X-linked congenital Addison's disease

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SUMMARY Two male cousins developed symptoms and signs of Addison's disease at age 3 weeks. The family history indicates that their disorder is inherited as an X-linked recessive.

Addison's disease in children is rare. It is occasionally familial, and in a few cases an X-linked mode of inheritance has been suggested. We describe here two male cousins both of whom developed signs of Addison's disease at age 3 weeks, their family history indicated that this was due to an X-linked recessive disorder.

Case report

Case 1. This boy was born on 14 November 1971 at term after a normal pregnancy and delivery. He was the first child of healthy, unrelated, English parents. His birthweight was 3.07 kg. He developed mild, prolonged neonatal jaundice and at age 3 weeks began feeding poorly and losing weight. At 4 weeks he started vomiting, and by 8 weeks he was dehydrated and weighed only 3 kg. Investigations showed hyponatraemia, hyperkalaemia, and acidosis: serum sodium 120 mmol/l, potassium 5.8 mmol/l, and bicarbonate 21.5 mmol/l. He responded rapidly to intravenous physiological saline but when this treatment was stopped his symptoms returned. At age 12 weeks he was noted to have a pigmented scrotum. Further investigations showed: low urine 17-hydroxy-corticosteroids 0.4 mg/24h (1.38 μmol/24h) but normal 17-ketosteroids 0.6 mg/24h (2.08 μmol/24h), a low basal plasma cortisol 7.0 μg/100 ml (193 nmol/l), and an inadequate response to Synacthen stimulation, plasma cortisol rising from 7 μg/100 ml (193 nmol/l) to 18 μg/100 ml (496 nmol/l). The urine oxygen index was normal (0.2) as was the plasma 17-hydroxyprogesterone (0.1 μg/100 ml (3.23 nmol/l)). Fractionation of the urine steroids showed no aldosterone and merely traces of deoxycorticosterone. These investigations indicated some degree of adrenal insufficiency which, at that time, was thought to be due to delay in maturation of the enzyme systems. The infant responded to treatment with oral sodium supple-

ments and 9 α-fluorohydrocortisone (0.025 mg twice a day). At age 4 months this treatment was gradually stopped. He remained well and in electrolyte balance without treatment until age 2 years 7 months, when he was readmitted with a history of vomiting, fatigue, and weight loss. He was dehydrated, with increased skin pigmentation, and a blood pressure of 65/40 mmHg.

Investigations showed hyponatraemia, hyperkalaemia, and acidosis (serum sodium 123 mmol/l, potassium 5.5 mmol/l, and bicarbonate 18 mmol/l). Plasma aldosterone was low—3 ng/100 ml (83.3 pmol/l) and plasma renin high—3000 units. Plasma cortisol levels were low—morning 8.8 μg/100 ml (243 nmol/l), afternoon 4.0 μg/100 ml (110 nmol/l), and there was poor response to Synacthen stimulation, plasma cortisol rising from 5.9 μg/100 ml (163 nmol/l) to 9.4 μg/100 ml (260 nmol/l). Plasma 17-hydroxyprogesterone was normal (0.3 μg/100 ml (0.96 nmol/l)), as was the urine oxygenation index (0.1). No adrenal, thyroid, or gastric antibodies were detected. Tuberculin test was negative, and serum thyroxine normal, 8.8 μg/100 ml (111.8 nmol/l). These investigations confirmed the diagnosis of Addison's disease and he was treated with cortisol acetate 5 mg three times a day, and fludrocortisone 0.05 mg twice a day. He remains well on maintenance treatment.

Case 2. This boy was born on 9 May 1979 after a normal pregnancy and labour. He was the first child of healthy, unrelated, English parents. His birthweight was 3.75 kg and he developed mild, prolonged neonatal jaundice. At age 3 weeks he began to feed poorly, at 3½ weeks he began vomiting, and at 4 weeks was admitted to hospital. He was dehydrated, weighed 3.64 kg, and had a pigmented scrotum. Investigations showed hyponatraemia, hyperkalaemia, and acidosis (serum sodium 123 mmol/l, potassium 7.4 mmol/l, and bicarbonate 11.6 mmol/l), low plasma aldosterone 140 pmol/l (5.04 ng/100 ml), and low plasma cortisol 190 nmol/l (6.9 μg/100 ml). Plasma 17-hydroxyprogesterone was normal (13 nmol/l (0.43 μg/100 ml)), as was the urine oxygenation index (0.6). These results indicated that he had adrenal insufficiency. As he was acutely ill, treatment was started without waiting for the results...
of a 24-hour urine collection for urinary steroid analysis. After resuscitation he was stabilised on maintenance therapy with cortisone acetate and fludrocortisone.

Enquiry into the family history revealed that Case 2 is the 1st-cousin of Case 1 (Figure). Their mothers are sisters and there is one other sister who has a healthy 14-year-old son. The fathers are unrelated. Two of the maternal grandmother’s brothers had died suddenly at age 3 months.

Discussion

It has been suggested that familial Addison’s disease of childhood might represent a milder form of the same genetic disorder responsible for congenital adrenal hypoplasia. Isolated congenital adrenal hypoplasia is very rare. A few familial cases have been reported. There is, as with familial Addison's disease of childhood, a preponderance of males. This condition has to be distinguished from other causes of adrenal insufficiency presenting in the neonatal period—such as congenital adrenal hyperplasia and bilateral adrenal haemorrhage.

Each boy has clinical and biochemical evidence of congenital adrenal insufficiency. The findings of normal urine oxygenation indices and normal plasma 17-hydroxyprogesterone levels in both, and the normal urine ketosteroids in Case 1, exclude congenital adrenal hyperplasia. The family history indicates that the disorder is inherited as an X-linked recessive. The history of Case 1 is important as it confirms that if an infant presents in the first few weeks of life with signs of adrenal insufficiency but somewhat equivocal adrenal function tests he will progress to total adrenal failure if he is diagnosed as suffering from a delay in maturation of the adrenal enzyme systems.

It is likely from their histories and investigations that these boys have a form of congenital adrenal hypoplasia, but clear evidence is not available as this diagnosis can only be confirmed histologically. Nevertheless they do have X-linked congenital Addison's disease and their histories lend support to the suggestion that familial Addison’s disease of childhood may represent a milder form of the same genetic disorder responsible for congenital adrenal hypoplasia.

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References


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