

Fanconi-Bickel syndrome versus osteogenesis imperfecta: An Iranian case with a novel mutation in glucose transporter 2 gene, and review of literature

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Fanconi-Bickel syndrome is an extremely rare hereditary metabolic disease, characterized by hepatomegaly due to glycogen storage, refractory hypophosphatemic rickets, marked growth retardation and proximal renal tubular acidosis. Recurrent bone fractures are one of the hallmark findings. It is a single gene disorder; the responsible gene belongs to the facilitative glucose transporters 2 (GLUT2) family gene or (SLC2A2) mapped to the q26.1-26.3 locus on chromosome 3, and encodes the GLUT protein 2. This protein is expressed in pancreatic β -cells, hepatocytes, renal tubules, and intestinal mucosa. Several mutations in the GLUT2 gene have been reported in different ethnicities. Herein we report an Iranian girl with a missed diagnosis of osteogenesis imperfecta. She was referred with the history of frequent fractures, and severe motor delay and was suspected to osteogenesis imperfecta. Following the case we detected refractory rickets instead of OI, severe growth failure, proximal renal tubulopathy and RTA, and enlarged kidneys, progressive hepatomegaly, and GSD on liver biopsy. Glucose and galactose tolerance tests confirmed abnormal carbohydrate metabolism. Molecular analysis on GLUT2 gene revealed a homozygous novel mutation in exon 5; it was 15 nucleotide deletion and 7 nucleotide insertion and caused a frame shift mutation, produced a premature truncated protein (P.A229QFsX19). This mutation has not been reported before in the relevant literature.

Key words: Fanconi-Bickel syndrome, glucose transporter 2 gene, Iranian novel mutation, missed diagnosis of osteogenesis imperfecta

Introduction

Fanconi-Bickel syndrome (FBS) is a rare metabolic disorder of carbohydrate metabolism with autosomal recessive mode of inheritance. It is characterized by hepatorenal glycogenosis, proximal renal tubular dysfunction, impaired utilization of glucose and galactose, and hypophosphatemic vitamin D dependent rickets with severe growth retardation.^[1-3] There is no evidence for underlying enzymatic defect in carbohydrate metabolism. Primary defect of monosaccharide transport across the membranes had been postulated.^[3-5] Use of the term glycogenosis type XI introduced by Hug is to be discouraged,^[6] because glycogen accumulation is not due to the proposed functional defect of phosphoglucomutase, an essential enzyme in the common degradative pathways of both glycogen and galactose, but is secondary to non-functional GLUT.

FBS is a single gene disease and is caused by defects in the facilitative glucose transporter 2 (GLUT2) gene or (SLC2A2).^[7] The gene was localized to human chromosome 3q26.1-26.3.^[7,8] It consists of 11 exons and 10 introns spanning approximately 30 kb.^[9] GLUT2 gene encodes for the GLUT protein 2, and expressed in basolateral side of enterocytes, hepatocytes, pancreatic beta-cells, and renal tubular cells.^[1,10] Since the first report of molecular assay in the GLUT2 gene, more than 30 different mutations have been identified, and most of the reported mutations are private and was belong to a

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10.4103/0971-6866.112906

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single family.^[11] Here we report an unusual Iranian FBS case due to a novel mutation in GLUT2 gene that has not been described before.

Case Report

AA is a 3.5-year-old Iranian girl, referred to the genetic clinic for cyclic pamidronate therapy with the diagnosis of osteogenesis imperfecta. She was the first and the only child of the family, product of an uneventful normal pregnancy and was delivered by C/S. BW was 2600 g and height 49 cm. Main symptoms was growth failure, severe bone pain, inability to stand and walk, and history of several bone fractures from about age 2 year. In the second admission for pamidronate treatment, her clinical and radiologic findings were re-evaluated. All the findings were in favor of hypo-phosphatemic resistant rickets. Ca 9.3 mg/dl, P 2.5 mg/dl, Alk. Phosphatase was markedly elevated 1100 IU/L, PTH was 72 pg/mL (mildly elevated) and 25(OH) vitamin D 180 ng/mL (normal range 7.5-75). We were not able to test 1,25 (OH) 2 vitamin D. There was not any clue for hepatic or renal involvement at that time. Cyclic pamidronate therapy was discontinued, and we administered rocartrol, Ca syrup, phosphate as jouli solution. She began to stand and walk after 3 month treatment. In the age of 4 years and 2 month we noticed on enlarged liver, confirmed by sonography, however, the size and shape of spleen, kidneys, and pancreas were reported as normal. Biochemical analysis for thyroid and renal functions, as well as routine analyses and serum electrolytes all were within normal limits. CBC was normal, but SGOT 155 IU/L (NL 0-46) and SGPT 206 IU/L (NL 0-49) respectively (they were strongly elevated). Serum total protein was 7.5 g, 65% of it was albumin, α 1 and β -globulins were normal, γ -globulin was decreased, but α 2 globulin was increased. Because of progressive liver enlargement we checked again liver function tests along with biochemical markers for Tyrosinemia, Wilson's disease, Galactosemia, and α -1-antitrypsin deficiency, all of the results were WNL. Ophthalmologic evaluation did not show cataract. Liver biopsy has been done and showed marked glycogen storage in hepatocytes (GSD).

One year later (when she was 4.5-years-old), we detected 4+ glucosuria, and trace protein in the urine. Measurement of abnormal metabolites excretion in

the urine showed glycosuria, phosphaturia, calciuria, uricosuria, and aminoaciduria. In renal ultrasound both of the were enlarged. Fasting hypoglycemia was (51 mg/dL), and on GTT, blood glucoses were 157, 199, and 248 respectively. Arterial blood gasses analysis revealed metabolic acidosis (pH, 7.318; bicarbonate 12.7 mmol/L). Urine pH was 5.0 (normal: 4.5-8), we put the cardinal findings together;

- Hypophosphatemic resistant rickets,
- Hepatomegaly due to glycogen storage and,
- Renal tubulopathy with the finding for Fanconi syndrome, FBS instead of osteogenesis imperfecta was suggested strongly.

With this impression, all coding exons, including flanking introns in the GLUT2 gene, were amplified by polymerase chain reaction (PCR) from genomic DNA. The PCR products were directly sequenced, and we found a novel mutation in GLUT2 gene, (c. 685_701 del GCCATCCTTCAGTCTCT ins CAGAAAA). It was a homozygous deletion-insertion mutation in exon 5. This mutation has not been reported before, however, due to the fact that it results in a frameshift mutation and premature termination of translation (p.A229 QfsX19), this indeed is a disease causing mutation.

Discussion

FBS is a rare autosomal recessive disease. The disorder has been reported in all ethnic groups all over the world. The exact prevalence of disease is not known, but consanguinity is a predisposing factor.^[1-2] Clinical characteristics of disease are a combination of hypophosphatemic refractory rickets, renal tubulopathy, and hepatomegaly due to glycogen accumulation in the hepatocytes. The patient is reported here had been referred to us because of frequent fractures with the diagnosis of osteogenesis imperfecta. The main presenting symptoms (osteoporosis and fractures) were due to severe resistant rickets. There were no hepatic and renal involvement at the beginning, and it was may be the reason of misdiagnosis. By following the case for a while gradually the phenotype was fully presented clinically.

The underlying pathophysiologic mechanism is a

primary defect of monosaccharide transport across the cell membranes, due to mutation in GLUT2 gene, one of the facilitative GLUT family members. In the last decade, many mutations in this gene have been described for FBS. In 1997, Santer *et al.*^[7] described homozygous mutations within the gene of the GLUT2 in four patients. These mutations represented the first detection of a congenital defect within a whole family of membrane proteins, which are the facilitative GLUT-solute carrier family 2; SLC2A2. Later, Santer *et al.*^[11] reported a total of 109 cases from 88 families worldwide who had been diagnosed as FBS. They reported their results of mutation analysis in 49 patients from 39 families from Turkey, Europe, the Near East, North Africa, and North America. Homozygosity or compound heterozygosity for GLUT2 mutations was found in 49 patients in these cases, and 23 novel mutations of the GLUT2 gene were detected. These mutations were scattered over the whole coding sequence of the GLUT2 gene and mutations have been found in all exons. None of these mutations was particularly frequent, which makes molecular genetic diagnosis laborious and difficult. It is interesting that most of the GLUT2 mutations were private and confined to a single family. None of these patients were Iranian. To our knowledge, this patient is the first and the only diagnosed Iranian case that is confirmed by mutation analysis. The mutation in this patient is novel and not previously reported in the literature. Now our patient is 9-year-old, by treatment with cornstarch, Rocartrol, and parenteral GH the symptoms are under satisfactory control.

Acknowledgments

The authors kindly thank the family for their co-operation on very long follow-up evaluation and Prof. Rene Santer for his very sincere help on mutation analysis of the case.

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Cite this article as: Hadipour F, Sarkheil P, Noruzinia M, Hadipour Z, Baghdadi T, Shafeghati Y. Fanconi-Bickel syndrome versus osteogenesis imperfecta: An Iranian case with a novel mutation in glucose transporter 2 gene, and review of literature. *Indian J Hum Genet* 2013;19:84-6.

Source of Support: Nil, **Conflict of Interest:** None declared.