Familial X-linked adrenocortical hypoplasia association with androgenic precocity

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SUMMARY Four male cousins showed clinical and biochemical features of X-linked recessive congenital adrenocortical hypoplasia. In addition, they showed varying degrees of androgenic precocity. One was virilised at birth. Another showed advanced growth and skeletal maturation. The remaining two had genital measurements greater than normal for age and showed raised testosterone levels, although pituitary gonadotrophins seemed normal and there was no response to luteinising hormone-releasing hormone testing. It is suggested that in X-linked adrenal hypoplasia, intrauterine adrenal androgen deficiency results in abnormal priming of the pituitary 'gonadostat', leading to an abnormal feedback with excess testosterone production and non-progressive virilisation.

Adrenocortical hypoplasia occurs in association with anencephaly or pituitary hypoplasia, but is also found as an isolated defect. Two types of idiopathic hypoplasia are known: an autosomal recessive form, in which the hypoplastic adrenal cortex is otherwise normal in histological appearance; and an X-linked recessive variety in which the histology is that of irregularly arranged, 'fetal type' eosinophilic cortical cells.1-3

In this report 4 children are described in whom X-linked recessive inheritance is suggested by the pattern of transmission, and who showed differing degrees of androgenic precocity.

Increased testicular maturity and advanced sexual development have been described in association with adrenal hypoplasia,4 whereas older boys with this condition fail to enter puberty spontaneously owing to hypogonadotrophic hypogonadism.5-9

It is suggested that there is failure to establish a normal hypothalamo-pituitary gonadotrophin-release feedback system, leading to excess testicular androgen secretion and maintenance of the feedback at a higher level. However, lack of a prepubertal rise in adrenal androgen output may be the reason for later failure of activation of gonadotrophin release and therefore for delayed entry into puberty.

Methods

Assays of luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone, cortisol, aldosterone, and adrenocorticotropic hormone (ACTH) were performed by Dr D Pillay at the University of Natal Medical School, Chemical Pathology Laboratories using standard techniques.

Family history and case reports (Figure)

Numerous male infants have died in previous generations with symptoms of vomiting and failure to thrive. In generation III, two brothers were known to have had adrenal insufficiency. Our 4 patients are all in generation IV.

Case 1. This boy had not regained his birthweight of 3·9 kg by 2 months. He was obviously virilised and had large external genitalia. Penis circumference was 6 cm and length of testis 2·2 cm. His serum sodium concentration at 2 months was 120 mmol/l, serum potassium 7·9 mmol/l, his 24-hour urine showed sodium 14 mmol and potassium 9·3 mmol. Excretion of 17-oxosteroids was 2·4 mg/24h (8·3 μmol/24h) (normal 2–4 mg/24h; 7–14 μmol/24h) and that of 17-ketosteroids 0·5 mg/24h (1·75 μmol/24h) (normal 0–0·5 mg/24h; 0–1·75 μmol/24h).

Treatment with fluorocortisone and cortisone acetate soon resulted in improvement. At age 5 years he was killed in a motor accident.

Case 2. This boy weighed 3·9 kg at birth on 28 December 1975. He had poor feeding and recurrent vomiting in the neonatal period. He was admitted at age 3 weeks when his serum sodium concentration was 116 mmol/l and potassium 6·8 mmol/l. His
urinary total 17-oxogenic steroid excretion was 0·7 mg/24h (2·4 µmol/24h) (normal 2–4 mg/24h; 7–14 µmol/24h); while his 17-ketosteroid excretion was 0·2 mg/24h (0·7 µmol/24h) (normal 0–0·5 mg/24h; 0–1·75 µmol/24h). He was also started on fluorocortisone and cortisone acetate and has been well, apart from repeated upper respiratory tract infections. His growth has been rapid, height at 12 months having been 84·5 cm and at 29 months 99 cm (both above the 97th Boston centile). At 2½ years genital measurements were greater than normal for age10 with penis circumference 5·3 cm and length of testis 2·5 cm. Basal plasma testosterone at 0800 hours was 480 ng/100 ml (16–6 nmol/l), virtually in the adult male range.11 However, LH (2·9 mIU/ml) and FSH (3·5 mIU/ml) were within normal limits12 and failed to rise after intravenous injection of LH-RH 50 µg/m² (Table 1).13

Case 3. At birth on 21 February 1975 this boy had been a large baby (4·9 kg). He had severe early feeding difficulties with frequent vomiting and had required intravenous fluids on several occasions. His condition then improved without any specific treatment. At 18 months he was above the 97th centile for both height and weight, and had a bone age of 3½ years (standards of Greulich and Pyle).14 At that stage his serum electrolytes were normal, as was his urinary steroid excretion (Table 2). He became ill a year later, when he developed a salt-losing state with recurrent vomiting. He improved initially on added salt, but then developed a klebsiella septicaemia and died suddenly. His urinary steroid excretion had shown a progressive decline. At necropsy no adrenal tissue could be identified, but the pituitary gland appeared normal.13

Table 1 Response to 50 µg/m² LH-RH administered intravenously

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Luteinising hormone (mIU/ml)</th>
<th>Follicle-stimulating hormone (mIU/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Case 2</td>
<td>Case 4</td>
</tr>
<tr>
<td>Case 2</td>
<td>2·9</td>
<td>3·2</td>
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<td></td>
<td>3·5</td>
<td>4·3</td>
</tr>
<tr>
<td></td>
<td>3·2</td>
<td>4·0</td>
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<tr>
<td>Case 4</td>
<td>3·6</td>
<td>3·6</td>
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<td></td>
<td>3·6</td>
<td>3·6</td>
</tr>
</tbody>
</table>

Table 2 Biochemical data on Case 3

<table>
<thead>
<tr>
<th></th>
<th>1976</th>
<th>1977</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Oct.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Sodium (mmol/l)</td>
<td>131</td>
<td>125</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3·8</td>
<td>5·5</td>
</tr>
<tr>
<td>24-hour urine Sodium (mmol/l)</td>
<td>50</td>
<td>80·6</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>23</td>
<td>31·9</td>
</tr>
<tr>
<td>Total 17-oxosteroids (umol/24 h)</td>
<td>47·6</td>
<td>16·6</td>
</tr>
<tr>
<td>(normal 14–73)</td>
<td>14·9</td>
<td>5·6</td>
</tr>
<tr>
<td>17-oxosteroids (umol/24 h)</td>
<td>4·5</td>
<td>1·11</td>
</tr>
<tr>
<td>(normal 3–14)</td>
<td>1·3</td>
<td></td>
</tr>
</tbody>
</table>

Case 4. This first child had weighed 3·1 kg at birth on 6 August 1974. He apparently had progressed normally until November 1977 when, at age 3½ years, he developed persistent vomiting leading to dehydration.

Investigations showed a salt-losing state with serum sodium concentration 123 mmol/l, potassium 4·9 mmol/l, 24-hour urine sodium 51·6 mmol and
aldosterone 0·130 μg/24h (3·6 nmol/24h) (normal 0·198–2·59 μg/24h; 5·5–72 nmol/24h). Total 17-
oxogenic steroid excretion was normal (2·4 mg/24 h; 8·5 μmol/24h). Treatment consisted of
fluorocortisone only. During the ensuing 6 months he developed increasing apathy and weakness, a
tendency to vomit, recurrent fevers, and increasing pigmentation. Plasma cortisol levels were less than
2·2 μg/100 ml (60·7 nmol/l) at 0800 hours and at
midnight, while the basal plasma ACTH level at
0800 hours was above 800 pg/ml. Soon after, he
presented with an Addisonian crisis. With steroid
treatment, he is again well. His genitalia at age 4
years are greater than normal, testis length being
2·5 cm. Basal testosterone level is increased at 180
ng/100 ml (6·2 nmol/l), but LH (3·5 mIU/ml) and
FSH (2·7 mIU/ml) are normal. LH/FSH release
was studied after intravenous injection of LH-RH
(Ayerst Laboratories) at 50 μg/m² as suggested by
Dickerman et al.18 (Table 1). Like Case 2 he too has
failed to show a significant rise in LH and FSH.

Discussion

All our patients presented with hyponatraemia and
hyperkalaemia. In Cases 3 and 4, a low aldosterone
level was found in the presence of hyponatraemia
and increased urinary sodium loss. The subsequent
development of severe glucocorticoid deficiency in
both Cases 3 and 4 virtually excludes hypoaldo-
steronism due to specific biosynthetic defects in the
conversion of corticosterone to aldosterone, as
patients with 18-oxidation defects have normal
cortisol levels. In addition, such defects can generally
be adequately treated with sodium chloride and
desoxycorticosterone acetate. Spontaneous clinical
improvement despite persistence of the defect has
been described, and the adrenal gland appears
macroscopically normal in such cases.4

Salt loss may be a prominent feature of con-
genital adrenal hyperplasia with 21-beta hydroxylase
deficiency, inherited as an autosomal recessive
condition. In our patients the urinary oxosteroids
were not increased, and there was a clear pattern of
X-linked inheritance, thus ruling out this diagnosis.
The clinical picture and biochemical features in all
patients are consistent with the diagnosis of con-
genital adrenal hyperplasia. Each showed the
symptoms and biochemical sequelae of mineralo-
corticoid deficiency. ACTH levels were high, ruling
out a hypothalamic or pituitary cause for adrenal
insufficiency. Those cases of adrenal insufficiency
due to congenital lack of response to ACTH show
normal salt handling and macroscopically normal
adrenals at necropsy.18

The patients described here showed considerable
variation in the age of onset of symptoms and the
rate of progression within a single family. Cases 1
and 2 presented in the neonatal period, and Case 4
at 3½ years. This variability has been described
before.5–4,16 The rate of progression is equally
variable. The patient of Golden6 had shown salt
craving for 4 years before being diagnosed. Our
Case 4 showed progression of symptoms to severe
adrenal insufficiency over 6 months, whereas
Hensleigh's case3 deteriorated over 10 days.
Petersen et al.5 found a similar progression from
mineralocorticoid to total adrenocortical insuffi-
ciency in their patient.

Our patients show a clear pattern of sex-linked
recessive inheritance. This mode of transmission is
observed in those instances where the adrenals show
the histological features of the fetal cortex only.1–3

The 'miniature adult' form of adrenal hypoplasia is
apparently much more common,4 occurring in
both males and females, accompanying anencephaly
and hypotalamic or pituitary defects, or inherited in
an autosomal recessive fashion.16 Our cases are
thought to represent an isolated defect of organo-
gensis of the permanent adrenal cortex, while the
fetal cortex persists.1

In normal fetal life, the fetal zone of the adrenal
cortex develops under chorionic gonadotrophin
stimulation and is maintained after mid-gestation by
a high level of ACTH secretion.17 With hypoplasia
of the permanent cortex, a relative lack of cortisol
production after birth fails to suppress ACTH and
thus contributes to maintaining the fetal cortex.

The occurrence of virilisation as a possible
manifestation of adrenal hypoplasia has been noted
before and Petersen et al.4 drew attention to
advanced testicular maturation and increased
testosterone in their patients. Our Case 1 appeared
to be virilised at birth. This was non-progressive and
tended to be less obvious with time. The other
patients showed genital measurements greater than
normal for age. Cases 2 and 3 showed advanced
growth, and in Case 3 there was advanced skeletal
maturation. Cases 3 and 4 had increased testo-
sterone levels but appropriate levels of LH and FSH
for their ages, and on LH-RH testing there was no
significant rise in LH and FSH. This suggests an
abnormal gonadal-pituitary feedback system with
increased testosterone production despite a low
level of gonadotrophin stimulation.

The factors determining the balance between
pituitary gonadotrophins and testicular androgens in
fetal life are poorly understood. The number and
steroidogenic activity of testicular Leydig cells
parallels the early supply of chorionic gonadotropin.17 18 There is a peak production of testosterone coinciding with the period of male sexual differentiation between 70 and 90 days' gestation. Thereafter, fetal testosterone levels decline towards term in parallel with chorionic gonadotrophin, despite measurable and rising levels of fetal pituitary LH and FSH which have their peaks at mid-gestation.19 This may reflect early autonomous secretion of LH/FSH with gradual development and maturation of the hypothalamic-pituitary gonadal feedback system.20 It is also possible that increasing placental oestrogens induce a decreased level of response of the testis to gonadotrophin.20

Both testicular and adrenal androgens appear to take part in the establishment of the sensitive pituitary gonadotrophin release feedback system. If there is hypoplasia of the permanent adrenal cortex, the characteristic deficiency of 3-beta hydroxysteroid dehydrogenase activity of the fetal cortex17 21 results in deficient intrauterine adrenal androgen secretion. This could lead to an abnormal priming of the hypothalamic-pituitary 'gonodostat', requiring increased testicular androgen release, with subsequent virilisation and maintenance of the feedback at a higher level. Similarly, it seems likely that failure of the normal prepubertal rise of adrenal androgen production, especially of dehydroepiandrosterone,22 will result in a failure to activate normal hypothalamic-pituitary gonadotrophin release mechanisms with delay in pubertal development. Prader et al.,5 and other workers,6-8 have shown that cases of adrenal hypoplasia fail to enter puberty normally due to gonadotrophin deficiency, again indicating a profound disturbance of the feedback system.

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