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NEPHROTIC SYNDROME AS A MANIFESTATION OF GALACTOSEMIA

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ABSTRACT

Galactosemia is an inborn genetic metabolic disorder which leads to the infant's inability to properly metabolize galactose.It is inherited in an autosomal recessive manner. Affected infants present shortly after birth when fed with milk products, (either breast milk or milk containing formula) as lactose is degraded by lactase into glucose and galactose.Galactose is then converted to glucose by the action of three enzymes. Deficiency of each one of these enzymes results in the three forms of galactosemia. Accumulation of toxic levels of galactose-1-phosphate in various tissues as in classic galactosemiaresults in the infant's presentation with multiple clinical features. These include hepatomegaly, cirrhosis, cataracts, failure to thrive, vomiting,hypoglycemia and central nervous system manifestations.The commonest renal injury in galactosemia is the Fanconi syndrome.Thus, aminoaciduria is frequently found.However, to the best of our knowledge, the occurrence of a nephrotic syndrome in galactosemiahas not been previously described. We present a case of galactosemia diagnosed at 20 days of age in a female infant who developed a nephrotic syndrome as part of her clinical spectrum. Upon appropriate dietary treatment, (lactose free diet), the nephrotic syndrome regressed.

INTRODUCTION

Galactosemia is divided into three types according to one of the three enzyme deficiencies responsible for the degradation of galactose **[**1-6**]**. Type I termed classic galactosemia is due to galactose-1 phosphate uridyl transferase deficiency (gene GALT), type 2 due to galactose kinase deficiency (gene GALK1) and type 3 due to galactose-6 phosphate epimerase deficiency (gene GALE) [7-10]. Of these, type 1 is the most common and most severe form.Galactosemia is a recognized cause of the renal Fanconi syndrome. This syndrome is a generalized dysfunction of the proximal tubule with no primary glomerular involvement **[**11-15**]**. It is characterized by variable degrees of phosphate, glucose, bicarbonate, uric acid and aminoacid wasting. Low molecular weight proteinuria in low to moderate amounts is almost always found in the Fanconi syndrome. We present a case of galactosemia type 1 who, in addition to demonstrating some features of Fanconi, had a nephrotic syndrome. Upon institution of a lactose free diet, the nephrotic proteinuria regressed. The above data suggest that apart from renal tubular damage, galactosemia can cause glomerular injury.

Case description

An Arabic female neonate was admitted at 20 days of age due to fever, diarrhea, irritability and icterus. She is the sixth living child of nine pregnancies of consanguineous parents (first degree cousins). The child was born at term after a normal pregnancy and uneventful delivery. Birth weight was 4320g. The first born child and one of the father's sisters died in infancy, both having been jaundiced. Diagnosis was not established at the time. One

other child, now 18 years old, also presented with neonatal icterus and was diagnosed with galactosemia. Prior to admission, our reported baby was exclusively breast fed.

On examination, body weight was 4200g, BSA 0.25 m^2, temperature 39^0C, she was jaundiced, peripheral edema, showed signs of dehydration and had a distended abdomen due to ascites. The liver was moderately enlarged at 4cm below the costal margin.Opthamological examination revealed bilateral incipient cataracts.

Laboratory data were Hb 9.0 g/dl, WBC 17,000/mcl, neutrophils 44%, glucose 76 mg/dl, Na 146mEq/L, K 3.3 mEq/L, Cl 122 mEq/L, creatinine 0.9 mg/dl, uric acid 1.8 mg/dl, total bilirubin 23.3 mg/dl, direct bilirubin 15.3 mg/dl, SGOT 123 IU/L, SGPT 57 IU/L, LDH 840 IU/L, INR 1.7, total protein 2.9 g/dl, albumin 2.1 g/dl, total cholesterol 34 mg/dl.Blood gas analysis showed a pH 7.27, $pCO_2$25 mmHg, bicarbonate 11.5 mEq/L, an anion gap (corrected for serum albumin) of 16 with a delta AG/delta HCO_3ratio of 0.32.

Urinalysis showed glycosuria, 100 mg/dl, protein 300 mg/dl, bilirubin – large and a pH of 5.0.A 24 hour urine collection for protein measured 359 mg equivalent to 59.8 mg/m^2/h (nephrotic range proteinuria defined as >40 mg/m^2/h). Aminoaciduria was detected. Fractional excretion of phosphateand uric acid were markedly increased.

Screening by the quantitative Beutler test was positive for galactosemia type 1 (GALT deficiency). The infant was rehydrated and commenced on a lactose free diet (Nutrilonpepti junior formula). For fear of coexistent sepsis, she was initially administered antibiotic coverage consisting of ampicillin, cephalexin and metronidazole. Once blood and urine cultures returned sterile, antibiotic treatment was stopped. Within several days after the beginning of the lactose free diet, the infant's condition markedly improved. Her fever abated, stool number and consistency returned to normal, jaundice decreased and ascites disappeared.

Laboratory values showed a gradual normalization of liver enzymes, INR and blood gas analysis. Serum creatinine returned to its basal value of 0.3 mg/dl. Notably, proteinuria improved to 111 mg/24h equivalent to 18.5 mg/m^2/h and serum albumin increased to 4.1 g/dl. She was discharged on Nutrilon formula and referred for continued follow up to metabolic and child development outpatient clinics.

DISCUSSION

This infant's diagnosis of galactosemia was unnecessarily delayed [7]. The medical staff was notaware of the family's history as outlined above (parental consanguinity and confirmed galactosemiain, at least, one sibling), she was not screened for the disease at birth or even prenatally. In the United States, newborns are routinely screened for galactosemia. Due to the delay in diagnosis, she was exclusively breast fed and thus presented at 20 days of age with the characteristic features of galactosemia type 1**[**8-10**]**. From a renal perspective, she developed a Fanconi syndrome and renal failure. The latter was probably due to dehydration brought about by diarrhea and possibly aggravated bynatriuresis and polyuria. It rapidly responded to intravenous saline loading. The Fanconi syndrome was manifested by renal tubular acidosis (RTA) type II (proximal RTA) as evidenced by a normal AG metabolic acidosis, a urine pH of 5.0 and a delta ratio < 0.4 implying a bicarbonate loss [8,9,12]. It was also manifested by aminoaciduria, phosphate and uric acid wasting. Although low molecular weight proteinuria in small amounts is a frequent accompaniment of the Fanconi syndrome, our case is unique in that it demonstrated nephrotic range proteinuria. This was associated with hypoalbuminemia and low cholesterol levels. The decreased cholesterol levels probably reflect impaired liver functionand malabsorption. Thus, our patient fulfils the 2 major criteria of the nephrotic syndrome, namely nephrotic proteinuria and hypoalbuminemia. It can be argued that the markedly decreased serum albumin is also a reflection of liver dysfunction coupled with it being a negative phase reactant. Nevertheless, nephrotic range proteinuria in the clinical spectrum of galactosemia is a feature previously undescribed. It suggests that, in addition, to proximal tubular toxicity, the disease can also cause glomerular damage, possibly to podocytes. These injuries, both tubular and glomerular are, however, reversible as seen by the disappearance of proximal tubular dysfunction and regression of the proteinuria on a lactose free diet.

CONCLUSION

The present case implicates the nephrotic syndrome, or at the very least, nephrotic range proteinuria as part of the clinical features of galactosemia. It also supports the practice of routine newborn screening for the disease.

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DECLARATIONS OF INTEREST

The authors declare that they have no conflicts of interest. The study was not funded.All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

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