Alkalinization with Shohl or bicarbonate solutions; supplementation of vitamin D and phosphate; a diabetes mellitus-like diet, presented in frequent meals with adequate caloric intake; and uncooked cornstarch are the recommended symptomatic treatments¹, and all were given to our patients.

In conclusion, FBS should be born in mind in patients presenting with hepatomegaly and tubular dysfunction. The diagnosis of FBS can be confirmed by mutation analysis of the GLUT2 gene.

Acknowledgement

The authors thank Dr. R. Santer for studying the mutation analysis of the patients.

REFERENCES

1. Santer R, Schneppenheim R, Suter D, Schaub J, Steinmann B. Fanconi-Bickel syndrome the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature. *Eur J Pediatr* 1998; 157: 783-797.
2. Santer R, Schneppenheim R, Dombrowski A, Gotze H, Steinmann B, Schaub J. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. *Nat Genet* 1997; 17: 324-326.
3. Sakamoto O, Ogawa E, Ohura T, et al. Mutation analysis of the GLUT2 gene in patients with Fanconi-Bickel syndrome. *Pediatr Res* 2000; 48: 586-589.
4. Yoo HW, Shin YL, Seo EJ, Kim GH. Identification of a novel mutation in the GLUT2 gene in a patient with Fanconi-Bickel syndrome presenting with neonatal diabetes mellitus and galactosemia. *Eur J Pediatr* 2002; 161: 351-353.
5. Santer R, Groth S, Kinner M, et al. The mutation spectrum of the facilitative glucose transporter gene SLC2A2 (GLUT2) in patients with Fanconi-Bickel syndrome. *Hum Genet* 2002; 110: 21-29.
6. Yüce A, Coşkun T, Koçak N, Özsoylu Ş, Özalp İ, Göğüş S. Type 1 glycogenosis with renal tubular dysfunction (presentation of two cases). *Turk J Pediatr* 1993; 35: 201-204.
7. Fukumoto H, Seino S, Imura H, et al. Sequence, tissue distribution, and chromosomal localization of mRNA encoding a human glucose transporter-like protein. *Proc Natl Acad Sci* 1988; 85: 5434-5438.
8. Özer EA, Aksu N, Uclar E, et al. No mutation in the SLC2A2 (GLUT2) gene in a Turkish infant with Fanconi-Bickel syndrome. *Pediatr Nephrol* 2003; 18: 397-398.
9. Chen YT, Coleman RA, Scheinman JI, Kolbeck PC, Sidbury JB. Renal disease in type 1 glycogen storage disease. *N Engl J Med* 1988; 318: 7-11.