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Congenital adrenal hyperplasia masquerading as periodic paralysis in an adolescent girl

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ABSTRACT Congenital adrenal hyperplasia is an uncommon diagnosis in routine clinical practice. 21-hydroxylase deficiency, which is its most common subtype, may be diagnosed at birth in a female infant by virilisation or by features of salt wasting in both genders. However, other uncommon subtypes of this condition such as 17-alpha-hydroxylase deficiency, 11-beta-hydroxylase deficiency may present much later in adolescence or adulthood. A high index of suspicion is necessary when evaluating children with hypertension, hypokalaemia, metabolic alkalosis or sexual infantilism.

Keywords: congenital adrenal hyperplasia, hypertension, hypokalaemia, periodic paralysis, sexual infantilism
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INTRODUCTION

Periodic paralysis is not uncommon in childhood. The common causes include familial channelopathies causing hypokalaemic/hyperkalaemic/thyrotoxic periodic paralysis, paramyotonia congenita and rarely, Andersen's syndrome characterised by short stature, clinodactyly, scoliosis, hypertelorism, low-set ears, a broad forehead, a poorly developed jaw and a prolonged QT interval. Other underlying aetiologies should be considered if hypokalaemia is associated with hypertension, sexual infantilism or metabolic acidosis. 17-alpha-hydroxylase deficiency, a very rare cause of congenital adrenal hyperplasia, was first recognised in 1966.[1] This disorder can cause hypokalaemia, hypertension and sexual infantilism.

CASE REPORT

A 15-year-old Indian girl who was known to have congenital bicuspid aortic valve was referred to our centre to rule out the possibility of primary hyperaldosteronism. She was born of consanguineous parentage and had initially presented with a history of recurrent episodes of periodic paralysis from three years of age. Hypokalaemia had been documented each time and corrected. A local physician had documented mild hypertension during one of these episodes and suspected Conn's syndrome. However, the patient's blood pressure settled at the time of discharge and she was placed on potassium chloride supplements and spironolactone due to hyperaldosteronism.

The patient had not attained her menarche till date, which was a matter of concern for her parents. Family history revealed that one of her sisters had passed away during a febrile illness at the age of ten years, but the details were not available as her medical documents had been destroyed. The patient's parents had also noticed that she was becoming darker with age. The patient presented to our hospital with another episode of flaccid paralysis. On examination, she weighed 38 kg, had a height of 153 cm (10th centile), an arm span of 165 cm and an upper/lower segment ratio of 78/88, cm i.e. eunuchoid body proportions. She was found to have severe proximal myopathy, mild hypertension (150/86 mmHg), diffuse hyperpigmentation of the skin and sexual infantilism. She had no pubic/axillary hair and her breasts were Tanner stage I. Cardiovascular system examination revealed normal heart sounds with a systolic click over the second aortic area.

Blood biochemistry revealed hypokalaemia (1.43 mmol/L), normal serum sodium (138 mmol/L), alkalosis (bicarbonate 35 mmol/L), elevated total creatine kinase (611 µ/L) and normal renal function. Ultrasonography of the pelvis revealed a hypoplastic uterus (4.3 cm × 1.1 cm × 1.7 cm) and enlarged ovaries (volumes 23.6 ml, 15 ml) with multiple small cysts. The adrenals were found to be normal on magnetic resonance (MR) imaging. The presence of hypokalaemic alkalosis, mild hypertension, sexual infantilism and hyperpigmentation led to a suspicion of congenital adrenal hyperplasia, probably associated with 17-alpha hydroxylase deficiency. Primary hyperaldosteronism or Conn's syndrome was not considered as it is more common in adults.

Laboratory tests revealed low serum cortisol of 115.9 nmol/L (normal range [NR] 138–690 nmol/L), low serum oestrogen of 50.04 pmol/L (NR 55–555 pmol/L) and low serum 17-hydroxy progesterone of 0.28 nmol/L (NR 0.6–3.0 nmol/L), with elevated levels of serum adrenocorticotrophic hormone (ACTH) of 44.02 pmol/L (NR 1.3–16.7 pmol/L). The patient also had raised gonadotrophins (serum luteinising hormone [LH] 27.7 IU/L [NR 0.1–6.0 IU/L] and follicle-stimulating hormone [FSH] 37.5 IU/L). Basal dehydroepiandrosterone sulphate (DHEAS) was low at 36.5 µg/L (NR 120–5,350 µg/L), aldosterone was elevated at 1925.0 pmol/L (NR 55–250 pmol/L), and

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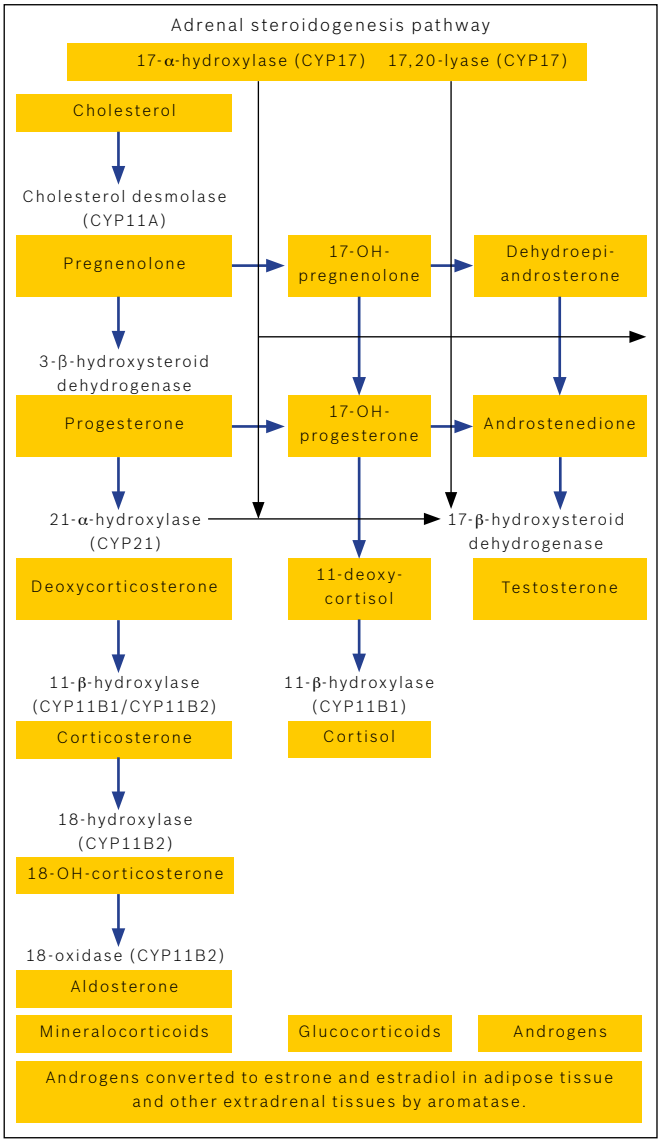

Fig. 1 Steroid biosynthetic pathway.

plasma renin activity was undetectable. Karyotype done by phytohaemagglutination method was 46,XX. She was started on hydrocortisone (12 mg/m^2) in split doses and oral potassium supplements for two weeks. At review two months later, her skin had become lighter, her serum potassium was 4.2 mmol/L (NR 3.5–5.0 mmol/L) without any potassium supplements and her blood pressure was normal.

DISCUSSION

17-alpha hydroxylase deficiency, which was first described by Biglieri et al,[1] is a rare form of congenital adrenal hyperplasia that results in decreased production of cortisol, androgens and oestrogens with a subsequent increase in ACTH and gonadotropin levels.[1-5] The *CYP17* gene has been mapped to chromosome 10q24-25;[6] P450c17 microsomal enzyme has both 17-alpha hydroxylase and 17,20-lyase activity in the adrenals and gonads. In the steroid biosynthetic pathway, 17-alpha hydroxylation of pregnenolone and progesterone is an essential step for cortisol and sex steroid production (Fig. 1). These 17-hydroxylated derivatives are further converted to C-19 steroids by 17,20-lyase to yield DHEA. Decreased cortisol synthesis increases ACTH, which in turn increases the production of deoxycorticosterone, corticosterone and 18-hydroxycorticosterone.[2] This leads to hypertension, hypokalaemic alkalosis, suppressed renin and aldosterone. Patients could have either combined or isolated deficiency of the two enzymes (17-alpha hydroxylase and 17,20-lyase). Patients with 17-alpha hydroxylase deficiency present with primary or secondary amenorrhoea[7] and have hypertension that can be treated with corticosteroids. The cortisol levels in untreated patients are low, but they do not have symptoms of cortisol deficiency, as corticosterone has mild glucocorticoid activity and is found in excess in these patients.

Our patient's presentation was unique,as she presented with periodic paralysis and elevated muscle enzymes related to underlying severe hypokalaemia. Another unusual feature of our patient was the age of presentation, and primary amenorrhoea and hypertension were still not dominant clinical findings. Her aldosterone levels were not suppressed, a finding that is typical of 17-alpha hydroxylase deficiency and which has been reported in several case reports.[3,5,7,8] Elevated or normal aldosterone levels are believed to be due to the endogenous secretion of aldosterone, along with 18-hydroxycorticosterone from the zona fasciculata under the influence of elevated ACTH in patients such as ours.

In conclusion, the diagnosis of congenital adrenal hyperplasia may not be made at birth. 17-alpha hydroxylase/17,20-lyase deficiency needs to be ruled out by appropriate hormonal studies in young adolescents or adult female patients with sexual infantilism, hypertension, hypokalaemia with periodic paralysis as well as male patients with ambiguous or feminine external genitalia.

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