

Cushingoid adrenal hyperplasia in infancy

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Abstract Cushing's syndrome, a characteristic pattern of obesity with hypertension due to the hyperfunction of the adrenal cortex, is relatively rare in infancy. Thirty-six infants have been reported in world literature,^{1,2} most of whom have had adrenal tumours. There are only eight reported cases of infants under the age of 1 year with adrenal hyperplasia responsible for Cushing's syndrome. This is a report of an 8 month old child with bilateral nodular adrenal hyperplasia.

Key words: adrenal hyperplasia; Cushing's syndrome; infancy.

This female child, of unrelated parents, had been under observation from the age of 3 months for obesity. Her birthweight was 3 kg and she weighed 8 kg at 3 months. Her supine length was 65 cm (between the 90th and 95th centile for age). She had mild right hemihypertrophy.

Her weight at 6 months was 13 kg and at 8 months 15 kg. At this time her blood pressure was 100/70 mmHg. Her length was 76 cm (greater than the 95th centile for age) with a crown rump length of 45 cm. Her face was rounded, there was a buffalo hump and generalized obesity. There was no hypertrichosis, enlargement of the clitoris, or other abnormality on general examination.

INVESTIGATIONS

Examination of blood showed packed cell volume of 25%, Hb 7.2 g/dl, and total white cell count 7300/ml with 12% eosinophils. Her urinary 17-oxosteroid was reported as greater than 173.5 $\mu\text{mol}/24\text{ h}$ (normal in infancy 3.5 $\mu\text{mol}/24\text{ h}$)³ and her 17-oxogenic steroid was also more than 173.5 $\mu\text{mol}/24\text{ h}$ (normal 10.8 $\mu\text{mol}/24\text{ h per m}^2$, s.d. = 3.8).⁴ Her 24 h free urinary cortisol was 266.8 nmol. After dexamethasone suppression (0.5 mg dexamethasone given 6 hourly for 48 h) her 24 hour excretion of 17-oxosteroid was 131.9 μmol , 17-oxogenic steroid 83.3 μmol and urinary free cortisol 139 nmol. Her fundus oculi examination, skull X-ray and intravenous pyelogram were all normal.

On account of the very unsatisfactory response to dexamethasone suppression and since most cases of Cushing's syndrome in infancy have been due to adrenal tumours, a provisional diagnosis of adrenal neoplasm was made and surgery advised.

Pre-operative preparation with Vitamin A and hydrocortisone was done in accordance with standard recommendations.⁵ The glands were approached via a posterior route and a bilateral adrenalectomy was performed. The right gland weighed 2.5 g and the left 2 g.

Histopathological examination showed adrenal tissue with marked widening of the zona fasciculata and occasional small

cortical nodules. The medulla appeared decreased. There was no evidence of malignancy. The histopathology was consistent with bilateral adrenal hyperplasia (Figs. 1, 2).

Postoperatively she continued to have Vitamin A and hydrocortisone.⁵ Her blood pressure remained steady at about 110/70 mmHg. There was no undue delay in wound healing. Fourteen days postoperatively, hydrocortisone was reduced to 5 mg twice a day and she started having 0.05 mg fluorocortisone once a day.

Four months later, at the age of 1 year, her weight was 14.7 kg, length 78 cm, head circumference 50.5 cm and chest circumference 54.5 cm. Plasma cortisol at 0800 h was 305.8 nmol/l (normal 139–695 nmol/l) and at 2000 h 44 nmol/l (normal 55.6–250.2 nmol/l), and urine 17-oxosteroid excretion was 3.5 $\mu\text{mol}/24\text{ h}$. X-ray of the wrist showed two carpal bones. Her ocular fundus has remained normal.

One year after surgery she remains well, with normal development of motor function. She has had three minor episodes of infection during this period, two respiratory and one gastrointestinal which responded promptly to treatment.

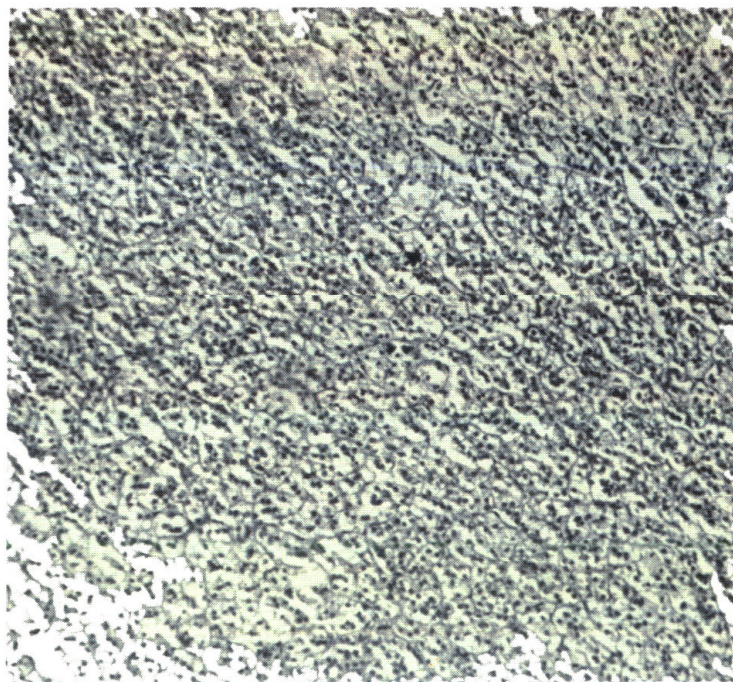


Fig. 1 Photomicrograph of the adrenal gland showing widened zona fasciculata (magnification $\times 90$; Haematoxylin — Eosin Stain).

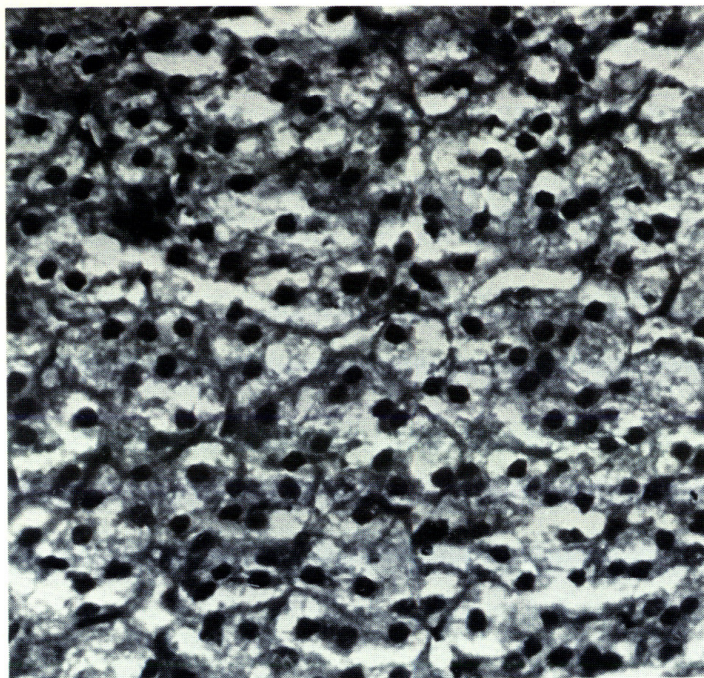
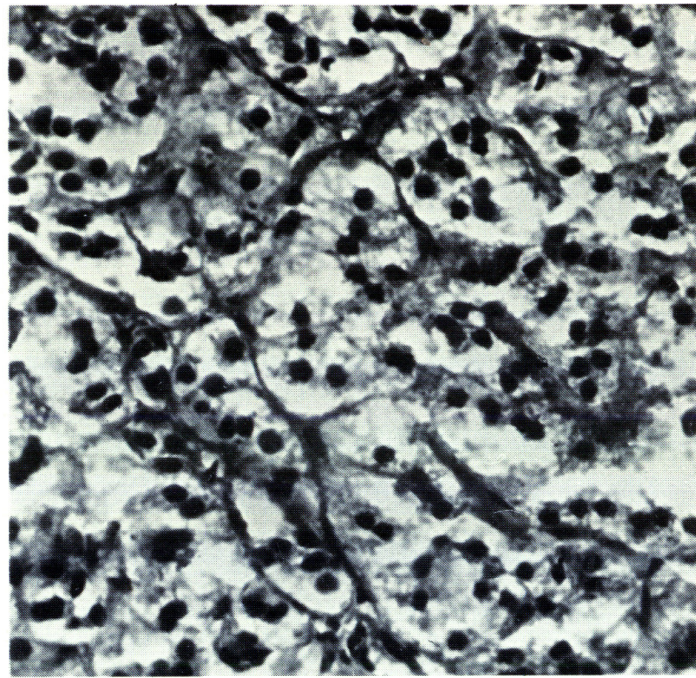


Fig. 2 Nodular hyperplasia of the adrenals. Zona fasciculata shows irregular cellular enlargement and locally increased lipid content (magnification $\times 360$; H and E Stain).



DISCUSSION

Cushing's syndrome is due to an excess of glucocorticoid production by an adrenal tumour or adrenal hyperplasia. Loridon *et al.* reviewed 30 cases of Cushing's syndrome in infancy and added three cases of their own.⁶ Recently there has been a report from India.² Of the cases reported, adrenal hyperplasia has been reported only in eight infants. Adrenal hyperplasia which produces excessive glucocorticoids should be referred to as Cushingoid adrenal hyperplasia to distinguish it from the hypoadrenal congenital adrenal hyperplasia, in which inborn defects in the biosynthesis of corticoids are responsible for low glucocorticoid levels, feed-back stimulation of ACTH production and adrenal hyperplasia.

The cause of Cushingoid adrenal hyperplasia is not usually found. Crook's changes, basophilic hyalinization of the pituitary, seen in Cushing's syndrome, is now reported in most hyperadrenal states and is said to represent stored ACTH due to the suppression of its release. One can therefore no longer contend, as was done by Cushing, that basophil adenoma of the pituitary is the primary cause of the syndrome.⁷ No gross pituitary tumour, as can be seen on the skull X-ray, was found in the child reported here.

Obesity was the presenting complaint in this case and in 31 out of 33 cases that have been reviewed.⁶ Patients with Cushing's disease are plethoric and have eosinopenia. This child's anaemia may have been due to food restriction imposed by her parents because of obesity. At the age of 8 months she was almost entirely breast fed. The eosinophilia (876/ml) was not explained.

An increase in 17-oxosteroid of more than $3.5 \mu\text{mol}/24 \text{ h}$ was found in 18 of 24 cases when estimated, and 17-oxogenic steroid increased by more than $14.6 \mu\text{mol}/\text{m}^2$ per 24 h in 10 of 13 cases. Excretion of more than $48.6 \mu\text{mol}/24 \text{ h}$ 17-oxosteroid was found only in infants with carcinomata.⁶ In the case

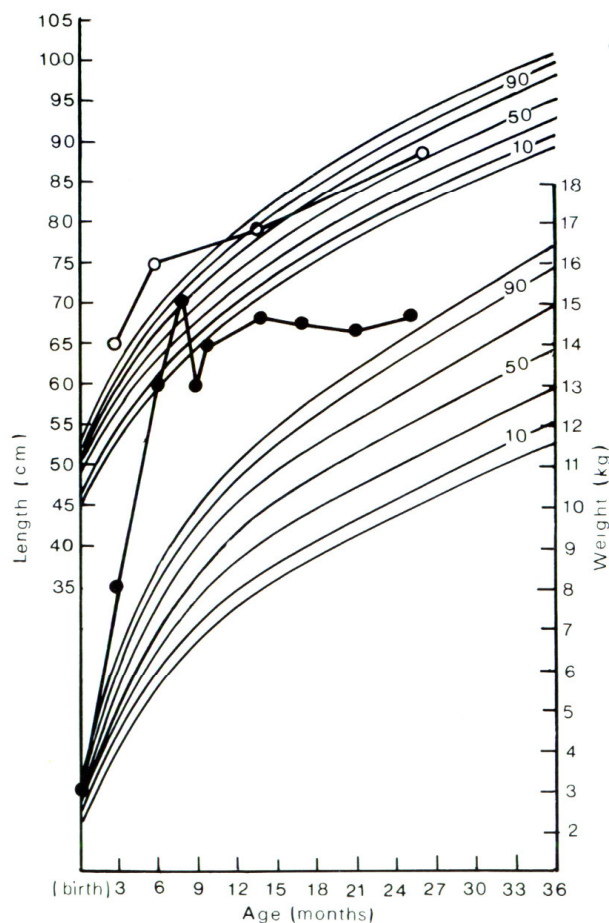


Fig 3 Growth curve showing length and weight centiles by age for girls aged 0–36 months. The growth curve for the child described in this study are also shown (●), (○).

reported here it was more than 173.5 $\mu\text{mol}/24$ h and even after dexamethasone suppression it was 131.9 $\mu\text{mol}/24$ h. The dexamethasone suppression test is thus not a very reliable test to distinguish adenomata from adrenal hyperplasia.

Growth failure is usual in Cushing's syndrome but this may not be present if it is associated with virilization.¹ The case reported here was tall for age and in relation to parental height (mother's height was 152.5 cm and father's height was 172.7 cm) (Fig. 3). There was no evidence of virilization but she had extremely high levels of urinary 17-oxosteroids. 17-oxosteroids are the metabolites of androgens and these were perhaps responsible for her increased length.

The adrenals in this child were not enlarged and the diagnosis could be confirmed only by histopathology. Gross appearance of the adrenals was normal in six of the patients reviewed by Loridon and he suggests that an autopsy would not have disclosed cause of death, until the adrenals were examined closely. In one patient the hyperplastic left and right adrenals weighed only 1.0 g and 1.5 g, respectively.⁶

The results of surgery in infants with adrenal hyperplasia have not been very encouraging. Of the eight cases reported,⁶ one died pre-operatively, four died postoperatively and only

three survived. Sepsis and shock were mainly responsible for death. Vitamin A is said to counteract the adverse effects of cortisol excess on wound healing.⁵ Preparation with Vitamin A and hydrocortisone may have contributed to the survival of this case.

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