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Case Report

Fanconi – Bickel Syndrome – two cases report

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Abstract

A one year eight month old male child and his nine month old female sibling were presented with Growth retardation, abdominal distension, doll-like faces, hepatomegaly, phosphaturia, proximal renal tubular dysfunction. The elder sibling also presented with glucosuria, hyperglycemia, hypoinsulinemia. The younger one later presented with galactosemia. Biopsy of liver on these two patients revealed the accumulation of glycogen in hepatocytes.

Key words: Fanconi- Bickel syndrome, glucosuria, phosphaturia, glycogenosis.

Introduction

FBS is known from 1949 as Hepato Renal glycogenosis, with proximal renal tubular alteration characterized by glucosuria. Within the classification of glycogenosis FBS is denominated as type XI. From the description made by Fanconi,[1] until now a little more than 100 cases were published in the world literature.[2]

An Autosomal Recessive Disease due to an enzymatic defect which has been not yet identified. A pathogenic mutation in GLUT- 2 gene of hepatocytes, β cells of pancreas and renal tubules, was discovered in 1997. This disorder is characterized by growth retardation, rickets, hepatomegaly due to hepatic accumulation of glycogen, may also present as fasting ketotic hypoglycemia, followed by postprandial hyperglycemia, during this stage there is also hypoinsulinism due to the altered sensitivity of β cells of pancreas to glucose. Due to the consequence of proximal renal tubular dysfunction, they also present hypophosphatemia and rickets.[2]

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Case report

Case 1

A one year eight month old male child who is first born of non consanguineous parents of 21 year old both, native of Caborca, Sonora. Parents are apparently healthy. However, maternal grandmother family has consanguinity.

This child is a product of first conception, during which the mother had regular antenatal visit and did not have any antenatal problem. Born of normal delivery, cried and respired spontaneously with birth weight of 3,600 g and discharged along with the mother, was not breast fed. Feeding was started with formula feeds, maintained with the same, until one year of age. Complimentary feeds started since 6 months of age with cereals and baby food. Development: Head control at 5th month, sitting with support and attempted to crawl from the age of 8th month. Child yet to walk.

At one year of age, the child presented with growth retardation, abdominal distension, doll- like face and hepatomegaly. Laboratory investigation showed Fasting hypoglycemia followed by postprandial hyperglycemia. Liver function tests were normal.

Ultrasonography of abdomen revealed hepatomegaly without any diffuse parenchymal abnormality. Liver biopsy was made, reported as large hepatocytes with clear cytoplasm, ballooning and positive for PAS staining, characteristic of glycogenosis *(Figure 1)*. Hence the diagnosis of Von-Gierke disease was made and advice was made regarding feeding frequency and corn starch feeds.

At the age of one year seven month, was presented with respiratory distress, the Silverman Anderson score of 3, signs of acidosis, pallor, diaphoresis, tachypnea and tachycardia, hence the child got hospitalized. The laboratory examination showed leucocytosis with shift to left. There was hyperglycemia. The Gasometry was reported as metabolic acidosis (P^H 7.10, PCO_2 11, PO_2 108, HCO_3 3.4, Base deficit 23.8, S O_2 96.5), on repeated gasometry also, the similar reports were obtained. X- ray of thorax demonstrated pulmonary condensation. Clinical condition continued to detoriate, mandating elective intubation and ventilatory support at Pediatric Intensive Care Unit. More than the treatment of antibiotics Penicillin and Aminoglycoside, Metabolic acidosis was treated

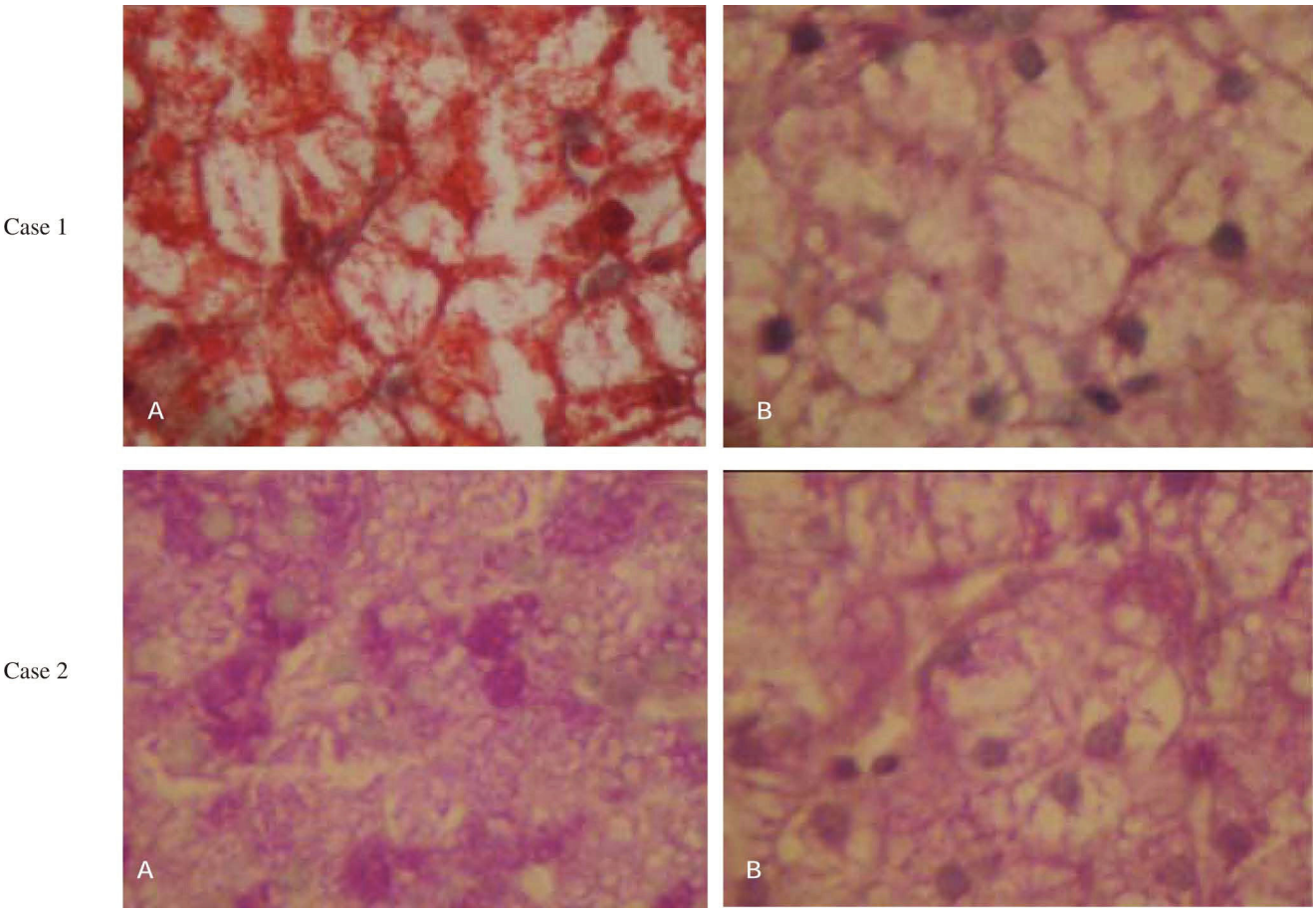


Figure 1. Liver tissue of Case 1 and Case 2: (A) PAS staining demonstrating glycogen accumulation and (B) Photograph of positive diastase test.

with continuous bicarbonate infusion calculated as per acid base deficit depending upon the gasometry. Due to persistent hyperglycemia, determination of C peptide level was requested, with result of 0.3 ng/mL, with reference value of 1.1- 5.0 ng/mL; Insulin level < 0.200μU/L with reference value of 5.0- 25μU/L. The antibiotic scheme was modified, started on Dicloxacillin, Cefotaxim and Fluconazole as Urine culture was positive for Candida Albicans of 100,000/HPF. With this, the child improved clinically, radiologically and values of laboratory examination, hence extubated and transferred to us for continued evaluation and treatment.

The physical examination showed, Head circumference of 48 cm (50th centile for age), length of 73 c (< 5th centile for age), weight of 11,100 g (< 25th centile for age); Doll-like face was more prominent, small thorax and rachitic changes noted in the costal cartilage. Distended abdomen with hepatomegaly of 6 x 5 x 5 cm *(Figure 2)*, with genitals relevant to his age and sex also noted. Rest of the systemic examination was normal.

Repeat Gasometry, C peptide, Insulin were requested and were continued to be below the normal values (metabolic acidosis, 0.3 ng/mL and 1.3μU/L respectively). Hence, the possibility of FBS associated with glycogenosis was considered. Due to persistent acidosis, Nephrology and Genetic opinion was sought. Serum and urinary electrolytes of 24 hours were repeated. While analyzing Phosphaturia, Negative anion gap curve of Hyperchloremic type was observed, this was compatible with tubulopathies *(Figure 3 and Table I)*.

Radiography of long bones showed evidence of rickets. Ultrasonography of Abdomen showed hepatomegaly without diffuse hepatic parenchymal lesions. Kidneys, Pancreas and Spleen were normal in shape and size.

In the beginning, the diagnosis of type I glycogenosis Von Gierke Disease was considered in this patient. However, during the course of evolution, the patient presented with metabolic acidosis, due to renal tubular dysfunction, pre-prandial hypoglycemia with ketosis followed by postprandial elevated blood glucose , associated decreased Insulin and C Peptide levels, but at the same time not following the clinical course of type I diabetes too. After the biochemical analysis and renal functional test to demonstrate the proximal renal tubular dysfunction, with the results of glucosuria, phosphaturia, bicarbonate

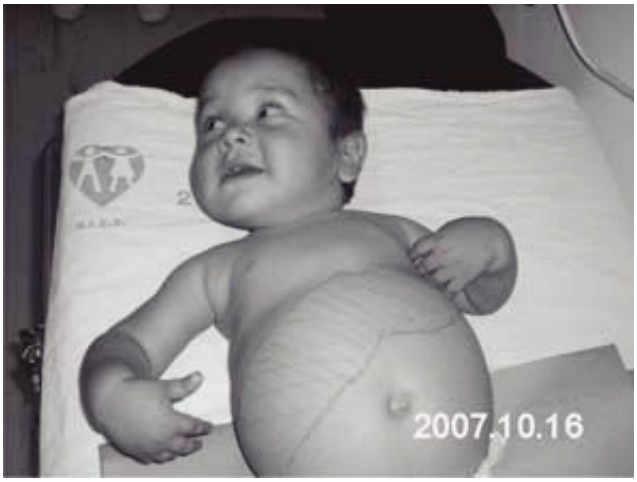


Figure 2. Case 1 showing typical Doll-like face and hepatomegaly (marked by lines).

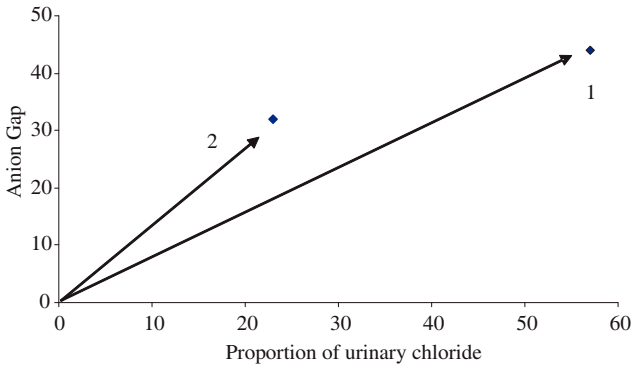


Figure 3. Demonstrating the displacement of anion gap curve towards left (hyperchloremic) in proportion to urinary chloride (1- Case 1; 2 – Case 2). AG = urinary Na + urinary K – urinary Cl (Case 1: 87 + 14 = 101-57 = +44; Case 2: 32 + 23 = 52-23 = +32).

Table I. Laboratory test.

	Blood/Serum				Urine		
Parameter	Case 1	Case 2	Reference value	Parameter	Case 1	Case 2	Reference value
Arterial blood P^H	7.10	7.33	7.35 – 7.45	Sodium (mEq/L)	87	32	85 – 250
Sodium (mEq/L)	142	131	135 – 145	Potasium (mEq/L)	14	23	2.5 - 125
Potassium (mEq/L)	3.9	3.9	3.5 – 5.0	Chloride (mEq/L)	57	23	15 - 40
Chloride (mEq/L)	110	98	95 – 105	Phosphorous (mg/dL)	28.4	23	0.6 – 1.5
Bicarbonate (mEq/L)	9	9.3	22 – 26	Glucose (mg/dL)	1,000	Negative	Negative
Calcium (mg/dL)	9	8.9	8.8 – 9.5	Ketone(Mm/dL)	150	Negative	or Neg
Phosphorous (mg/dL)	2.3	2.2	4.0 – 7.0	Amino acid	Negative	Negative	Negative
Urea (mg/dL)	11	14	15 – 40	Chromatography			
Creatinine (mg/dL)	0.4	0.1	0.6 – 1.2				
Glucose (mg/dL)	117	117	70 - 110				
Uric acid (mg/dL)	1.5	–	2.0 – 2.7				
Alkaline phosphatase IU	14	12	30 – 120				
Cholesterol (mg/dL)	125	139	< 200				
Trigliceride (mg/dL)	370	215	85 – 150				
Insulin (uU/L)	0.20	1.9	5.0 – 25				
C Peptide (ng/mL)	0.3	0.41	1.1 – 5.0				
Alanin amino tranferase U/L	51.0	37.0	0-38.0				
Asparte amino transferase U/L	37.0	28.0	7- 41				
Prothrombin time (sec)	14 .0	13.0	11 – 14				
Thrombo plastin time (sec)	24 .0	21.0	20 – 40				
Total Bilirubin (mg/dL)	0.7	1.4	0-1.1				
Direct Bilirubin (mg/dL)	0.1	0.7	0-0.3				
Unconjugated Bilirubin (mg/dL)	0.6	0.7	0-0.9				
Total protein (g/dL)	7.6	6.8	6-8.7				
Galactose (mg/dL)	4.5	46.8	0-5.0				

loss, hypoglycemia, hypophosphatemia, hypocalcemia, hypoglycemia with radiological evidence of rickets, the diagnosis of FBS was made in this case as regard to the clinical picture.

The treatment was started with 25 hydroxy Vitamin D (0.25μg/24 h or 2,000 MI/kg/24), Disodium phosphate with Phosphoric acid as 85% (58.5 g in 1,200 mL of normal water) 5 times a day and Bicarbonate of 15 mEq/k/24 h. Dietary advice was made as maternized cow's milk in the beginning, later whole milk was given as the galactose level in the blood was normal. In addition to that, fruits, frequent small feeds and use of corn starch in the diet of the child also recommended. The diet was calculated to provide the calorie of 140 kcal/kg of body weight and 5 grams of protein/kg of body weight. Regular follow up on outpatient basis was advised with Pediatric and Nephrology departments.

Case 2

Eight month old female infant, who is born of second conception (sibling of case 1), delivered via naturalis with birth weight of 2,500 g, length of 48 cm and head circumference of 32 cm. During the neonatal period, was hospitalized for transient tachypnea, transient unconjugated hyperbilirubinemia and hypoglycemia not associated with seizures. The newborn metabolic screening was negative, however the estimation of blood galactose level later reported to be elevated.

At the age of 7 month, infant was brought to hospital for delay attaining age appropriate milestones (not attained head control, not started sitting and crawling).

The physical examination revealed weight of 7,950 g, length of 63 cm, which are less for age (3rd centile), Doll-like face, prominent abdomen and hepatomegaly of about 6 cm below the right costal margin *(Figure 4)*. Because of these finding, FBS was suspected and the following laboratory analysis were requested: Arterial blood gas, Serum and Urinary Electrolytes, calcium, phosphorous, cholesterol, triglyceride, ultra sonogram of abdomen and x-ray of thorax and long bone. They were reported as metabolic acidosis (Table I), rickets and hepatomegaly devoid of any specific ultrasonographic pattern. Based on these results, liver biopsy was done and revealed histopathological changes typical of glycogenosis *(Figure 1)*. Hence, the suspicion of FBS was confirmed and treatment was continued with phosphate and bicarbonate replacement. The dietary advice was given based on the calculation of 140 kcal/kg of body weight, protein of 4.5 gm/kg of body weight in the form of maternized cow's milk, formula of soya, puree of fruits and vegetables.

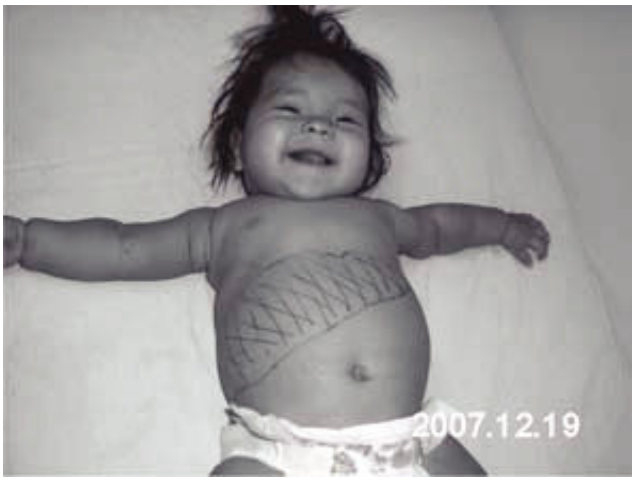
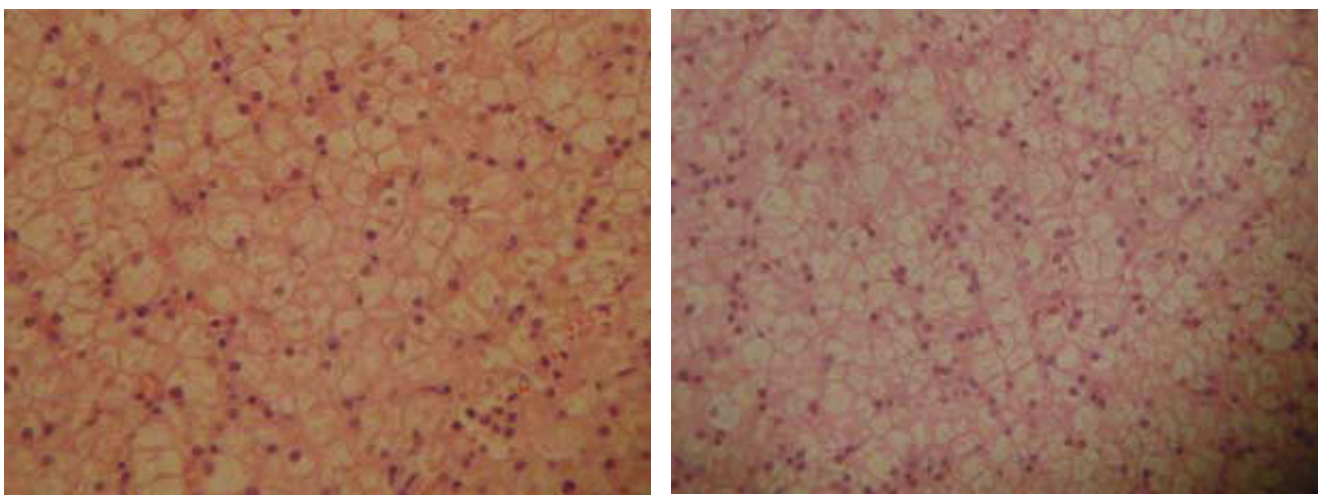


Figure 4. Case 2 exhibits Doll-like face and hepatomegaly (marked by lines).

Discussion

FBS is a rare clinical entity and rare presentation with in the same family affecting the infants between the ages of 2 month to 1 year of life. The clinical picture, which is noticed in majority of the patients, is characteristic faces «Moon- shaped» face or «Doll- like» face. In addition, short stature, rickets, protuberant abdomen, and hepatomegaly[3-5] are associated features in FBS. In addition, biochemical changes encountered as a consequence of the altered Proximal Renal Tubular function (glucosuria, phosphaturia, bicarbonate loss and hypophosphatemia, aminoaciduria). Preprandial ketotic hypoglycemia and significant post prandial hyperglycemia and hypergalactesemia are noted due to low hepatic uptake. There is also hypoinsulinemia due to altered sensitivity of β cells of Pancreas to glucose, associated with reduced release of monosachroide by hepatic cells during fasting



Case 1 Case 2

Figure 5. Percutaneous liver biopsy of Case 1 and Case 2 (HE 40x) showed large and ballooned hepatocytes with clear cytoplasm.

and intra cellular accumulation with inhibition of glycogenolysis leading on to glycogen accumulation and hepatomegaly.[6,7]

During the period of fasting, there is reduced blood glucose level which is generally not associated with convulsions. This hypoglycemia is accompanied by ketosis followed by postprandial hyperglycemia, making to consider the possibility of ketosis to have a neuro protective effect.[2,8] It is also possible to encounter elevation of cholesterol and triglyceride in these patients due to accumulation of secondary metabolite.[6,7]

With respect to recent discovery in Genetic aspect of the disease, mutations in GLUT-2 gene was detected in 34 cases.[7,9,10] Parental consanguinity was observed in 2/3rd of these patients. Some of these cases were identified through Neonatal Screening for Galactosemia. This gene is localized much in hepatocytes like in the β cells of pancreas, enterocytes and renal tubules.[2]

There is no specific treatment exist for this disease in the therapeutic form, besides intravenous hydrations, to provide with Vitamin D in the form of 1, 25 dihydroxy Vitamin D3. Citrate up to 15 mEq/kg/day given every 4th hourly to maintain bicarbonate more than 20 mEq/dL, phosphate solution orally; to offer with fructose and corn starch to provide glucose in slow release form and also which do not require diseased metabolic pathway. Because of the possible association of Galactosemia with FBS, it is recommended to provide the diet free of Galactose, until the results of metabolic studies are known.[2,6,10]

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