

Cushing's disease presenting with growth failure: clinical remission during cyproheptadine therapy

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SUMMARY A 14.7 year-old boy had almost complete suppression of growth as a result of mild pituitary-dependent Cushing's disease. There was complete clinical remission during treatment with cyproheptadine (12 mg/day) and this was maintained when treatment was stopped after 18 months.

There have been several reports of children with Cushing's disease in which the salient clinical feature has been retardation of growth (Copinschi *et al.*, 1969; Streeten *et al.*, 1975; Lee *et al.*, 1975; Solomon and Schoen, 1976). Such a patient is described who underwent complete clinical remission during treatment with the serotonin-antagonist cyproheptadine.

Case report

Clinical features. The patient was first seen at age 14.7 years because he had not grown during the previous 4 years. His parents had kept a record of his heights from age 1½ years, and this showed fairly abrupt cessation of growth between ages 10 and 11 (Fig. 1). At about this time he gained weight rather quickly and his appearance changed as his face became rounder. Pubic hair appeared at about 11 years but there was no further progression in pubertal development.

When he was 6 years he had a successful course of treatment with gonadotrophin for an undescended testis, and a hydatis of Morgagni was excised when he was 10. In all other respects his health had been normal and he had no other symptoms.

On examination he was short (142.3 cm) and slightly obese (40.4 kg), with a round face (Fig. 2). With the exception of moderate hypertension (BP 135/95 mmHg), and slight bilateral gynaecomastia with mild generalised hirsutism, there were no other abnormal findings. His testes were prepubertal

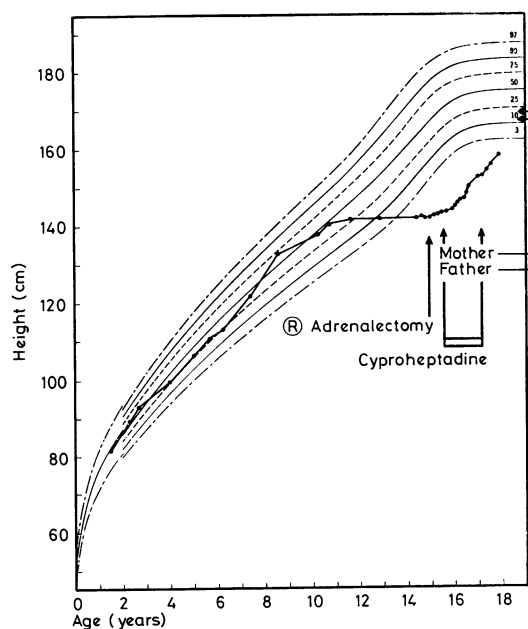


Fig. 1 Patient's growth curve between ages 1½ and 18 years. Heights of his parents are also shown. Arrows show the timing of adrenalectomy and cyproheptadine therapy.

(1-2 ml), but he had a moderate amount of pubic hair with some development of the penis and scrotum.

Laboratory investigations. The initial investigations confirmed the clinical diagnosis of mild Cushing's disease. Urine free-cortisol was high at 565 nmol/24h

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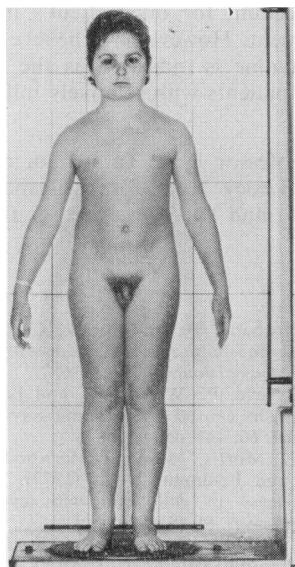


Fig. 2 Appearance of the patient at age 14.7 years.

(20.5 $\mu\text{g}/24\text{h}$), urine 17-hydroxycorticoid excretion was 82 $\mu\text{mol}/24\text{h}$ (23.6 mg/24h), the cortisol production rate was raised at 83 $\mu\text{mol}/\text{m}^2$ per 24h; 30.6 mg/ m^2 per 24h (normal 34.5 ± 7.9 SD), and the urine 17-oxosteroids were high at 44 $\mu\text{mol}/24\text{h}$ (12.7 mg/24h). Plasma cortisol showed loss of normal circadian variation (260 nmol/l; 9.4 $\mu\text{g}/100$ ml at 0900h; 364 nmol/l; 13.1 $\mu\text{g}/100$ ml at 2300h). After 3 days' treatment with high-dose dexamethasone (2 mg 6-hourly) urine 17-hydroxycorticoids fell to 5.6 $\mu\text{mol}/24\text{h}$ (1.6 mg/24h) and the 17-oxosteroids to 22.4 $\mu\text{mol}/24\text{h}$ (6.4 mg/24h). However, plasma ACTH was undetectable (<32 ng/l) at times when the plasma cortisol ranged between 340 and 660 nmol/l (12.3 and 24 $\mu\text{g}/100$ ml). In view of the last finding, an adrenal tumour was suspected and an iodocholesterol scan was carried out. This showed apparently normal uptake by both adrenal glands, thus excluding the presence of a tumour.

Other endocrine causes of growth failure could be readily excluded. Plasma growth hormone rose from <1.0 to 25.4 mU/l 20 minutes after IV injection of 0.1 U/kg insulin. Plasma cortisol rose from 460 to 725 nmol/l (16.7 to 26.3 $\mu\text{g}/100$ ml) during this test. Plasma thyroxine was normal (121 nmol/l; 9.4 $\mu\text{g}/100$ ml), but a subsequent test with IV TRH (200 μg) showed an insignificant rise in plasma TSH from 1.0 to 1.6 mU/l after 30 minutes. Basal prolactin was normal (112 mU/l) and rose normally to 300 mU/l 15 minutes after TRH.

X-ray of the left wrist and hand showed a bone age of 11.4 years (Tanner *et al.*, 1975). Skull x-rays and IV-urogram were normal.

Clinical course. Two-stage adrenalectomy was planned and the right adrenal was removed when the patient was aged 15.1 years. The gland appeared normal in size (weight 6 g) and there was no evidence of hyperplasia on histological examination. In view of these findings, left adrenalectomy was deferred, and his adrenal function was reassessed after 2 months. Again, high urine free-cortisol levels were obtained (350–675 nmol/24h; 127–245 $\mu\text{g}/24\text{h}$). Serial estimation of plasma cortisol suggested episodic activity of his Cushing's disease. On one particular day, plasma cortisol varied from 860 nmol/l (31.2 $\mu\text{g}/100$ ml) at 0900 hours to 440 nmol/l (15.9 $\mu\text{g}/100$ ml) at 2300 hours, but the next day the levels were almost normal—280 nmol/l (10.1 $\mu\text{g}/100$ ml) at 0900 hours; 113 nmol/l (4.1 $\mu\text{g}/100$ ml) at 2300 hours. On both days plasma ACTH was low to normal (<22 –58 ng/l).

During the next 6 months he grew very little and there was no appreciable advance in his bone maturation or pubertal development. When he was 15.8 years old, his height was 144.3 cm, and treatment with cyproheptadine (12 mg/day) was started. During the next 4 months he grew 1.2 cm, and after 6 months there was a definite increase in testicular size and his BP had fallen to 110/70 mmHg. At this time, normal values for plasma cortisol were found (80–225 nmol/l; 2.9–8.1 $\mu\text{g}/100$ ml) and his urine free-cortisol fell to 180–300 nmol/24h (65–109 $\mu\text{g}/24\text{h}$). A year after starting cyproheptadine his bone age was 12.6 years.

Treatment with cyproheptadine was stopped after 18 months when he was 17.3 years old. At this time his height was 153.7 cm, blood pressure 125/65 mmHg, further pubertal development had taken place (testicular volume 16–20 ml), and his gynaecomastia was unchanged. He has been followed up for 9 months since stopping cyproheptadine and has continued to grow normally without gaining weight; at age 18 years his height was 158.5 cm, his weight 45 kg, and his bone age 14.9 years. Urine free-cortisol levels have remained normal (90–182 nmol/24h; 33–66 $\mu\text{g}/24\text{h}$) since stopping treatment. Plasma cortisol estimated 3 months after stopping cyproheptadine showed very similar morning and late evening values: 210–300 nmol/l (7.6–10.9 $\mu\text{g}/100$ ml) at 0900 hours and 275–290 nmol/l (10–10.5 $\mu\text{g}/100$ ml) at 2200 hours, but 6 months later normal circadian variation appeared to be present: 240 nmol/l (8.7 $\mu\text{g}/100$ ml) at 0900 hours; 120 nmol/l (4.3 $\mu\text{g}/100$ ml) at 2200 hours.

Discussion

It is well known that excess secretion of cortisol in Cushing's disease greatly suppresses growth but only recently has it been widely appreciated that in some patients the disorder may be mild and, apart from growth retardation, there may be few of the classic clinical features (Lee *et al.*, 1975; Solomon and Schoen, 1976). In this case, there was some evidence that the disorder was episodic, as shown by the plasma cortisol profiles on two consecutive days. Plasma ACTH was at no time raised and at times it was undetectable, an unusual finding in pituitary-dependent Cushing's disease. Both these findings are probably in keeping with the observation that the resected right adrenal gland was normal in size and showed no histological evidence of hyperplasia. In the case reported by Lee *et al.* (1975), the adrenal glands were also normal on histological examination.

Our patient's normal growth hormone (GH) secretion is also unusual, as patients with Cushing's disease almost invariably have suppressed GH secretion (Copinschi *et al.*, 1969; Streeten *et al.*, 1975). This probably reflects the mildness of his disorder, as it appears that suppression of GH is largely related to high levels of plasma cortisol, rather than being due to a primary disturbance of hypothalamic or pituitary function (Tyrrell *et al.*, 1977).

In nearly all previously reported cases, patients with Cushing's disease presenting with growth failure were treated by bilateral adrenalectomy, and this was planned in our patient. Such treatment results in renewed growth but commits the patient to life-long replacement therapy with corticosteroids. There is also a significant risk that Nelson's syndrome (pituitary adenoma with hyperpigmentation) will develop later. Pituitary irradiation (Jennings *et al.*, 1977), or trans-sphenoidal exploration of the pituitary to remove an ACTH-secreting microadenoma (Tyrrell *et al.*, 1978), have also been successful in children with Cushing's disease.

As the disorder was mild in our patient a trial of cyproheptadine was given. This drug, which antagonises the effects of serotonin and suppresses ACTH secretion in normal subjects (Plonk and Feldman, 1976), was used successfully by Krieger *et al.* (1975) in the management of three adults with Cushing's disease. So far the use of this drug in children with Cushing's disease has been disappointing (Allgrove *et al.*, 1977; D'Ercole *et al.*, 1977), but in our case its use was associated with a pronounced acceleration of growth and bone maturation, and remission of hypertension. Spontaneous remission has been described in children with Cushing's disease (Putnam *et al.*, 1972) and

this could account for our patient's improvement during treatment. However, we believe that a trial of cyproheptadine is indicated as the first line of treatment in patients with relatively mild Cushing's disease.

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