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 adrenocorticotrophin (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 μ mol/24h) (normal 2–4 mg/24h; 7–14 μ mol/24h) and that of 17-ketosteroids 0.5 mg/24h (1.75 μ mol/24h) (normal 0–0.5 mg/24h; 0–1.75 μ mol/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

Figure Familial adrenocortical hypoplasia pedigree.

urinary total 17-oxogenic steroid excretion was 0.7 mg/24h (2.4 μ mol/24h) (normal 2–4 mg/24h; 7–14 μ mol/24h); while his 17-ketosteroid excretion was 0.2 mg/24h (0.7 μ mol/24h) (normal 0–0.5 mg/24h; 0–1.75 μ mol/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 μ g/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

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

Time (minutes)	Luteinising hormone (mIU/ml)		Follicle-stimulating hormone (mIU/ml)	
	Case 2	Case 4	Case 2	Case 4
0	2.9	3.2	2.5	2.3
15	3.5	4.3	3.2	4.6
30	3.1	4.0	2.7	3.9
45	3.2	4.0	3.6	3.6
60	—	3.6	—	3.8

Table 2 Biochemical data on Case 3

	1976	1977	
	12 Oct.	3 Nov.	29 Nov.
Plasma			
Sodium (mmol/l)	131	125	121
Potassium (mmol/l)	3.8	5.5	8.1
24-hour urine			
Sodium (mmol/l)	50	80.6	51
Potassium (mmol/l)	23	31.9	14.9
Total 17-oxogenic steroids (μ mol/24 h)	47.6	16.6	5.6
(normal 14–73)			
17-oxosteroids (μ mol/24 h)	4.5	1.11	1.3
(normal 3–14)			

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.

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 $\mu\text{g}/24\text{h}$ (3.6 nmol/24h) (normal 0.198–2.59 $\mu\text{g}/24\text{h}$; 5.5–72 nmol/24h). Total 17-oxogenic steroid excretion was normal (2.4 mg/24 h; 8.5 $\mu\text{mol}/24\text{h}$). 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 $\mu\text{g}/100\text{ ml}$ (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 $\mu\text{g}/\text{m}^2$ as suggested by Dickerman *et al.*¹³ (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 hypoaldosteronism 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 congenital 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 congenital adrenal hypoplasia. Each showed the symptoms and biochemical sequelae of mineralocorticoid 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.¹⁵

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.^{2–4,6} 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.*⁴ found a similar progression from mineralocorticoid to total adrenocortical insufficiency 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 adrenal glands 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 hypothalamic or pituitary defects, or inherited in an autosomal recessive fashion.¹⁶ Our cases are thought to represent an isolated defect of organogenesis 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 testosterone 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 gonadotrophin.^{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 hypothalamo-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 cortex^{17 21} results in deficient intrauterine adrenal androgen secretion. This could lead to an abnormal priming of the hypothalamic-pituitary 'gonadostat', 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,⁶⁻⁹ 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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References

- Sperling M A, Wolfsen A R, Fisher D A. Congenital adrenal hypoplasia: an isolated defect of organogenesis. *J Pediatr* 1973; **82**: 444-9.
- Pakravan P, Kenny F M, Depp R, Allen A C. Familial congenital absence of adrenal glands; evaluation of glucocorticoid, mineralocorticoid, and estrogen metabolism in the perinatal period. *J Pediatr* 1974; **84**: 74-8.
- Hensleigh P A, Moore W V, Wilson K, Tulchinsky D. Congenital X-linked adrenal hypoplasia. *Obstet Gynecol* 1978; **52**: 228-32.
- Petersen K E, Tygstrup I, Thamdrup E. Familial adrenocortical hypoplasia with early clinical and biochemical signs of mineralocorticoid deficiency (hypoaldosteronism). *Acta Endocrinol (Kbh)* 1977; **84**: 605-19.
- Prader A, Zachmann M, Illig R. Luteinizing hormone deficiency in hereditary congenital adrenal hypoplasia. *J Pediatr* 1975; **86**: 421-2.
- Golden M P, Lippe B M, Kaplan S A. Congenital adrenal hypoplasia and hypogonadotropic hypogonadism. *Am J Dis Child* 1977; **131**: 1117-8.
- Hay I D. Letter: Pubertal failure in congenital adrenal hypoplasia. *Lancet* 1977; **ii**: 1035-6.
- Hay I D. Letter: Pubertal failure in congenital adrenal hypoplasia. *Lancet* 1977; **ii**: 1360-1.
- Black S, Brook C G D, Cox P J N. Congenital adrenal hypoplasia and gonadotrophin deficiency. *Br Med J* 1977; **ii**: 996.
- Winter J S D, Faiman C. Pituitary-gonadal relation in male children and adolescents. *Pediatr Res* 1972; **6**: 126-35.
- Forest M G, Cathiard A M, Bertrand J A. Evidence of testicular activity in early infancy. *J Clin Endocrinol Metab* 1973; **37**: 148-51.
- Winter J S D, Faiman C, Hobson W C, Prasad A V, Reyes F I. Pituitary-gonadal relations in infancy. I. Patterns of serum gonadotropin concentrations from birth to four years of age in man and chimpanzee. *J Clin Endocrinol Metab* 1975; **40**: 545-51.
- Dickerman Z, Prager-Lewin R, Laron Z. Response of plasma LH and FSH to synthetic LH-RH in children at various pubertal stages. *Am J Dis Child* 1976; **130**: 634-8.
- Greulich W W, Pyle S I. *Radiographic atlas of skeletal development of the hand and wrist*, second edition. Stanford, California: Stanford University Press, 1959.
- Spark R F, Etzkorn J R. Absent aldosterone response to ACTH in familial glucocorticoid deficiency. *N Engl J Med* 1977; **297**: 917-20.
- Roselli A, Barbosa L T. Congenital hypoplasia of the adrenal glands. *Pediatrics* 1965; **35**: 70-5.
- Reynolds J W. Steroid endocrinology. In: Smith C A, Nelson N M, eds. *The physiology of the newborn infant*, fourth edition. Springfield: Thomas, 1976; **1**: 672-6.
- Reyes F I, Winter J S D, Faiman C. Studies on human sexual development. I. Fetal, gonadal, and adrenal sex steroids. *J Clin Endocrinol Metab* 1973; **37**: 74-8.
- Reyes F I, Boroditsky R S, Winter J S, Faiman C. Studies on human sexual development. II. Fetal and maternal serum gonadotrophin and sex steroid concentrations. *J Clin Endocrinol Metab* 1974; **38**: 612-7.
- Kaplan S L, Grumbach M M. The ontogenesis of human foetal hormones. II. Luteinising hormone (LH) and follicle stimulating hormone (FSH). *Acta Endocrinol (Kbh)* 1976; **1**: 808-29.
- Shirley I M, Cooke B A. Metabolism of dehydroepiandrosterone by the separated zones of the human foetal and newborn adrenal cortex. *J Endocrinol* 1969; **44**: 411-9.
- Sizonenko P C, Paunier L. Hormonal changes in puberty. III. Correlation of plasma dehydroepiandrosterone, testosterone, FSH, and LH with stages of puberty and bone age in normal boys and girls and in patients with Addison's disease or hypogonadism, or with premature or late adrenarche. *J Clin Endocrinol Metab* 1975; **41**: 894-904.

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