First case of Fanconi-Bickel syndrome genetically diagnosed in Sri Lanka

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Sri Lanka Journal of Child Health, 2019; **48**(2): 176-178
DOI: http://dx.doi.org/10.4038/sljch.v48i2.8718
(Key words: Fanconi-Bickel syndrome, Sri Lanka)

Introduction
Fanconi-Bickel syndrome (FBS) was first described in 1949 in a Swiss boy who was followed up over five decades[1]. Less than 200 FBS patients have been reported in the literature[2-5]. Extensive literature survey did not show any cases of FBS in Sri Lanka. We present the first case of FBS with genetic diagnosis in Sri Lanka.

Case report
An eleven month old boy, third child of second degree consanguineous healthy parents, presented with progressive abdominal distension since birth. He did not have recurrent infections. Two elder brothers are healthy. He was exclusively breast fed up till six months with poor complementary feeding practices since then. His first cousin who was also born to consanguineous parents died at eighteen months of age following a similar disease course which was not investigated.

Anthropometry showed a length of 65cm (< -3 SD), a weight 6.85 kg (-3SD) and an occipito-frontal circumference of 44cm (5th centile). He had a 'doll like face', mild pallor, hepatomegaly and features of rickets such as frontal bossing, widened wrists and rachitic rosary (Figure 1).

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(Received on 23 June 2017: Accepted after revision on 18 August 2017)
The authors declare that there are no conflicts of interest Personal funding was used for the project.

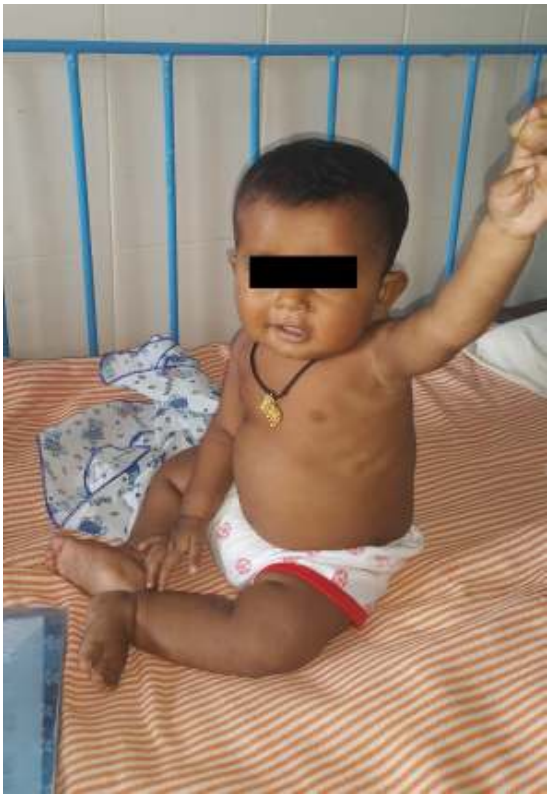

Figure 1: ***The patient***

Liver was palpated 4 cm below costal margin. Spleen and kidneys were not palpable. Development assessment revealed gross motor delay with age appropriate fine motor, speech and social development.

He had fasting hypoglycaemia (capillary blood sugar 38mg/dl with four hour fasting), positive urinary ketone bodies and glycosuria. Urinary reducing substances were positive. Guthrie test was positive for galactosaemia. His serum triglyceride level was 352 mg/dl (normal <99 mg/dl) Serum uric acid level was 39micromol/l (normal 119-327micromol/l). Blood gas analysis showed metabolic acidosis with a normal anion gap (7-16 mmol/l) as shown in Table 1.

Table 1: ***Venous blood gas and serum electrolytes***

Venous blood gas and serum electrolytes	Result
pH	7.3
pCO_2	38 mmHg
HCO_3	18.5 mmol/l
Base excess	-5.7 mmol/l
Serum sodium	140 mmol/l
Serum potassium	4.2 mmol/l
Serum chloride	109 mmol/l
Anion gap	12.5 mmol/l

His blood amino acid and acyl carnitine profiles were normal. Caeruloplasmin level was 539 U/l (normal 330-430 U/l). Clotting profile was normal. Ultrasound scan of abdomen showed a prominent liver of 9.5cm with normal spleen and kidneys. Plain radiographs of chest and wrist showed features of rickets. (Figure 2). His serum corrected calcium level was 2.75mmol/l (normal 2.2-2.7), phosphate 0.98 mmol/l (normal 1.45-2.16) and alkaline phosphatase 2249.6 U/l (normal 110-320) which was compatible with hypophosphataemic rickets.

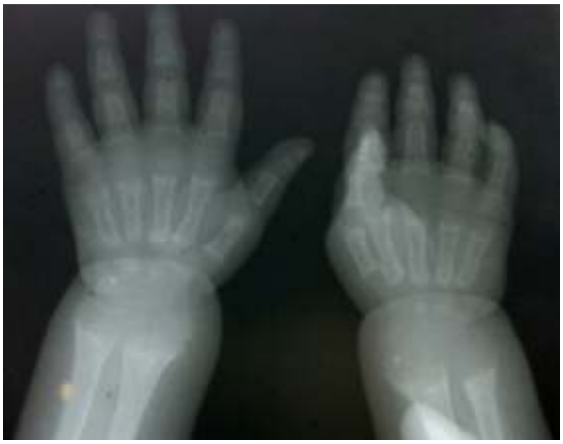

Figure 2: ***Radiograph of both hands***

Urine analysis showed a pH of 6.5, no cells or casts, protein ++, Clinitest – yellow and Clinistix - ++++. Further analysis of spot urine sample showed urinary loss of electrolytes, phosphates, and proteins (Table 2).

Table 2: ***Spot urine sample results***

Investigation	Value	Normal range
Urinary Na^+ (mmol/l)	43.7	<20
Urinary K^+ (mmol/l)	22	<20
Protein/creatinine ratio (mg/micromoles)	679	<20
Calcium/creatinine ratio (mmol/micromoles)	2.52	0.09-2.2
Phosphate/creatinine ratio (mmol/micromoles)	8.0	1.2- 19
Fractional excretion of phosphate	24.51	15-20
Magnesium /creatinine ratio (mmol/micromoles)	2.42	0.4-2.2

Bilateral posterior capsular cataracts and mild concentric left ventricular hypertrophy were found on ophthalmoscopy and 2D echocardiography respectively. Liver biopsy revealed preserved architecture. Hepatocytes were enlarged with empty vacuolated cytoplasm, small pyknotic nuclei and thickened cell membranes. Portal tracts were normal without significant peri-cellular or peri-sinusoidal fibrosis or cholestasis. Although routine histology favoured glycogen storage disease (GSD), glycogen was not demonstrated by PAS/PASD stain. Analysis of all coding regions and exon/intron boundaries of the SLC2A2 gene by Sanger sequencing showed homozygosity for a SLC2A2 splicing mutation, c.963+1G>T. which confirmed the diagnosis of FBS. Both parents were heterozygous.

Discussion

FBS (OMIM 227810) is an autosomal recessive disorder due to a defect in SLC2A2 gene which codes for GLUT 2[6]. The defective GLUT 2 receptors in the renal tubules, hepatocytes and pancreas lead to symptoms due to defective glycogen storage, glucose and galactose metabolism and renal tubular dysfunction[2]. Clinical features include hepatomegaly, hypophosphataemic rickets, fasting hypoglycaemia, failure to thrive and proximal renal tubular acidosis with renal Fanconi syndrome which is evidenced by glycosuria, aminoaciduria, phosphaturia, bicarbonate loss and hypophosphataemia[2,3]. Currently patient is being managed symptomatically. The prognosis of the disorder is unknown[6]. Short stature is known to occur[1]. Both parents were found to be carriers. The cause of death of the child's cousin remains unanswered.

Acknowledgements

We thank the Molecular Genetics Laboratory, the Medical School of University of Exter, for carrying out the genetic testing for our patient, Dr. Eresha Jasinghe, Consultant Chemical pathologist, Dr. Dulani

Benaragama and Dr. C. S. Perera, Consultant Histopathologists, for the support given in investigating the patient.

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