CASE REPORT

Cyproheptadine treatment in Cushing's disease

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ABSTRACT. Cyproheptadine, a nonselective 5-hydroxytryptamine receptor blocking agent, reduces ACTH and ß-endorphin secretion from the ACTH-producing tumors. A 35-year-old female suffering from Cushing's disease due to microadenoma of the pituitary gland has been followed since the age of 15. Subtotal adrenalectomy followed by total adrenalectomy, pituitary irradiation, and transsphenoidal hypophysectomy, combined with second radiotherapy of the pituitary, were unsuccessful in achieving remission of the disease. Remission was achieved with cyproheptadine up to a dosage of 24 mg/day. Every attempt to discontinue cyproheptadine treatment was accompanied by recurrence of the disease. This is the first case of Cushing's disease in which cyproheptadine treatment has been the only efficacious therapy for a period of 11 yr. Cyproheptadine may be an alternative long-term therapy for Cushing's disease when other methods of treatment fail.

INTRODUCTION

Clinical and biochemical remission may be achieved in almost 60 percent of patients with Cushing's disease with cyproheptadine treatment, though this treatment is still controversial (1-6). The drug may reduce ACTH secretion either directly at the adenomatous corticotrope cell level or at the hypothalamic level (7).

We present a case of Cushing's disease due to pituitary adenoma which has responded to cyproheptadine treatment after failing to respond to all other methods of therapy.

MATERIALS AND METHODS

Plasma concentrations of cortisol and other hormones were measured by established radioimmunoassays with commercial kits. Urinary free cortisol levels, urinary 17-hydroxycorticosteroids (17-OHCS) and 5-hydroxyindolacetic acid (5-HIAA), plasma levels of cortisol and other hormones were determined by previously established methods (8-10). ß-endorphins were determined by commercial radioimmunoassay kits (New England Nuclear, Dupont, USA) (11).

CASE REPORT

In 1975, a 15-year-old girl sought medical help for purplish striate on her legs, weight gain, and muscular weakness. Physical examination revealed that her face was rounded with side burns of light lanugo hair. Fullness was present in the shoulder and supraclavicular fat pads. Initial laboratory values displayed elevated baseline urinary 17-OHCS level of 52.6 µmol/24 h and basal plasma cortisol level of 2759 nmol/L. The administration of 0.5 mg dexamethasone orally every six h suppressed the plasma cortisol level to 1407 nmol/L and urinary 17-OHCS level to 27.3 µmol/L. In September 1975, she had left total and right subtotal adrenalectomy (Fig. 1). Soon after the operation, recurrence occurred with a compression fracture at the level of D12-L1 of the vertebral column. In December 1975, external pituitary irradiation with a total dose of 50 Gy was applied. After a few months, the free urinary cortisol excretion gradually increased to a level of 5076.5 nmol/day. She was operated a second time in April 1976; multiple nests of hyperplastic adrenal tissue, which had been implanted accidentally in the previous operation, were found within the abdominal cavity (Fig. 2). Subtotal adrenalectomy was completed to total adrenalectomy, and implanted heaps of adrenal tissue were resected as thor-

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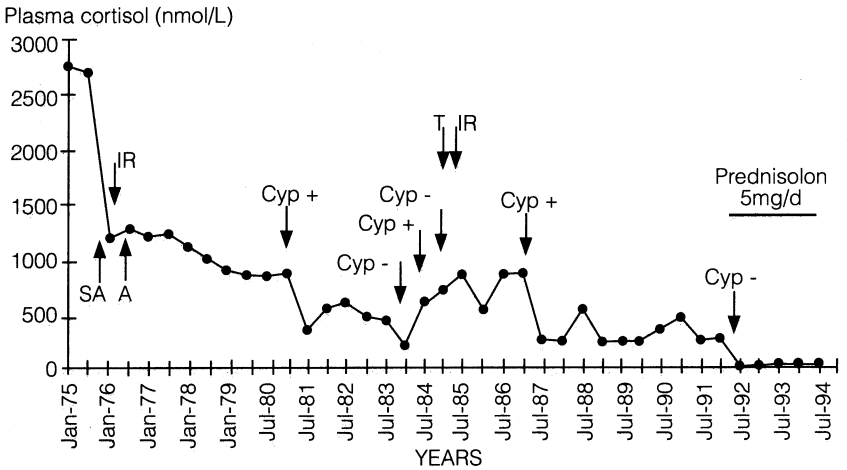

Fig. 1 - *Basal plasma cortisol levels of the patient (Cortisol levels during suppression and stimulation tests are not represented in the Figure). SA: Subtotal adrenalectomy, A: Total adrenalectomy, T: Transsphenoidal adenomectomy IR: Pituitary irradiation, Cyp+: Cyproheptadine started, Cyp-: Cyproheptadine stopped. The dashed line represents the normal upper limit of basal plasma cortisol (690 nmol/L).*

oughly as possible. Following the second operation, no improvement was noted. At that time, basal plasma cortisol level of 441 nmol/L could only be suppressed to 275 nmol/L after 2-mg dexamethasone test and to 303.6 nmol/L following 8-mg dexamethasone test, respectively.

In 1981, cyproheptadine (CYP) treatment was prescribed and gradually increased to a dose of 24 mg per day. For the first time, her plasma cortisol level gradually decreased to 165.54 nmol/L (Fig. 1). In fact, CYP induced hypocorticism, necessitating corticosteroid substitution therapy. In January 1984, CYP was interrupted for six months after which clinical and biochemical recurrence of Cushing's syndrome occurred. CYP was restarted, and it suppressed basal plasma cortisol and ACTH levels. When CYP was discontinued for 14 days in August 1984, the levels of cortisol elevated from 510 nmol/L to 707 nmol/L, ACTH from 11.1 to 110 pmol/L, and ß-endorphins from 55 to 250 fmol/L, necessitating the administration of CYP. Computerized tomography of the sella revealed a microadenoma. In December 1984, a basophil adenoma was resected by the transsphenoidal route, and CYP treatment was stopped. Since remission was not achieved, pituitary irradiation with a total dose of 40 Gy was applied in February 1985. Administration of 24 mg CYP was again associated with a gradual decrease in basal plasma cortisol levels from 830 nmol/L to 220 nmol/L during the period between 1986 and 1987.

In 1988, she became amenorrheic. When CYP treatment was discontinued again for 4 days, plasma ACTH and cortisol rose to 110 pmol/L and 717 nmol/L, respectively. Under CYP treatment, plasma levels of ACTH and cortisol and urinary free cortisol excretion decreased to 6.6 pmol/L, 496 nmol/L, 82.7 nmol/day, respectively. After stopping CYP treatment for one week, *iv* administration of 100 µg LHRH and 400 µg TRH as a single bolus raised plasma cortisol from resting concentration of 1103 nmol/L to 1269 nmol/L at 90 min. In nuclear magnetic resonance (NMR) imaging, pituitary tissue was hardly seen within the sella, and no mass was observed in the adrenal regions (Figs. 3, 4). In May 1991, T4 was measured 45 nmol/L and 54 nmol/L on two different occasions. Thyroid hormone replacement therapy was started at a dose of 100 µg per day. Menstrual periods returned after cyclic oral conjugated estrogen and progestogen treatment. In June 1992, she was admitted to our hospital with a 1-week history of anorexia, nau-

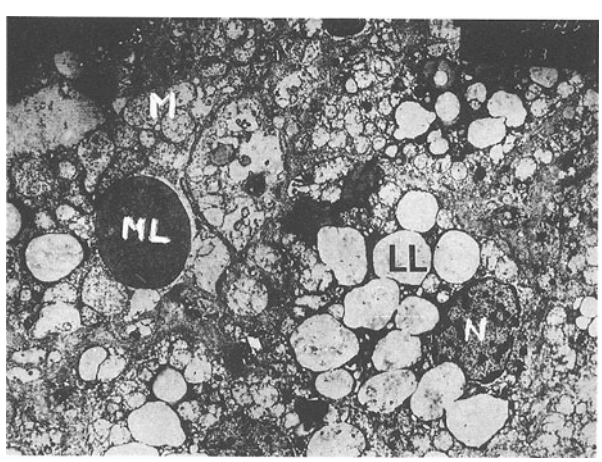

Fig. 2 - *Electron microscopic appearance of the perirenal implants of the adrenal tissue (LL: Low electron density lipid droplets, ML: Moderate electron density lipid droplets, M: Mitochondria with destruction of the cristae, N: nucleus (uranyl acetate and lead citrate x 6,000).*

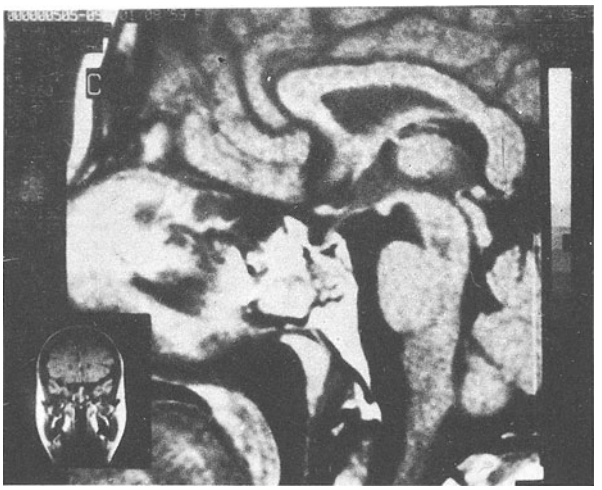

Fig. 3 - *NMR of the sella after transsphenoidal adenomectomy and successive pituitary irradiations. Pituitary tissue was hardly seen within the sella turcica (empty sella) but Cushing's syndrome was ready to recur without CYP treatment at that time.*

sea, and weakness while she was using 20 mg cyproheptadine. Her basal plasma cortisol level was 8.27 nmol/L. CYP was stopped because of hypocorticism, and treatment with hydrocortisone resulted in a prompt resolution of her symptoms. Afterwards, corticosteroid replacement therapy was started.

She is now well under replacement therapy, without any clinical or biochemical evidence of Cushing's syndrome.

The possibility of ACTH-or CRH-secreting tumor was investigated by cytologic examination of the sputum and computerized tomography of the lungs, chest, and abdomen. None of them revealed any abnormality. NMR imaging of the abdomen was also normal. Urinary excretion of 5-HIAA was 10.4 µmol/24 h.

Bone mineral density was 0.661 gr/cm^2 at the femoral neck area (z score: -3) and 0.372 gr/cm^2 at the lateral L3 vertebra (z score: -2.4). During the period of cyproheptadine treatment, no unduly side effects were noted.

Histology

The paraffin embedded hematoxylin and eosin stained sections of the pituitary tumor revealed that the cells had fairly large, basophilically-stained granules in the cytoplasm and large, darkly-stained nuclei. Electron micrographs of the pituitary tumor showed that the cytoplasm was filled with secretory granules. Filamentous material was found around the nucleus.

DISCUSSION

There is evidence for the direct action of 5-hydroxytryptamine (5-HT) via 5-HT$_{1a}$ receptor subtypes (5-HT$_{1a}$, 5-HT$_2$) in mediating the release of ACTH and cortisol either at the pituitary level (7, 12, 13) or at the level of hypothalamic CRH-producing neurons located in the paraventricular nucleus (7, 14, 15). Cyproheptadine, which is a nonselective 5-HT receptor antagonist, reduces basal and insulin- or metyrapone-stimulated ACTH secretion by suppressing hypothalamic-pituitary-adrenal axis activation (13, 16). CYP also has a direct and dose-related suppressive effect on ACTH and ß-endorphin secretion from the ACTH-producing tumors (7, 17). We demonstrated the effectiveness of long-term (11 yr) CYP treatment in a case with Cushing's disease in which remission could not be achieved by various methods of treatment. The recurrence of the disease was because of unsuccessful management of the pituitary adenoma and of accidental contamination of the abdominal cavity by adrenal cells on the subtotal adrenalectomy operation, an historical approach that should have had no place in the treatment of Cushing's disease according to current opinion. The unsuccessful management of the pituitary adenoma might be due to either only a partial adenomectomy with some remaining adenomatous cells responsible for the recurrence of the disease or to primary hypothalamic dysfunction causing corticotroph hyperplasia. Cyproheptadine therapy was associated with suppression of plasma ACTH and cortisol levels and

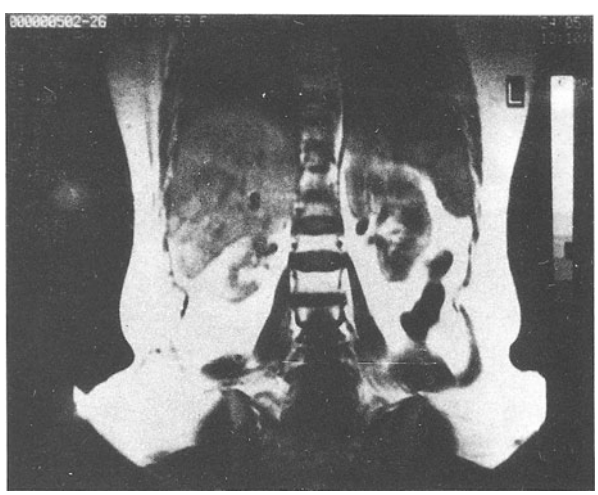

Fig. 4 - *NMR of the adrenal region. No adrenal glands are seen. Perirenal fat tissue is increased. Cortisol has been secreted by microscopical heaps of adrenal cells that have been implanted accidentally throughout the abdominal cavity.*

with resumption of normal circadian cortisol rhythm, similar to that in Krieger's studies (1). At first, remission seemed to be due to late effects of radiotherapy. However, when CYP was discontinued for a few days on different occasions, significant increases in levels of ACTH, ß endorphins, and cortisol occurred. The possibility of an ectopic ACTH and CRH syndrome in the present patient could not be ruled out with certainty, but no evidence for an occult neoplasm, *i.e.* bronchial adenoma of carcinoid type, tumor of the thymus, pancreas, lung, etc., was found during the follow-up period of 20 yr. Furthermore, after ablation of the pituitary adenoma and the pituitary itself, ACTH and cortisol levels decreased below normal, which could not have been possible in the presence of ectopic ACTH syndrome.

Our patient became hypothyroid and amenorrheic during the clinical course. Although CYP partially suppressed ß-endorphins, the levels of opiates were still above the normal limits. Therefore, excessive hypothalamic opiate activity concurrent with reduced frequency of GnRH secretion due to hypothalamic-pituitary irradiation might be the causes of secondary amenorrhea, since other causes were excluded (18-24).

In the medical literature, no other case was found which used CYP longer than we did in the treatment of Cushing's disease. CYP therapy, at a dosage of 24 mg/day for a period of 3-6 months, was reported to achieve clinical and biochemical remission in three patients with Cushing's disease (1) and,in another study, in 3 of four patients with Nelson's syndrome (2). Also, restoration of normal cortisol periodicity in 2 patients with Cushing's disease was demonstrated following one year of therapy (2, 25). However, cessation of the treatment resulted in recurrence of the disease. On the other hand, cyproheptadine-induced remission persisted for more than 3 yr after withdrawal of the drug in one patient with Cushing's disease and in another with Nelson's syndrome (14). A 15-year-old girl with Cushing's disease was successfully treated with CYP for a year (3). CYP treatment resulted in marked lowering of plasma ACTH in a patient with Nelson's syndrome and paratesticular adrenal rest tumors (26). Jordan et al.(15) reported a patient with cyclic Cushing's syndrome due to Cushing's disease, in whom urinary free cortisol concentration was greatly diminished with CYP at a dose of 20 mg per day. Koppesschaar et al.(27) reported a patient with Cushing's disease who was unsuccessfully treated by pituitary surgery and external pituitary irradiation but was responsive to CYP or to sodium valproate treatment. They proposed that the disease was due to an ACTH-producing tumor of pituitary intermediate lobe origin. In a patient with Cushing's syndrome, normal nocturnal fall in blood pressure was restored with low dose CYP treatment, which also normalized urinary free cortisol levels (28). In fact, CYP was superior in restoring 24-h blood pressure profile compared to low-dose beta-blocker therapy. In a 37-year-old woman with Cushing's disease, CYP therapy normalized basal cortisol levels and cortisol responses to dexamethasone, metyrapone, CRH, and insulin-induced hypoglycemia (29).

In our case, the paradoxical increase in plasma cortisol following TRH and LHRH administration and the failure to achieve remission after various methods of treatment, in association with resistance to dexamethasone suppression, suggested the presence of intermediary lobe adenoma (30, 31). However, suggestive evidence for intermediate lobe adenoma, such as the presence of neural tissue within the pituitary adenoma and high prolactin levels, were not present in our case (30). On the other hand, such heterogeneity of clinical and laboratory findings in Cushing's disease may be difficult to explain in terms of anterior versus intermediate origin of the disease. For example, in almost half of the patients with untreated Cushing's disease and Nelson's syndrome, a paradoxical increase of plasma cortisol may occur after LHRH and/or TRH administration (25, 32-34). It was suggested that this response might be the result of either alteration in the hypothalamic-pituitary pathways or alteration of the pituitary receptors (33, 34). In a patient with Nelson's syndrome, Krieger and Condon (25) observed that CYP administration resulted in remission and abolished the anomalous responsiveness of plasma ACTH levels to TRH, in contrast to that seen prior to treatment.

In conclusion, cyproheptadine may be an alternative long-term therapy for Cushing's disease resistant to other methods of treatment, and it might also be useful in controlling the symptoms until the late effects of radiotherapy appear.

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