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The boy with massive glucosuria

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Case

A 3.5-year-old boy living in a remote Armenian village was admitted to the hospital in Yerevan in March 2002 with a history of polydipsia since the age of 6 months, bowed legs since he started to walk at the age of 1 year and an increasingly large abdomen. The child was very small [height: 74 cm (−5.9 SDS)] but alert, had a moonlike face, a grossly enlarged liver (10 cm below the costal margin) and a waddling gait due to severe rickets with genua vara (Figure 1). Psychomotor development was adequate for age. The liver was markedly enlarged at ultrasonography, but of homogeneous structure. The kidneys were large (length: 76 mm; normal for height: 45–70 mm).

Laboratory examination showed proximal tubular dysfunction with generalized amino aciduria, but glucosuria was excessive with 213 mmol = 38.4 g per 24 h or 133 g/1.73 m^2/day (normal: 0.13–0.32 g/1.73 m^2/day) at blood glucose levels of 4.9 mmol/l fasting (normal: 3.8–6.4 mmol/l) and of 9.4 mmol/l after feeding (normal: <7.8 mmol/l). Tubular reabsorption of glucose was only 13% (normal: 100%) of the filtered load at normal blood glucose. Serum sodium was 128 mmol/l (normal: 134–144 mmol/l), phosphorus 0.74 mmol/l (normal: 1.2–2.1 mmol/l) and uric acid 79 μmol/l (normal: 110–350 μmol/l). Elevated values were found for liver enzymes; cholesterol was 7.12 mmol/l (normal: 1.6–4.9 mmol/l) and triglycerides were 3.15 mmol/l (normal: 0.4–1.8 mmol/l).

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We suspected Fanconi–Bickel syndrome (MIM 227810), which is characterized by generalized renal tubular dysfunction with massive glucosuria and by hepatorenal glycogen accumulation [1,2]. Genetic analysis confirmed this diagnosis and revealed homozygosity for a novel missense mutation (*GLUT2 c*.887 A→G) leading to the substitution of histidine at position 192 by arginine (H192R) and heterozygosity in the parents. The patient markedly improved on treatment with vitamin D_2 (16 000 U/day), frequent feedings and a generous intake of fluid and electrolytes.

Discussion

The first description of Fanconi–Bickel syndrome dates back >50 years [1] and more than 100 cases have been reported since, mainly from Europe, but also from Turkey, Israel, the Arab Countries, Japan and the United States. There are no reports on cases from China, Central Africa or among blacks in the USA [3]. In 1998 this disease was shown to result from a defect of the facilitative glucose transporter GLUT2 [4]. So far, 10 missense, seven non-sense, 10 frameshift and seven splice-site mutations have been reported in 64 patients with Fanconi–Bickel syndrome [5,6].

Monosaccharide transporters can be assigned to two major groups, the SGLTs ('active' sodium-dependent glucose transporters) and the GLUTs ('passive' glucose transporters) [7]. GLUT2, like all GLUT proteins, has 12 transmembrane domains. Patients with the Fanconi–Bickel syndrome demonstrate the important role of GLUT2. The metabolic consequences of the defective GLUT2 protein are primarily related to altered glucose equilibrium at the liver cell [3,6]. Elevated intracellular glucose concentrations, despite *fasting* hypoglycaemia, lead to glycogen storage through impaired glycogen degradation. Conversely, glucose and galactose concentrations in blood are elevated in the *fed* state due to decreased hepatic

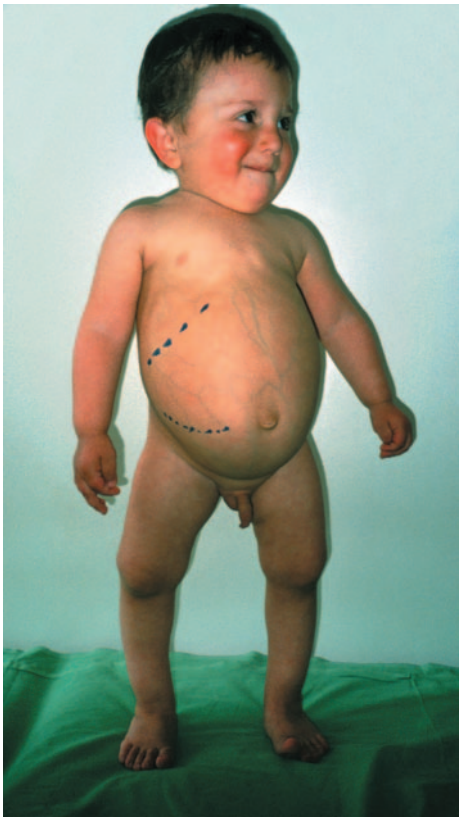

Fig. 1. The patient at the age of 3.5 years. Note the small stature (height: 74 cm), the moonlike face, the grossly enlarged liver and the genua vara due to severe rickets.

monosaccharide uptake and inappropriately low insulin secretion. The proximal tubular dysfunction might be the result of the storage of glycogen and of the elevation of free glucose within the cell; the exact mechanism, however, is not well understood. The enormous glucosuria is associated with osmotic diuresis, resulting in polyuria and electrolyte loss. However, unlike the situation in diabetics where the amount of filtered glucose is strongly elevated, glomerular hyperfiltration and glomerular damage are exceptional. Lifelong treatment is directed to compensate for losses of water, electrolytes, phosphate and bicarbonate. Frequent feeds and the use of slowly absorbed carbohydrates are recommended to avoid hypoglycaemia and to suppress futile gluconeogenesis. *Prognosis* is fairly good; only few patients have died because of an acute metabolic derangement with severe acidosis. The original patient of Fanconi and Bickel is now 58 years old [3]. Short stature is the main subjective problem.

Three additional clinical conditions have been linked so far to a defect of a glucose transporter, (i) the glucose transporter protein syndrome due to mutations of *GLUT1* (De Vivo syndrome; MIM 138140) with low glucose in the cerebrospinal fluid, (ii) congenital intestinal glucose/galactose malabsorption, which can be accompanied by mild glucosuria, due to mutations of *SGLT1* (MIM 182380) and (iii) isolated benign renal glucosuria (MIM 182381) [7]. The latter condition, which is not uncommon, is caused by mutations of *SGLT2* [8]. Glucosuria in this condition may also be massive. However, in contrast to the situation in Fanconi–Bickel syndrome, there is no secondary impairment of other tubular transport systems.

Teaching points

Renal glucosuria may occur as an isolated finding or as part of a more widespread tubular dysfunction that is either genetically determined (e.g. Fanconi–Bickel syndrome or cystinosis) or is acquired (e.g. malignant focal segmental sclerosis or tubulointerstitial nephritis with uveitis).

Patients with Fanconi–Bickel syndrome exhibit generalized tubular dysfunction, but glucosuria is excessive. These findings, although present from birth, seem to be compatible with a nearly normal life span.

Defects of the monosaccharide transporters GLUT2, SGLT1 and SGLT2 have been identified as underlying mechanisms of renal glucosuria.

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Conflict of interest statement. None declared.

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