24 year-old male with Fanconi-Bickel Syndrome

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HPI

- 23 yo AAM with a hx of Fanconi-Bickel Syndrome and hypophosphatemic Rickets is admitted to the Medicine Service with:

- decreased po intake
- Subjective fevers
- nausea, and vomiting.

- Reports 2-3 episodes of loose bowel movements

- Has not taken his medications including supplements for the past week

- Reports 2 sick contacts (neighbor and family member) with similar symptoms

- Patient of Dr. Vokes but has missed multiple recent appointments. Endo consulted for evaluation.

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PMHx, Meds

Past Medical History

- Fanconi-Bickel Syndrome
- Hypophosphatemic Rickets
- Restrictive Lung Disease
- Asthma
- Multiple Fractures
- Multiple Orthopedic reductions, fixations, rods, and pins
- Depression (Hx of suicide attempts in past)

Home meds

-Ibuprofen 400 mg po q6h prn pain
-Calcitriol 0.5 mg po TID
-Calcium carbonate 500 mg po TID
-Ergocalciferol 50,000 units weekly
-K-Phos Neutral tablets 500 mg 6 tabs BID
-Amitriptyline 10 mg po qhs
-Gabapentin 100 mg po TID
-Colace prn
-Zofran prn

Social Hx, Family Hx, ROS

Social Hx

- Lives with his adopted mother and father
- Confined to a wheel-chair
- unable to ambulate due to severe skeletal deformities
- On disability
- Denies smoking, etoh, illicit drug use

Family Hx

-Adopted and does not know his family history

ROS: + for nausea, vomiting
+subjective fevers
+loose BM x several days
arthralgias

Physical Exam

- VS: Temp-100^{0}F, BP- 140/91 RR 20 O2 sat-97% on RA, Height- 4'7'' Weight 86 lbs
- General Appearance: NAD, appears smaller than his stated age
- HEENT: NCAT, Eomi, dry mucous membranes
- Neck: supple, no thyromegaly
- Heart: +S1/S2, no murmurs
- Lungs: cta b/l
- Abdomen: distended, soft, nontender, +bs,
  + hepatomegaly
- Extremities: severe skeletal deformities,

Unable to walk

Labs

131 | 100 |15 / 240
2.0 | 9 |1.1\

Ca-8.1 (8.4-10.2 mg/dl)
Mg- 2.2 (1.6- 2.5 mg/dl)
Phos-0.9 (2.5-4.4 mg/dl)

28 | 787| 7.8
90 | 0.7 | 4.1

11.3 \ 15.9 / 156
/ 46.2 \

B-OH butyrate 3.6 (<0.3 mmol/L)
lipase 28 (11-65 U/L)

1, 25 OH vit D-18 (18-64 pg/ml)
PTH- 40 (50-75 pg/ml)

- What is Fanconi-Bickel Syndrome?

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Fanconi-Bickel Syndrome

- a rare autosomal recessive disorder of carbohydrate metabolism
- Caused by mutations in the Glut 2 gene
- FBS patients are frequently the product of consanguineous parents
- Affects both males and females, only 112 patients reported in the literature
- Disease first described in a 3 year old Swiss boy by Fanconi and Bickel in 1949

Typical Clinical and Laboratory Findings of FBS

- Hepatomegaly secondary to glycogen accumulation
- Glucose and galactose intolerance
- Fasting hypoglycemia
- Post-prandial hyperglycemia
- Proximal tubular nephropathy
  - Electrolyte disturbances
  - Metabolic acidosis
  - Severe glucosuria (independent serum glucose value)
  - Aminoaciduria, phosphaturia, uricosuria, calciuria, mild proteinuria
- Severe stunted growth (hypophosphatemic Rickets)

Original Patient

-born to consanguinous parents in a remote valley in the Swiss Alps

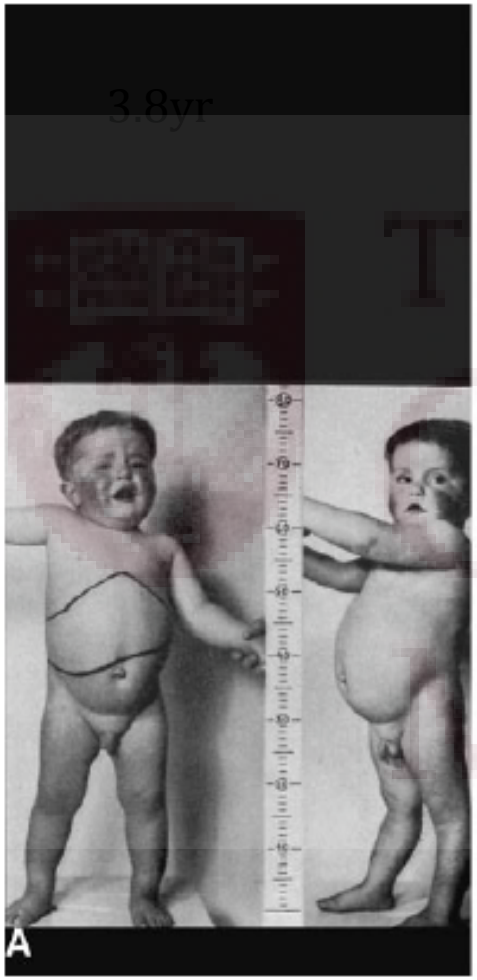
(1945) 6 mo: FTT, polydipsia, constipation, hepatomegaly, treated with calcium and vitamin D supplements

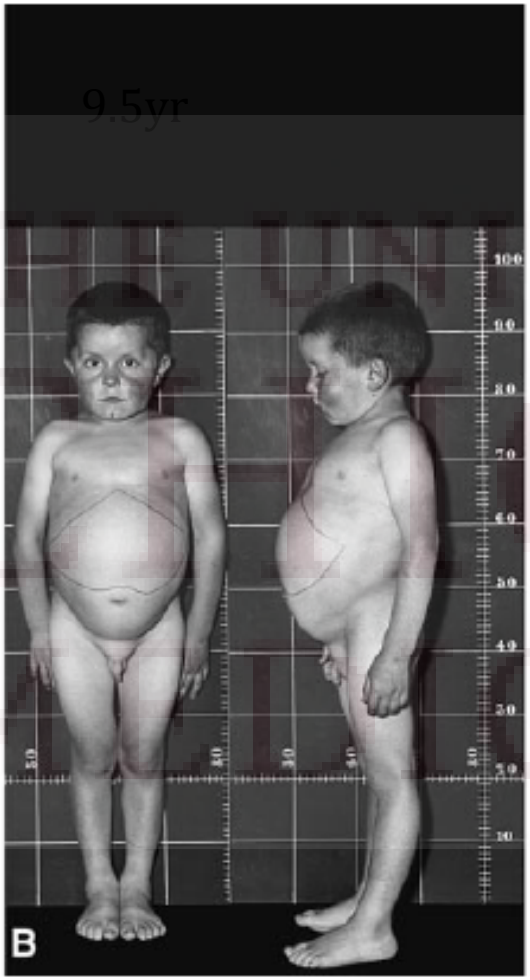
(1947) 2.8 yrs: short stature, protuberant abdomen, facial obesity, osteopenia

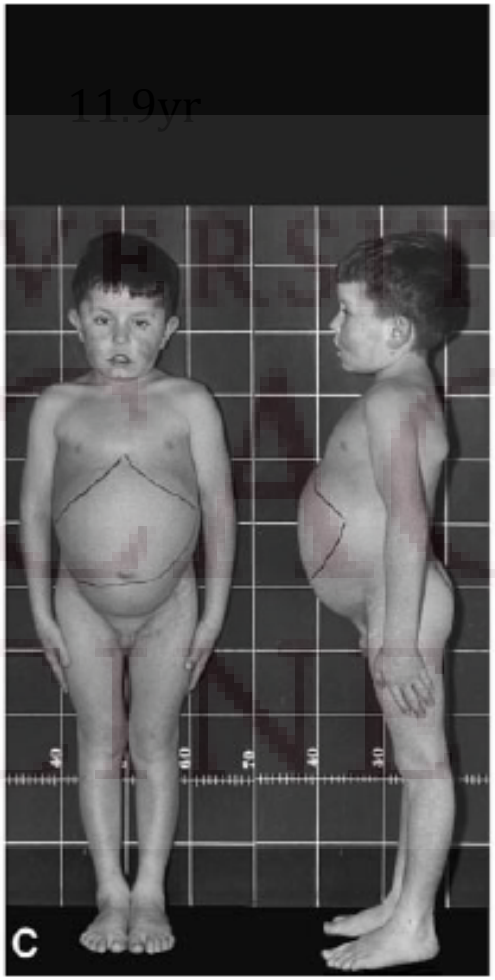
(1949) 3.8yrs: tubular nephropathy
-moderate hyperphosphaturia
-constant hypophosphatemia
-hyperuricemia
-hyperaminoaciduria
-intermittent albuminuria

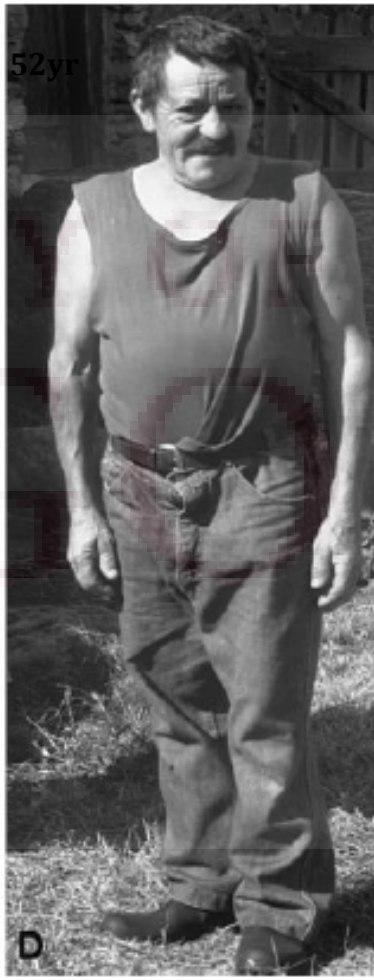
(1991) 46 yrs: zoster, liver biopsy revealed excessive amounts of glycogen, osteoporosis

(1997) 52yrs:Spent life as a shepherd, never married, described as withdrawn, never took meds, consumed large quantities of milk









Age 3.8 yrs | 9.5 yrs | 11.9 years | 52 years 4'6, 43kg

Santor et. al, Eur J Ped (1998) 157:783-797

1987 Study in Germany

- In a 1987 study by researchers at the Research Institute for Child Nutrition in Dortmund, Germany, nine cases of FBS were compared for clinical symptoms and physical appearance.
- The initial symptoms reported were fever, vomiting, growth failure, and rickets between the ages of three and ten months.
- Later, these same patients showed signs of dwarfism, a protruding abdomen, enlarged liver, moon-shaped face, and abnormal fat deposits around the shoulders and abdomen.
- Also, cutting of teeth and puberty were delayed.
- Complications present included fractures.
- Later in life, rickets and osteoporosis were constant features.

Typical Features of FBS

CATEGORY	FEATURES
GU	Renal tubular disease
Neuro	Retarded psychomotor development
Metabolic	Impaired galactose metabolism
Inheritance	Autosomal recessive
Abdomen	Distended abdomen
Lab	Normal red cell galactokinase Normal red cell galactose-1-phosphate uridyltransferase Generalized aminoaciduria Glucosuria Hyperphosphaturia Chronic acidosis Hypouricemia Hypokalemia Hypophosphatemia High serum alkaline phosphatase No cystinosis
Skel	Osteomalacia
Growth	Poor weight gain Sparse subcutaneous fat Thin limbs
GI	Malabsorption Poor appetite

Online Mendelian Inheritance in Man. 1966-2011. Johns Hopkins University.

Pathogenesis

- Functional loss of GLUT2 -> hyperglycemia and hypergalactosemia due to decreased monosaccharide uptake by the liver
- Hyperglycemia enhanced by an inappropriately low insulin secretion due to impairment of the glucose-sensing mechanism of the beta-cells.
- Data on insulin levels in FBS are limited; however, Manz et. al (1987) reported that intravenous glucose loading failed to raise serum insulin levels in one patient examined.
- Santer et. al (1997) postulated that hypoglycemia during fasting may be explained by altered glucose transport out of the liver→an increased intracellular glucose level → inhibit glycogen degradation→leading to glycogen storage and hepatomegaly.

Pathogenesis

- Hypoglycemia is exacerbated by renal loss of glucose due to a transport defect for glucose and galactose across the basolateral membranes of the tubular cells.
- Santer et al. (1997) suggested that renal glycogen accumulation may occur, resulting in the impairment of other functions of the tubular cells and the characteristic clinical picture of Fanconi nephropathy with disproportionately severe glucosuria.
- The impairment of intestinal monosaccharide absorption is not sufficient to prevent the increase of plasma glucose above the normal range.
- The altered transport of monosaccharides out of the enterocytes may be responsible for enterocyte glycogen accumulation
- Diarrhea and malabsorption are observed in some patients with FBS.

Treatment

- Symptomatic: water and electrolyte replacement
- Alkalinizing substances (bicarb, citrate)
- Vit D supplementation
- Phosphorus repletion
- Restriction of galactose
- Diabetes-like diet (low carb, low sugar)
- Small, frequent meals

Hospital Course

- Phos was repleted IV until he could tolerate po
- Electrolyte abnormalities corrected with IV fluids and aggressive repletion
- Outpatient medications were restarted
- Discharged home with outpatient f/u

Take Home Points

- Fanconi-Bickel Syndrome is rare but distinct clinical entity inherited in an autosomal recessive mode due to a genetic defect in Glut 2.
- FBS is associated with hypophosphatemic Rickets.
- Symptomatic treatment is directed towards compensation for renal losses of various solutes.

References

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