

Disease in the Elderly

Successful control of Cushing's disease in the elderly with long term metyrapone

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Summary: A 77-year old woman with pituitary-driven Cushing's disease is described. The condition was completely controlled on long-term treatment with metyrapone.

Introduction

There is remarkably little published about Cushing's disease in advanced old age and nothing about the effectiveness of its treatment with metyrapone. We therefore report a rare case of a 77 year old woman with Cushing's disease. Her critical condition only permitted palliative treatment with metyrapone.

Case report

The patient was admitted to hospital in April 1985 for investigation of myopathy. She gave an 18-month history of mild diabetes, which had been diagnosed 12 months previously and treated with glibenclamide. For 12 months she had difficulty climbing stairs and getting out of chairs, owing to muscle weakness.

Clinically she looked Cushingoid, with a moon face, truncal obesity, bruises on the arms and an increase of facial hair (Figure 1a). Her pulse rate was 80/min and blood pressure 140/90 mm Hg. There was a marked proximal myopathy, making walking impossible even with a frame.

An initial diagnostic assessment showed a very high urine free cortisol of 3,840 nmol/24 hours (normal 100–330 nmol/24 hours), which on dexamethasone 8 mg/day suppressed to 1,480 nmol/24 hours. At midnight, the serum cortisol was raised at 285 nmol/l (normal < 200 nmol/l), as was the plasma ACTH at 140 ng/l (normal < 10 ng/l). At 09.00 h the serum cortisol was normal at 386 nmol/l (normal 195–670 nmol/l) with the plasma ACTH elevated at

160 ng/l (normal 10–80 ng/l). Coned views and lateral tomography of the pituitary fossa were normal, but a computed tomographic (CT) scan showed a central enhancing area suggestive of a pituitary tumour. A CT scan of the abdomen suggested bilateral adrenal hyperplasia. Other investigations showed an average fasting blood sugar of 4.4 mmol/l (on glibenclamide), a full blood count and electrolytes were normal, serum thyroxine was 114 nmol/l (normal 70–150 nmol/l), but the gonadotrophins were remarkably low for the postmenopausal age, the FSH being < 1 U/l and LH 2.2 U/l.

Shortly after admission she bumped her leg and suffered a large laceration of the left shin. In view of this, and her general critical state, it was decided to start treatment with metyrapone immediately, and forego a definitive endocrine assessment.

Treatment was commenced with metyrapone 750 mg 4 hourly, and the serum cortisol dropped at once, with a rise in compound S (Figure 2). After 3 days she become drowsy, so the drug was stopped and she soon recovered. Metyrapone was re-started on a lower dose (250 mg 8 hourly) which controlled the serum cortisol levels, albeit with higher ACTH and compound S levels (Figure 2) and was without adverse clinical effects. Urinary free cortisol was then 57 nmol/24 hours (normal 100–370 nmol/24 hours).

During the 9th week of treatment, confirmation of continuing need was sought by withdrawal of the metyrapone. This at once led to recurrence of excessive serum cortisol levels (Figure 2).

After 3 months treatment with metyrapone, the patient had improved considerably and was able to walk about on her own. The face was completely

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Figure 1 Shows the face (a) before and (b) after 15 weeks of metyrapone treatment.

remodelled (Figure 1b), the laceration of the left shin healed completely and the diabetes could now be controlled on diet alone.

Discussion

Cushing's disease in this age group is very rare (Table I), the oldest patient we noted from several large series being 72 years. The peak age of incidence is between 35 and 50 years (Hall *et al.*, 1980).

Different treatments have been proposed for correc-

ting the hypercortisolism of Cushing's disease, but the most popular is transsphenoidal surgery. We tend to favour yttrium-90 pituitary implantation, but we judged our patient to be too frail for anaesthesia. However, medical treatment at the adrenal level has still a role to play (Bricaire & Luton, 1980; Bergstrand & Nilsson, 1982). Mitotane (o,p'DDD), an adrenolytic drug, has been used specifically for Cushing's disease (Luton *et al.*, 1979), although its main use is in the management of adrenal carcinoma. Aminoglutethimide, which blocks the conversion of cholesterol to δ^5 -pregnenolone has been used successfully in

Table I Age of patients with Cushing's disease

	Mean age at diagnosis (years)	Age of oldest patient in series (years)	No. of patients in series
Orth & Liddle (1971)	37	68	64
Welbourne <i>et al.</i> (1971)	37	72	43
Burke <i>et al.</i> (1973)	39	—	57
Boggan <i>et al.</i> (1983)	35	—	104
Fahlbusch (1986)	37	64	101
Sandler <i>et al.</i> (1986) (in preparation)	38	61	54

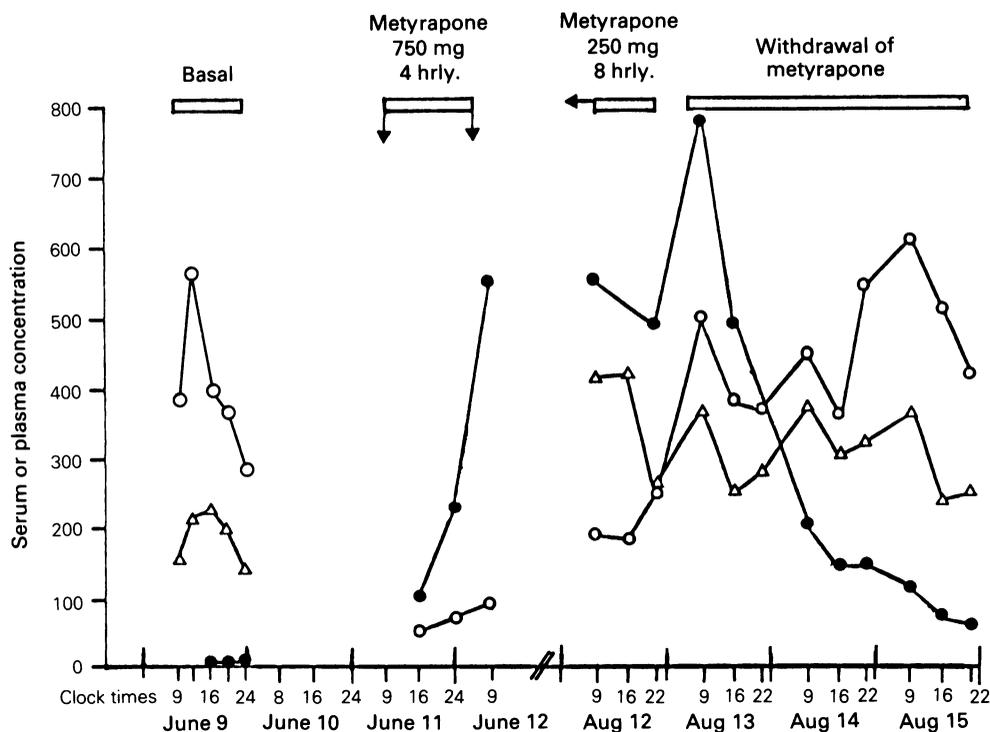


Figure 2 Twenty four-hour hormone profiles on different regimens. ○—○ serum cortisol (nmol/l); △—△ plasma ACTH (ng/l); ●—● serum compound S (nmol/l).

conjunction with metyrapone by our own group (Child *et al.*, 1976). Metyrapone remains one of the most effective drugs used to treat Cushing's disease (Jeffcoate *et al.*, 1977), and is usually linked with a course of external beam radiotherapy. However, our patient was not able to face the month of daily hospital attendance for such treatment, and in any case, it usually takes some years to gain control of the pituitary hypersecretion, if ever. It was thus decided to attempt treatment with metyrapone only. The side effects encountered with this drug are mainly gastrointestinal symptoms (which could be due to overdose and hence hypocortisolism), and hirsutes (Jeffcoate *et al.*, 1977). Our patient suffered hypocortisolism at the beginning of the treatment; this was due to the high

initial dose that we used in order to gain immediate control. She also had a slight increase of pre-existing facial hair. Our long term strategy, which proved to be successful was to obtain the correct maintenance dose, rather than to give a blocking dose coupled with maintenance steroids. Concerning the monitoring of therapy, difficulties can be created by 11-deoxymetabolites reacting in some assay systems for cortisol. The cross reactivity of the antiserum used in our cortisol radioimmunoassay for 11-deoxycortisol was very low (4.5%).

In conclusion, we recommend a trial of the use of metyrapone either as a preparation for surgical procedures or as a palliative treatment in such elderly and frail cases of Cushing's disease.

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