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HEREDITARY FRUCTOSE INTOLERANCE IN A PATIENT WITH PHENYLKETONURIA*

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SUMMARY: Coşkun T, Özalp I, Tekinalp G. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Hereditary fructose intolerance in a patient with phenylketonuria. Turk J Pediatr 33: 181-184, 1991.

Classical phenylketonuria (PKU) and hereditary fructose intolerance (HFI) are two inborn errors of metabolism that have an autosomal recessive mode of inheritance. In this paper, we described a 3 - year - old girl with PKU and HFI. The occurrence of these two defects in the same patient is thought to be fortuitous and not genetically related since this is the first reported case and the statistical probability of such an occurrence is very low. *Key words: phenylketonuria, hereditary fructose intolerance.*

Classical phenylketonuria (PKU), resulting from a deficiency of the enzyme phenylalanine hydroxylase (PAH) is transmitted as an autosomal recessive trait[1]. Hereditary fructose intolerance which is caused by a deficiency of the enzyme fructaldolase B (HFI) also has an autosomal recessive mode of inheritance[2]. The probability of these two inborn errors in the same patient must be low since it has not been described before in the literature. This paper describes a 3-year-old girl with PKU and HFI.

Case Report

B.E., a 3-year-old girl, was transferred to the Neonatal Intensive Care Unit of our hospital two hours after birth, because of a history of sibling deaths in the family occurring within the first few months of life. Pregnancy and delivery were uneventful. Birth weight was 3760 g (75^{th} percentile), length 53 cm (95^{th} percentile), and head circumference 36 cm (95^{th} percentile). The parents were first cousins. The first-born child, a 7-day-old boy, had been admitted to our hospital with an abdominal mass, but died shortly after admission. Hamartoma of the liver had been found at autopsy. A urine sample from the second-born child, a 3-month-old boy, had been analyzed in our laboratory. A generalized aminoaciduria associated with glucosuria and proteinuria led to the diagnosis of the Fanconi syndrome. Subsequently, the child died and further investigations could not be carried out to find the etiology of the Fanconi syndrome.

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The initial physical examination in the nursery revealed unremarkable findings. The early neonatal course was complicated by hypoglycemia, and was treated with an intravenous glucose solution. She was breast-fed thereafter.

A complete routine blood count and urinalysis produced normal results. A test for reducing substance in the urine was negative. The blood sugar level fluctuated between 15-120 mg/dl. Transaminase activities were within the normal range. The leukocyte glycogen content was 10 µg / mg protein (normal ≤ 50 µg/mg protein); blood lactate was 34 mg/dl (normal 10-14 mg/dl) and pyruvate 1.33 mg/dl (normal 0.5 - 1 mg/dl). Serum and urinary amino acid patterns were normal. A repeat chromatogram of serum at the end of the first month demonstrated a high level of phenylalanine (23 mg/dl).

The patient was placed on a low phenylalanine diet. Sucrose and vegetable oil were added to her dietary regimen to meet energy requirements. She vomited the first two or three feedings and developed severe acidosis (CO_2 content 5.8 mEq/L). She was comatose, and the liver was palpable 5 cm below the right costal margin. SGOT was 200 IU, SGPT 310 IU, blood sugar 9 mg/dl, phosphorus 2.5 mg/dl, uric acid 9.5 mg/dl, potassium 3.5 mEq/L, lactate 209 mg/dl, and pyruvate 5 mg/dl. There was a generalized amino aciduria.

Intravenous fluid and bicarbonate therapy were initiated. The acidosis did not respond to bicarbonate therapy and peritoneal dialysis was performed. Her general condition improved gradually and she began to tolerate oral feedings. Sucrose was eliminated from the low phenylalanine diet.

When she was 15-months-old, she experienced a second attack, after the ingestion of fruit, which was similar to the first one noted at the age of 1.5 months. The second attack responded to the infusion of bicarbonate and glucose.

She received a low phenylalanine and sucrose/fructose free formula. She did not experience another such episode. The blood phenylalanine level was maintained within the normal range, and the renal tubular functions returned to normal. Her physical growth and mental-motor development were normal.

Discussion

The association of PKU with scleroderma[3], Duchenne muscular dystrophy[4], Charcot - Marie - Tooth disease[5], Down's syndrome[6], cystinuria[7], homozygous hypobetalipoproteinemia[8], and bilateral iris coloboma and optic atrophy[9] have been reported previously. Also, there have been cases reported in the literature describing PKU and galactosemia[10] and PKU and glycogenosis[11] within the same family. A review of the literature revealed neither the occurrence of PKU and HFI in the same patient nor within the same family.

A phenylalanine level of 23 mg/dl with a normal tyrosine level and a positive ferric chloride test of the urine led to the diagnosis of PKU in our patient. A subsequent BH_4 loading test showed no BH_4 deficiency.

Although fructaldolase B activity was not measured, the development of vomiting, lethargy, hepatomegaly following the ingestion of fructose from sucrose which was added to the low phenylalanine diet and from the fruit, coupled with a positive family history in which one sibling had died having similar clinical signs and symptoms led to the diagnosis of HFI. Biochemical evidence of hepatic malfunction, generalized hyperaminoaciduria due to defective renal tubular reabsorption, hypoglycemia, hyperuricemia, hypophosphatemia, a low serum potassium level and metabolic acidosis supported the diagnosis of HFI[2].

In Turkey PKU has a frequency of 1/3954 and is not uncommon[12]. The gene controlling the production of PAH is located on chromosome 12[13]. Although, the actual incidence of the deficiency of fructaldolase B, an enzyme that is controlled by a gene locus on chromosome 9, is not known, it is presumed to be around 1:20,000 as reported from Switzerland[2, 14]. If these figures are taken into consideration, the statistical probability of the two defects co-existing is 1:79,080,000.

Since this is the first case reported in which the two defects were associated, we believe that the combination of these two hereditary diseases, with different chromosomal locations, are not genetically related and that their occurrence was purely coincidental. The consanguinity of the parents should be considered the most important factor regarding this coincidence.

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