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Case Report

Fanconi Syndrome: Report of 2 Cases

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Abstract

Fanconi syndrome is a disorder of inadequate reabsorption in the proximal renal tubules of the kidney. Common causes of Fanconi syndrome in children are genetic defects that affect the body's ability to break down certain compounds such as: cystine (cystinosis), fructose (fructose intolerance), galactose (galactosemia), glucose and galactose impaired utilization of glucose and galactose impaired utilization of glucose and galactose (Fanconi-Bickel or GLUT 2) and tyrosine (tyrosinemia type 1). Symptoms include dehydration, bone pain, weakness, growth failure, osteomalacia ,rickets and type 2 renal tubular acidosis. Laboratory tests showed large amounts of the following substances that may be lost in the urine: amino acids, bicarbonate, glucose, magnesium, phosphate, potassium, sodium and uric acid.

We present 2 cases of Fanconi syndrome. The case 1, is a 23 months old boy with polyuria, polydipsia, failure to thrive, retardation of motor development started at 10 months of age with severe malnutrition and rickets when was admitted. Subsidiary examination revealed hypourecemia, liver dysfunction, very high level of a-fetoprotein and respiratory acidosis. Urine test showed severe glycosuria and reduced tubular reabsorption of phosphorus. Metabolic screening in plasma showed increased tyrosine and generalized hyperaminoaciduria with the presence of great amount of the acids derived from tyrosine metabolism, succinylacetoacetic acid and succinylacetone. Tyrosinemia type I was confirmed after we found no activity of fumarylacetoacetase in cultured fibroblasts. The case 2, is a 3 year-old boy with failure to thrive since 6 month old, fasting hypoglycemia, hypophosphatemic rickets, renal tubular nephropathy, hepatomegaly, altered liver function, hyperlipidemia and normal mental development. We suspected of glycogen storage disease and Fanconi tubular nephropathy. Liver biopsy found moderately abundant glycogen present in the cytoplasm which was consistent with glycogen storage disease but not consistent with type I, II or IV by enzyme study and under electronic microscopy study. Fanconi-Bickel syndrome was suggested. Mutation analysis of all 11 coding exons of GLUT2 gene was sequenced on leucocyte DNA extract from the proband and parents. Father was found heterozygous for a novel frame-shift mutation (E85fsX177) and mother was heterozygous for another novel missense mutation(G189D). The boy was a compound heterozygous for E85fsX177 and G189D inherited from his parents.

Keywords: *Rickets; Fanconi Syndrome; Tyrosinemia Type 1; GLUT 2*

Introduction

Fanconi syndrome is a disorder of inadequate reabsorption in the proximal renal tubules of the kidney.

Fanconi syndrome can be caused by faulty genes, or it may result later in life due to kidney damage. Sometimes the cause of Fanconi syndrome is unknown.

Common causes of Fanconi syndrome in children are genetic defects that affect the body's ability to break down certain compounds such as: cystine (cystinosis), fructose (fructose intolerance), galactose (galactosemia), glucose and galactose (Fanconi-Bickel or GLUT 2) and tyrosine (tyrosinemia type 1).

Cystinosis is the most common cause of Fanconi syndrome in children. Other causes in children include: exposure to heavy metals such as lead, mercury, or cadmium, Lowe's disease, (a rare genetic disorder of the eyes, brain, and kidneys), and Wilson's disease.

In adults, Fanconi syndrome can be caused by various things that damage the kidneys, including: certain medications (azathioprine, cidofovir, gentamicin, and tetracycline), kidney transplant, light chain deposition disease, multiple myeloma and primary amyloidosis.

Symptoms include dehydration, bone pain, weakness, growth failure, osteomalacia, rickets and type 2 renal tubular acidosis.

Laboratory tests showed large amounts of the following substances that may be lost in the urine: amino acids, bicarbonate, glucose, magnesium, phosphate, potassium, sodium and uric acid.

The prognosis depends on the underlying disease [1].

Cases Reports

Case 1: a 23 months old boy with history of polyuria, polydipsia, failure to thrive, retardation of motor development started at 10 months of age, was treated with vitamin D2 at 20 months of age for rickets. Because of no improvement, he was admitted at 23 months with severe malnutrition and lost weight, respiratory distress, abdominal distention, hepatomegaly of 8 cm, retardation of motor skills and rickets signs (anterior fontanelle 2,5 x 3,5 cm with soft boards, rachitic rosary, wrists and ankles enlargement) (Figure 1).

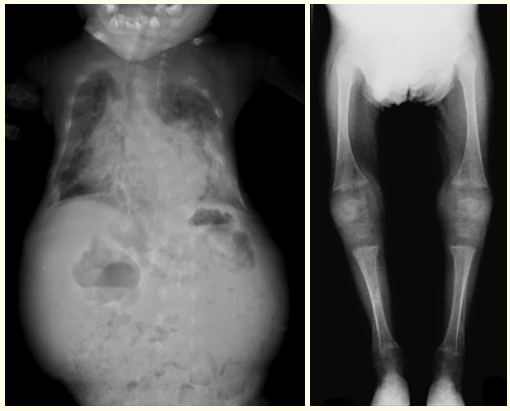

Figure 1: *Rickets signs with rachitic rosary, wrists and ankles enlargement.*

The laboratory and imagiologic evaluations revealed: uric acid 0,45 mg/dL (N: 2,0 - 5,0); phosphorus 1,5 mg/dL (N: 2,5 - 6,4); ASP 54 U/L (N: 1 - 37); g-GT 685 U/L (N: 5 - 18); alkaline phosphatase 1650 U/L (N: 54 - 280); total bilirubin 1,75 mg/dL (N: 0,1 - 1,0); a-fetoprotein > 30000 UI/mL (N: 0,0 - 5,0). Glucose, creatinine, urea, Na^+, K^+, Cl^-, total calcium, total protein, albumin were all normal. Urine: glucose ++++, protein +++. Tubular reabsorption of phosphorus: 45,3% (N: 80 - 95%). Blood gases: pH 7,242; pCO_2 62,3 mmHg; pO_2 78,5 mmHg; HCO_3^- 26,6 mmol/L; BE -2,5 mmol/L; $SatO_2$ 95%. Coagulation profile: INR - 1,54; PTT – 53,1 sec (N: 26 - 40); TP - 54% (N: > 70); fibrinogen – 120 mg/dL (N: 200 - 400). Metabolic screening in plasma: tyrosine - 145 mmol/L (N: 25 - 60), phenylalanine - 44 mmol/L (N: 28 - 68), methionine - 34 mmol/L (N: 4 - 44). The urine amino acidis showed: generalized hyperaminoaciduria with the presence of great amount of the acids derived from tyrosine metabolism, succinylacetoacetic acid and succinylacetone. Abdominal CT showed liver moderatly increased, heterogeneous, with little, spread, hypodense nodules, translating hepatopathy and kidneys enlarged. Tyrosinemia type I was confirmed after we found no activity of fumarylacetoacetase in cultured fibroblasts. Started treatment with NTBC: 1 mg/kg/day, bid, hypoproteic, hypercaloric diet, with restriction in tyrosine and phenylalanine. We also gave oral vitamin D, phosphate, potassium and sodium citrate, calcium to control the renal losses caused by Fanconi syndrome . Seven

days after treatment, we found normalisation of coagulation profile and tyrosine plasmatic concentration,succinylacetone in urine was negative. After discharged, the child improved his motor skills, recovered nutritional state and so far no sign of hepatocarcinoma.

Case 2: The boy first presented at age 3y for failure to thrive since 6 months old. He was normal delivery at term, birth weight 3.0 kg, height 49 cm, head circumference 33cm with no special neonatal history, including neonatal jaundice and hypoglycemia recorded. He is the 2nd child of non-consanguineous young parents. His brother died of sepsis at 1.5 years old and was found hepatomegaly but detail history was unknown. The boy was fed with normal formula and started semisolid food about 5 months. He could tolerate mashed fruit, juice and no any abnormal movement, jittering, floppiness. His developmental milestones were essentially appropriate for age but unsupported walk at about 2 years old. He was 8.6 kg, 75 cm and head circumference 46.5 cm at 3y5m. All growth parameter were below 3rd percentile. He had no dysmorphic feature but was noticed having doll face, distended abdomen but thin limbs, rachitic rosary and wrist enlargement, genu valgum and hepatomegaly which was 7 cm below the costal margin, with no splenomegaly. Ophthalmology checkup was normal.

His previous blood tests in clinical record showed normal complete blood count and coagulation profile. Plasma urea, creatinine, uric acid, albumin and creatine kinase were within normal range. Further investigations including ionized calcium 1.19 mmol/l; phosphorus 0.51 mmol/l; Mg 0.98 mmol/l; Na/K, thyroid function , serum 1,25-$(OH)_2$-cholecalciferol 35 pg/ml (N 14 - 78 pg/ml), 25(OH) cholecalciferol 46.2 ng/ml (N 8.9 - 46.7 ng/ml), PTH 23 pg/ml (N: 11 - 55), a-fetoprotein 5.5 ng/ml, urine reducing substance, were also normal. We found changes in: blood glucose that revealed fasting hypoglycemia 2.3 - 2.8 mmol/l, cholesterol 8.4 mmol/l (N < 6.2); triglyceride 2.38 mmol/l (N < 2.0); LDL-cholesterol 6.3 mmol/l (N < 4.9), AST 111U/L (N: 10 - 50); ASL 115U/L (N: 5 - 50); γ-GT 56U/L (N: 11 - 50); alkaline phosphatase 1468U/L (N: 36 - 120), PH 7.322, HCO_3 14 mmol/l, BE -12.3 mmol/l, PCO_2 27 mmHg. Urine PH 6.0 - 7.0, Cr Clearance 152ml/min/1.73m^2, generalized aminoaciduria, urine protein 28.15 mg/m^2/h, mass glucosuria 3.2 mol/24h, urine calcium 11.7 mg/kg/24h, tubular reabsorption of phosphate (TRP) 40%, FeNa 4.77%. X-ray of tibia and wrist reviewed enlarged metaphyses with "brush-like" margins and cupping. The growth plates were widening and epiphyses is irregular, suggesting rickets. Ultrasound of abdomen and kidneys showed homogenic hepatomegaly. Spleen/pancreas/kidneys were normal. Because of his failure to thrive, fasting hypoglycemia, hypophosphatemic rickets, renal tubular nephropathy, hepatomegaly, altered liver function, hyperlipidemia and normal mental development, we suspected of glycogen storage disease and Fanconi tubular nephropathy. The boy was put on cornstarch to avoid hypoglycemia. He needs multiple minerals supplementation including phosphate, calcium, potassium, vitamin D and sodium bicarbonate for his renal tubular acidosis. The 3rd tier analysis included OGTT that reviewed fasting hypoglycemia but impaired glucose tolerance. Glucagon test showed insufficient response with a fasting glucose 2.5 mmol/l and a peak glucose only 3.9 mmol/l at 30 mins. Baseline lactate 2.8 mmol/l, lactate and pyruvate did not rise with glucagon stimulation. Liver biopsy found moderately abundant glycogen present in the cytoplasm which was consistent with glycogen storage disease but not consistent with type I, II or IV by enzyme study and under EM study. Fanconi-Bickel syndrome was suggested. Mutation analysis of all 11 coding exons of GLUT2 gene was sequenced on leucocyte DNA extract from the proband and parents. Father was found heterozygous for a novel frame-shift mutation (E85fsX177) and mother was heterozygous for another novel missense mutation (G189D). The boy was a compound heterozygous for E85fsX177 and G189D inherited from his parents.

Discussion

Fanconi syndrome is a very severe disorder with consequences over the patient when is not treated or diagnosed in the early stages of the disease. The case 1, type 1 tyrosinemia (TYR 1) is a metabolic disorder, inherited as an autosomal recessive trait, caused by deficiency of fumarylacetoacetase (FAH), the last enzyme in the tyrosine degradation pathway. The FAH gene has been localized to chromosome 15. Two extremes of the clinical phenotype have been described: the "acute" (early onset and severe) and "chronic" (delayed onset and slow course) phenotype. The clinical manifestations, which involve mainly the liver, kidney and peripheral nerves, stem from the cytotoxicity of tyrosine metabolites, fumarylacetoacetate, maleylacetoacetate, succinylacetoacetate and succinylacetone, accumulating proximal to the metabolic defect. Treatment with a diet restricted in phenylalanine and tyrosine does not prevent progression of the liver disease and development of hepatocellular carcinoma and liver transplantation was previously the only option for these patients. NTBC, a potent

inhibitor of 4-hydroxyphenylpyruvate dioxygenase, has transformed the natural history of tyrosinemia. The aim is to block tyrosine degradation at an early step so as to prevent the production of toxic down-stream metabolites. Case 1 is a delay diagnosis situation with the symptoms started at 10 months of age with polyuria, polydipsia, failure to thrive, retardation of motor development. He was treated as common vitamin dependent case at 20 months. Only 3 months later, because his clinical situation was very bad, with respiratory distress, he was admitted and lately the correct diagnosis was done. When patients with TYR 1 are treated until the 2 years of age, the risk of liver cancer is lower. In our case, the treatment with nitisone started before that age. So far, the patient don't showed any clinical sign and the a-fetoprotein level normalized few months later [2,3].

Fanconi-Bickel syndrome (FBS) caused by GLUT2 deficiency, is inherited in an autosomal recessive manner, typically present at 3-10 months of age with a combination of hepatomegaly, a Fanconi-type nephropathy with severe glycosuria, a propensity to hypoglycemia in the fasted state and glucose and galactose intolerance in the fed state. Cataracts have occasionally been observed as the first sign. At an early stage, hepatomegaly, which is caused by massive accumulation of glycogen, may not yet be present, and nonspecific symptoms such as fever, vomiting, chronic diarrhea and failure to thrive may predominate. With increasing age, the clinical presentation is a protuberant abdomen and short stature. The kidneys also accumulate glycogen, and their enlargement can be detected by ultrasound.

Hypophosphataemic rickets is the major manifestation of tubular dysfunction, resulting in joint swelling, bowing of legs and pathological fractures. They have normal mental development, but growth and puberty are severely retarded. Impaired transport of glucose out of renal tubular cells results in the accumulation of glycogen and free glucose within these cells. This impairs other transport functions, resulting in a generalised tubulopathy with disproportionately severe glycosuria and hypoglycemia. A diagnosis of FBS is suggested by the characteristic combination of an altered glucose homeostasis, hepatic glycogen accumulation, and the typical features of a Fanconi-type tubulopathy. Fasting hypoglycemia and impaired glucose and galactose tolerance may be documented during oral loading tests.

Laboratory signs include mildly elevated transaminases, plasma lipids, uric acid and lactate. Hyperaminoaciduria, hyperphosphaturia, hypercalciuria, renal tubular acidosis, mild tubular proteinuria and polyuria are indicative of a generalised proximal tubular dysfunction. A hallmark of the diagnosis of FBS is the relatively severe glycosuria. Calculated tubular glucose reabsorption is dramatically reduced or even zero in most patients.

The diagnosis of FBS is ultimately confirmed by the detection of homozygosity or compound heterozygosity. Only symptomatic treatment is available. FBS patients should receive frequent feeds using slowly absorbed carbohydrates. Continuous carbohydrate supply by tube feeding of oligosaccharide solutions during the night may be indicated. The administration of uncooked corn starch has been demonstrated to have a beneficial effect on metabolic control, particularly on growth. Regarding tubulopathy, water and electrolytes must be replaced in appropriate amounts. Administration of alkali may be necessary to compensate for renal tubular acidosis. Hypophosphataemic rickets requires supplementation with phosphate and vitamin D preparations. With these measures, prognosis is fairly good. The main problem are short stature, hypophosphataemic rickets and osteomalacia in adulthood. Hepatic adenomas or tumours, as described for other glycogen storage diseases, have never been observed in FBS [4]. Case 2, the patient showed failure to thrive since 6 months of age. At 3 years old, he already presented with symptoms, laboratory and radiology signs of FBS, with rickets, hepatomegaly and renal problems. FBS is inherited as autosomal disorder. The father was heterozygous for a novel frame-shift mutation (E85fsX177) and mother was heterozygous for another novel missense mutation(G189D). His elder brother that died with sepsis and have hepatomegaly, can have the same disease, although we cannot confirm.

Conclusions

Whenever we find patients with rickets, failure to thrive, hepatomegaly and hypoglycemia associated with renal dysfunction, Fanconi syndrome must be included in the diagnosis. In both our two cases, we can offer genetic counseling and prenatal diagnosis for the future pregnancy.

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