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Cushing's Disease: Spontaneous Remission Following Severe Headache

Raymond C. Mellinger, MD*

A young woman was found to have persistent Cushing's syndrome one year after surgical removal of both hyperplastic adrenal glands. Improvement followed pituitary irradiation but she developed skin pigmentation. Remission of the adrenal hyperfunction occurred only after several months of therapy with o,p’-DDD. Within 15 months, the recurrent disorder required a second course of DDD with resulting adrenal insufficiency. Eighteen months later, however, steroid supplements were no longer required and increasing cortisol levels indicated still another imminent relapse. There was no enlargement of the sella turcica. The patient had received no treatment whatever for nearly nine months when she experienced a sudden severe headache associated with vomiting. Plasma cortisol was undetectable thereafter, dermal pigment abated and menstrual periods stopped. Gonadotropin and ACTH levels were very low. The final remission is believed to have resulted from infarction of the anterior pituitary.

Spontaneous remission of Cushing's disease has been reported infrequently. Remission of the disorder depends on elimination of the excessive corticotropin secretion which causes adrenal hyperplasia and increased steroid hormone secretion. In one reported case complete spontaneous remission was associated with infarction of a pituitary adenoma demonstrated post mortem. We have observed a patient whose clinical course suggests that a similar mechanism produced the ultimate remission of Cushing's syndrome. During eight years of treatment the disorder had recurred after adrenalectomy, pituitary irradiation and two courses of o,p’-DDD. The final persistent remission followed a violent headache.

Case report

JF, a 25-year-old white widow and mother of two children, was first admitted to our hospital in March 1969 after a suicide attempt.

The patient's emotional problems were said to have begun three years previously when her husband was killed in a bar. She compensated sufficiently to return to work and to care for her two children for a period of a year. At that time her physician found her blood pressure had risen above normal. She also had developed diabetes, irregular menstruation, weight gain and changes in her body configuration characteristic of adrenal hypercorticism. Following appropriate study, bilateral "total" adrenalectomy was performed in a community hospital with excision of glands weighing 8 and 6 grams respectively. Histologic study disclosed no significant abnormality. The patient was given regular replacement therapy with cortisone and her course was considered generally satisfactory. However, a year after the bilateral adrenalectomy she was admitted for care following the suicide attempt.
Although the patient had been taking only one cortisone tablet daily, she had the florid physical characteristics of Cushing’s syndrome. For this reason she was transferred to our institution for further care. Analyses of adrenal steroid levels in plasma and urine confirmed severe persistent adrenocortical hyperfunction which was suppressible with dexamethasone administered in a dose of 8 mg daily. The patient’s skin was thin, bruised and presented many striae but was not hyperpigmented. Skull X-ray disclosed a normal sized sella turcica. Pituitary radiation was administered with Cobalt teletherapy 5,000 R completed by May 1969 (Figure 1).

Within two months the patient’s condition was clinically improved although increased skin pigmentation was noted for the first time. Urinary 17-hydroxy and 17-ketosteroid levels and the plasma 17-hydroxycorticosteroid concentration had come within the normal range although plasma cortisol failed to exhibit any diurnal change. The patient’s precarious psychiatric state prompted two additional hospital admissions as well as a brief commitment to a mental hospital in the succeeding 11 months. One year after completion of the radiation treatment, plasma 17-hydroxycorticosteroid concentration was again significantly above normal and was suppressed very little by administration of dexamethasone (1 mg).

To secure remission of the hypercorticism, o,p’-DDD was administered in a dose of 2 to 4 grams daily from June through November, 1970 (Figure 2). During the first two months of this treatment, plasma 17-hydroxycorticosteroid concentration continued to increase although the urinary metabolites were reduced to fairly low levels. However, plasma cortisol levels fell dramatically at the fourth month and reached the very low level of 0.8 mcg/dl six months after the initiation of the treatment. Spontaneous menstruation returned and the patient underwent a complete clinical remission including restoration of her normal emotional stability. The hyperpigmentation did not increase although it did persist.

The induced remission lasted 15 months. In February 1972 the patient again complained of increasing weight, bruisability and pigmentation. She was found to have an elevated blood pressure. Plasma 17-hydrocorticosteroid levels were persistently above 20 mcg/dl. Therapy with DDD was re instituted and continued for 13 months through April, 1973, with a dose of 2 to 4 grams a day (Figure 3). Pigmentation continued to increase but clinical remission of the Cushing’s syndrome was again demonstrated after six months of therapy. The striking fall of plasma 17-hydroxycorticosteroid levels correlated with clinical signs of adrenal insufficiency but the daily administration of only 10 mg of hydrocortisone proved sufficient for the patient to remain well.

In March 1974, 18 months after the second remission had been induced with DDD and 12 months after the medication had been withdrawn entirely, clinical suggestions of yet another recurrence were observed. Plasma cortisol was 17.1 mcg/dl five hours after ingestion of the 10 mg hydrocortisone tablet and the supplemental therapy was withdrawn. However, 2 PM plasma cortisol level was only 6.6 mcg/dl with the patient receiving no medication and she remained reasonably well without any treatment. In October and November, 1974, weight gain and fatigue
Cushing’s Disease

Further suggested the possibility of adrenal hyperfunction and plasma cortisol was 15.1 and 12.3 mcg/dl in the mid-afternoon of two days. Urinary free cortisol was 240 mcg/24 hours and a full blown relapse was anticipated although no treatment was yet instituted.

On December 15, 1974, the patient experienced a violent headache associated with nausea and vomiting. She was hospitalized on an urgent basis. The symptoms subsided in 24 hours with analgesic and intravenous fluid therapy. Although there was no vascular collapse, plasma 17-hydroxycorticosteroids were undetectable in blood obtained at 8 AM and 3 PM the day following admission. Urinary free cortisol had fallen to 16 mcg/24 hours. The undetectable plasma cortisol was confirmed on the fourth hospital day and, although the patient was now free of serious symptoms, hydrocortisone supplements were resumed. (Table 1)

During the next three months the hyperpigmentation disappeared. The patient experienced hot flushes and amenorrhea. When hydrocortisone was omitted, plasma cortisol remained at undetectable levels and urinary free cortisol was also undetectable. At the time of the second missed menstrual period FSH was 4.9 and LH 7.8 mlU/ml. Serum T4 iodine was 3.5 mcg % and TSH 1.9 uU/ml. On March 28, 1975, when hydrocortisone was omitted for 24 hours, the plasma 17-hydroxycorticosteroid level was below the detectable range and plasma ACTH was 23 pg/ml (normal <20 to 80 pg/ml*).

Skull X-ray has remained normal. EMI scan and visual field examination has disclosed no demonstrable pituitary abnormality. The patient continues to be symptomatically very well taking hydrocortisone 10 mg daily and estrogen supplements to relieve hot flushes. There has been no further menstruation.

Discussion

Apparently spontaneous remission in Cushing’s disease has been observed in six other patients reported in American medical journals in the last two decades.1 5 A few additional earlier case reports lack bio-
FIG. 3 RESULTS OF DDD THERAPY—SECOND COURSE

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o,p' - DDD  2-4 gm/day

PLASMA 17-OHCS

NORMAL RANGE
Cushing's Disease

chemical documentation necessary for evaluation of the pituitary-adrenal defect. In addition, several patients with Cushing's syndrome due to functioning adrenal adenoma had observable unexplained lasting remission. The remissions observed in Cushing's patients with adrenal hyperfunction secondary to corticotropin excess occurred suddenly with headache in three patients besides the subject of this report. In one of these, infarcted pituitary adenoma was demonstrated post mortem. In three others, the disorder remitted gradually over a period of many months, leaving no evidence of pituitary insufficiency. Givens' patients, who experienced a sudden remission after severe headache, had normal residual adrenal function although there was demonstrable reserve ACTH deficiency by metyrapone testing.

Our patient demonstrated several difficulties encountered in the treatment of Cushing's disease: 1) persisting hyperfunctioning adrenal remnants after "total" adrenalectomy; 2) partial temporary remission induced by pituitary irradiation; 3) recurrence of adrenal hyperfunction twice after induction of severe cortisol insufficiency by the use of o,p'-DDD; and 4) progressive skin pigmentation.

Although sella turcica enlargement was not demonstrated, these events indicate that the patient had severe, persistent excessive ACTH secretion which subsided only after a violent headache. Many patients who became hyperpigmented after adrenalectomy for Cushing's disease have been shown to have ACTH secreting adenomas. Our patient had no evidence of pituitary enlargement; however, a vascular accident in the gland, its stalk or the hypothalamus is the presumed mechanism of remission. The ACTH level must have been very high to have induced cortisol hypersecretion by an adrenal remnant previously rendered functionless by two courses of DDD therapy. This level, which had also produced persistent generalized melanosis, was found to be, after remission at the lower limit of normal, insufficient to sustain a detectable blood level of cortisol. The concomitant occurrence of amenorrhea with low gonadotropin levels suggests that presumed infarction occurred in the anterior pituitary.

TABLE I

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<tr>
<th>DATE</th>
<th>PLASMA 17 OHCS ug/dl</th>
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HEADACHE

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N.D.—NOT DETECTABLE
* ACTH — 23 pg/ml (N = <20-80 pg/ml)

Change in plasma and urinary steroids associated with the final remission

* Bio Science Laboratories
Mellinger

References


