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Distal Renal Tubular Acidosis and Hereditary Elliptocytosis in a Single Family

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ABSTRACT

Distal renal tubular acidosis (RTA) and hereditary elliptocytosis (HE) are apparently distinct, genetic conditions. We report a family with 3 children having both hereditary elliptocytosis and distal renal tubular acidosis. The simultaneous occurrence of these two conditions in three siblings could be due to covariations in the same family, although a possible contiguous gene syndrome for distal RTA and HE cannot be excluded. This report emphasises the importance of excluding a renal tubular defect in any child who presents with elliptocytosis and failure to thrive.

Keywords: covariation; contiguous gene syndrome; genetic counselling

INTRODUCTION

Distal renal tubular acidosis (RTA) is an uncommon renal disorder with a distal tubular acidification defect. It is characterised by inadequate net acid excretion resulting in a urine pH consistently above 6, hyperchloraemic metabolic acidosis, growth impairment and in untreated cases, nephrocalcinosis and renal failure. It may occur as a primary condition, or as a secondary manifestation of a variety of underlying disorders, such as Sjogren's Syndrome, use of amphotericin B and certain blood disorders such as sickle cell anaemia.

Hereditary elliptocytosis (HE) is diagnosed if the blood smear reveals more than 50% of the erythrocytes to be elliptical in shape. The disease is most commonly asymptomatic but may cause chronic haemolysis or very rarely, an aplastic crises[1,2]. In Malaysia, stomatocytic HE, a subtype of HE, is common among the Malays with incidence of 5.1% - 13.2% having been reported[3,4]. It is usually asymptomatic and is said to confer resistance to malaria[2].

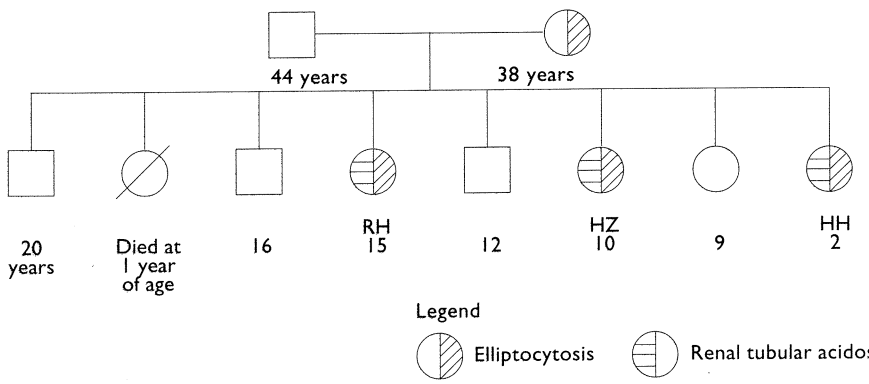
Both distal RTA and HE are inherited in an autosomal dominant fashion. The association of HE with distal RTA has been reported but was assumed to be random[5]. To our knowledge, this is the second report of this association.

CASE REPORT

HH is a 17-month old Malay girl and the eighth and youngest child of non-consanguinous parents. She was referred to our hospital for suspected renal tubular acidosis (RTA) because of her strong family history, as illustrated in Fig 1.

HH first presented to the referring hospital at the age of 12 months for investigation of pallor and growth retardation. She was given blood transfusions and although there was a strong family history of elliptocytosis and renal tubular acidosis, her parents declined referral to a tertiary institution for further investigation. At the age of 16 months, she required treatment for pallor and gastroenteritis. Following another blood transfusion, she was discharged well but was re-admitted with metabolic acidosis and hypokalaemia (serum potassium 1.9 mmol/L). Physical examination revealed a growth retarded child with a weight of 4.5 kg (birth weight 3.2 kg). The length and occipito-frontal circumference corresponded only to the 50th percentile of a 3-month old baby. She was anicteric, pale and had mild

Fig 1 - Family pedigree



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splenomegaly. In addition, she had rickets, evidenced by absence of primary dentition, widely opened sutures and fontanelles, widened wrists and a rachitic rosary. There was mild hypotonia and delayed motor development equivalent to that of a 4-month-old.

The family was first brought to our attention over twenty years ago in 1975 when the eldest sister died suddenly at one year of age, probably of intracranial haemorrhage. Efforts to trace her medical records were unsuccessful. The second and third sisters (RH and HZ) presented with pallor and failure to thrive in 1979 and 1984 at 15 and 24 months of age, respectively. Investigations then revealed hyperchloraemic metabolic acidosis and a persistently alkaline urine (Table I). Ammonium chloride loading tests confirmed the diagnosis of distal RTA in both sisters. In addition, both sisters had anaemia and marked elliptocytosis. They were started on alkali therapy but compliance was poor and they were lost to follow-up in 1987.

Screening of both parents, the third brother and fourth sister revealed normal acid-base balance and renal functions. The mother is short with a height of 144 cm. In addition, she had marked elliptocytosis. The third brother and the fourth sister both had normal blood films, renal functions and growth parameters. The two older brothers are also of good health and normal stature. However, no laboratory data are available regarding these 2 brothers as they declined to be investigated.

Laboratory studies of HH revealed a haemoglobin level of 73 g/L and a reticulocyte count of 10%. The peripheral blood smear demonstrated predominance of common elliptocytes. Despite the hyperchloraemic metabolic acidosis (serum chloride 113 mmol/L, pH 7.31, total HCO_3 10.3 mmol/L, base excess -13.9), her urine pH was consistently above 7.0 (Table I). Polyuria and a poor urine concentrating ability were present. There was no glycosuria or aminoaciduria. Urine culture however grew *Klebsiella pneumoniae*. Rickets was confirmed radiologically and biochemically, as evidenced by raised serum alkaline phosphatase of 498 μmol/L. Serum phosphate and calcium levels were within normal limits. Abdominal ultrasonography demonstrated bilateral nephrocalcinosis and this was confirmed by computerised tomography. Haemoglobin electrophoresis was normal.

Treatment commenced with potassium citrate and Shohl solution (mixture of 10% sodium citrate and 6% citric acid) initially, with a total base replacement equivalent to 4 mmol/kg/day gradually increasing to 12 mmol/kg/day to maintain adequate acidbase balance. Her urinary tract infection was treated with antibiotics and her anaemia corrected with blood transfusions.

On re-evaluation of the affected sisters, growth retardation with hyperchloraemic metabolic acidosis and nephrocalcinosis were still evident. They were restarted on alkali therapy. On review 3 months later, all three sisters showed clinical and biochemical improvement.

DISCUSSION

Distal renal tubular acidosis (RTA) is inherited in an autosomal dominant fashion[6] but most cases of distal RTA are sporadic. Rarely, distal RTA occurs in autosomal recessive forms but this is unlikely in this family as the parents are not related and the father is normal. In a proportion of affected families, selective expressivity in females has been described. The acidification defect has been known to disappear spontaneously, although the reason for this is

Table I - Biochemical and urinary indices of the mother and three sisters

	Mother	RH	HZ	HH
Hb (g/L)	139	79	65	73
Reticulocyte	0.4	10.0	23.1	10.0
Blood urea (mmol/L)	-	6.8	3.2	6.2
Serum sodium (mmol/L)	-	146.0	134.0	143.0
Serum potassium (mmol/L)	-	3.8	2.6	3.9
Serum chloride (mmol/L)	-	121.0	114.0	115.0
Blood pH	7.49	7.22	7.26	7.31
$PaCO_2$ (mmHg)	31.0	27.0	25.0	21.0
Plasma bicarbonate (mmol/L)	23.0	10.8	11.1	10.4
Base excess	+1.0	-15.4	-13.8	-13.9
Urine pH	5.5	7.0	7.2	7.0
Urine specific gravity	1.025	1.009	1.004	1.005

unclear[7]. The mother's short stature may be the result of an earlier but unrecognised and untreated RTA which had resolved spontaneously.

The hereditary elliptocytosis syndrome encompasses a heterogenous group of red cell membrane disorders transmitted in an autosomal dominant fashion. Although the common feature is the presence of elliptical red cells on peripheral blood film smear, a related condition designated as stomatocytic elliptocytosis is widespread in parts of Southeast Asia. This peculiar abnormality, which results in a rigid red cell wall resistant to malarial parasite invasion, is due to a deletion in the gene for band 3 protein located on chromosome 17[8]. This family has the common and not the stomatocytic subtype of elliptocytosis in view of the red cell morphology, splenomegaly in the index case and chronic haemolysis as evidenced by reticulocytosis. Thus, the eldest sister who died suddenly of an intracranial haemorrhage, may have succumbed to an aplastic crisis, a rare complication secondary to common HE.

Both distal RTA and HE are distinct genetic conditions with no apparent relationship to one another. The gene sites for HE are located on several sites in the human genome with E1, E2 and E3 elliptocytosis being located on chromosomes 1p36-34, 1q24 and 14q22-23, respectively[9-11]. In addition, the gene site for the Malaysian-Melanesian type of HE is identified to be on chromosome 17q21-22[8]. Although the gene site for renal tubular acidosis (distal) - osteopetrosis syndrome is located on chromosome 8q22, other possible candidate gene sites for distal RTA may exist[11]. In the only previous report in the literature where these two diseases occurred in the same family, they were regarded as separate entities[5]. We report a family where 3 female siblings have similar distal renal tubular acidosis and elliptocytosis. Their mother also has elliptocytosis and is of short stature. In view of the limited pedigree available for analysis and the diversity of documented gene sites for HE, the suggestion of a genetic linkage between distal RTA and HE is at best, speculative. Nevertheless, the possibility of a tentative contiguous gene syndrome for distal RTA and HE cannot be totally excluded, as new gene sites for distal RTA may yet be identified in the on-going human genome research. Until more data from molecular genetic studies are available, the simultaneous occurrence of the above two disorders represents covariations in the same family.

Alternatively, it may be possible that elliptocytosis can induce a renal tubular defect in susceptible individuals. It is therefore reasonable that any child with elliptocytosis and failure to thrive should be investigated for the possibility of an associated renal tubular defect.

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