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# Prolonged Remission of Cushing's Disease Following Bromocriptine Therapy

Malachi J. McKenna, MD,\* Marc Linares, MD,† and Raymond C. Mellinger, MD‡

*A 33-year-old woman developed hypercorticism of fulminant onset following delivery of a full-term, normal child. An ectopic hormone-producing neoplasm was excluded by extensive studies. Pituitary-dependent hypercorticism of intermediate lobe origin was suggested on the basis of onset following pregnancy, failure of cortisol suppression by high-dose dexamethasone, hyperresponsiveness of prolactin to thyrotropin-releasing hormone stimulation, and reduction in adrenocorticotropin titers following oral administration of bromocriptine. Initial remission of disease achieved with bromocriptine was followed by recurrence on discontinuation of the agent. However, complete remission which occurred following a prolonged course of bromocriptine has persisted for a total of 22 months. (Henry Ford Hosp Med J 1987;35:188-91)*

Pituitary-dependent adrenocortical hyperplasia, Cushing's disease, is the most common cause of spontaneous hypercorticism (1). Some believe that the primary abnormality resides in the anterior pituitary, usually manifested by a corticotroph adenoma. However, recent studies suggest that in a number of cases hypothalamic dysfunction is the primary abnormality leading to corticotroph proliferation (2,3). A variety of neurotransmitters and neuropeptides have been implicated in this process, and chemotherapeutic agents that affect hypothalamic regulation of ACTH secretion may play a role in treatment (2). One such agent, bromocriptine, has been shown by different investigators to induce temporary remission in some patients (3-11). We report a case of a patient with Cushing's disease in whom prolonged remission has been attained following bromocriptine therapy.

## Case Report

A 33-year-old white female presented with hypercorticism of fulminant onset. Seven weeks previously she had delivered a full-term, normal child. The pregnancy and delivery were unremarkable, and she received a medication (probably bromocriptine) to prevent postpartum lactation. A few days thereafter she noted the onset of tongue swelling, and the medication was discontinued because of a presumed allergic reaction. However, over the next six weeks she developed severe emotional symptoms including nervousness, irritability, depression, sleeplessness, and unpredictable activity. She became weaker, and noted thinning of her extremities, easy bruisability, and increasing enlargement of her face, neck, and trunk. She experienced severe polydipsia and muscle cramps, and her weight increased by 6 kg in five days. After an episode of rectal bleeding, she attended an emergency room for evaluation and was admitted to the community hospital. Sigmoidoscopic and colon x-ray examinations were negative, but hypokalemia was noted and Cushing's syndrome was suspected. Serum cortisol was elevated at 56  $\mu\text{g}/\text{dL}$ , so she was referred to us for evaluation. When admitted to Henry Ford Hospital six weeks after delivery, she was noted to

be plethoric with facial rounding, supraclavicular fullness, and a modest cervicodorsal pad. Her proximal muscles were weak, and she had a number of ecchymoses. Several flat, blackened moles of recent onset were seen on her anterior chest, and diffuse pigmentation was present over her gums, face, nipples, and dorsum of hands and feet. However, the patient maintained that her complexion, always dark, had not changed. Blood pressure was 130/78 mm Hg.

Initial studies revealed a high serum cortisol of 31  $\mu\text{g}/\text{dL}$  in the afternoon, associated with a high ACTH level of 97  $\text{pg}/\text{mL}$  (Figure). Urine-free cortisol values were 257 and 412  $\mu\text{g}/24$  hours. Serum potassium was low at 2.5  $\text{mEq}/\text{L}$ , but this abnormality was readily corrected by a small, oral dose of potassium chloride. In view of the precipitous onset of the disorder, the unexplained rectal bleeding, and the low serum potassium, an ectopic hormone-producing neoplasm was suspected as the cause of the disorder. However, no tumor was identified by extensive studies which included abdominal computed tomography and a visceral angiogram. Computed tomography of the sella turcica was interpreted as demonstrating pituitary enlargement, which, however, was considered to be compatible with the patient's postpartum state. No intrasellar abnormality was described. For personal reasons the patient was discharged from the hospital, and interval medical management was initiated with 250 mg of aminoglutethimide four times daily. This medication was stopped one week later, and the patient was readmitted for further studies. Two weeks later, aminoglutethimide therapy was restarted and continued for another three weeks. Serum cortisol fell to 13  $\mu\text{g}/\text{dL}$ . Although her weakness and edema improved, she complained of scalp hair loss, and aminoglutethimide therapy was stopped. Without treatment, weakness and facial swelling recurred; the patient developed acne and seemed increasingly hyperpigmented. Serum cor-

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tisol rose to 60  $\mu\text{g}/\text{dL}$  and urine cortisol to 1,189  $\mu\text{g}/24$  hours. At this stage a trial of bromocriptine therapy was instituted.

## Methods

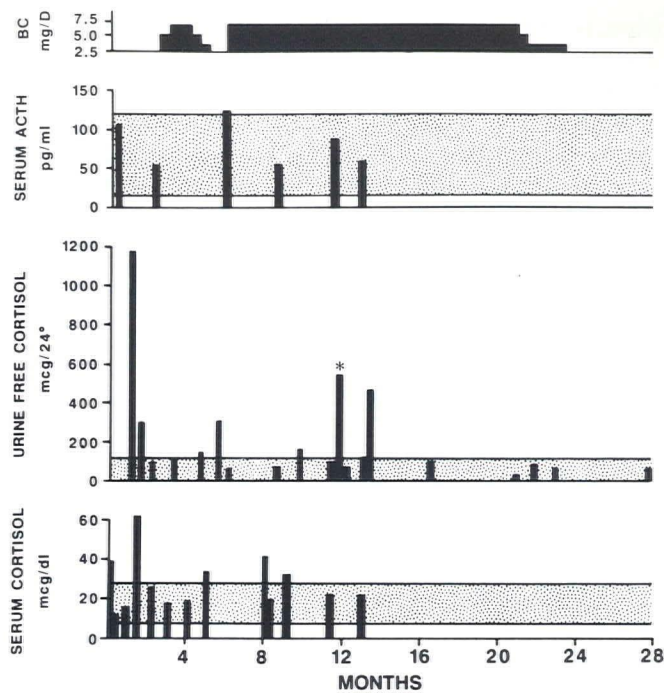
Three provocative tests were performed: 1) a high-dose dexamethasone study, 2) a combined thyrotropin-releasing hormone and gonadotropin-releasing hormone test, and 3) an oral bromocriptine challenge. For the dexamethasone suppression study, the patient received 2 mg orally every six hours for three days following three days of baseline studies. Serum and urine cortisol were measured daily, and serum ACTH was measured prior to and on completion of the tests. Thyrotropin-releasing hormone (200  $\mu\text{g}$ ) and gonadotropin-releasing hormone (100  $\mu\text{g}$ ) were administered together intravenously during the second course of aminoglutethimide. Blood was drawn at 0, 15, and 30 minutes for estimation of ACTH, prolactin, luteinizing hormone, and thyroid-stimulating hormone. The patient received the oral test dose of bromocriptine (2.5 mg) ten days after stopping the second course of aminoglutethimide. Blood was drawn at 0 and 240 minutes for estimation of ACTH and  $\beta$ -endorphin.

The following substances were measured by standard radioimmunoassay techniques: cortisol (reference range: 8 to 28  $\mu\text{g}/\text{dL}$  in serum, and < 120  $\mu\text{g}/24$  hr in urine [Amerlex, IL]); prolactin (reference range: < 25 ng/mL [Abbot, IL]); thyroid-stimulating hormone (reference range: < 5  $\mu\text{IU}/\text{mL}$  [Leeco, MI]); and luteinizing hormone (basal range of 4 to 29  $\mu\text{IU}/\text{mL}$  [Leeco, MI]). Serum ACTH was measured at the Nichols Institute with expected morning values of < 130 pg/mL. Serum  $\beta$ -endorphin and concomitant ACTH titers were measured using previously described techniques (12,13). Serum  $\beta$ -endorphin is not detectable in healthy adults by this assay, which has a sensitivity of 5 femtomole/mL.

## Results

A paradoxical response occurred with the dexamethasone test. Twenty-four hour urinary cortisol excretion, corrected for creatinine levels, rose remarkably to 2,779, 5,043, and 3,724  $\mu\text{g}$  from baseline values of 394 and 359  $\mu\text{g}$ . On completion of the study, serum ACTH (160 pg/mL) was also higher than the baseline values of 129, 131, and 115 pg/mL. The effect of the prior one week of aminoglutethimide therapy on this unusual response is not known, but the rise in ACTH titer which occurred contemporaneously with the rise in urinary cortisol substantiates the failure of pituitary suppression by dexamethasone.

Following combined thyrotropin- and gonadotropin-releasing hormone administration, serum ACTH levels did not change (baseline = 99 pg/mL; 15 min = 83 pg/mL; 30 min = 81 pg/mL). The serum prolactin, however, rose from 14 to 120 ng/mL at 30 minutes, while the serum luteinizing hormone rose from 9.5 to 52.3  $\mu\text{IU}/\text{mL}$  at 30 minutes, and the thyroid-stimulating hormone rose from 1.7 to 5.1  $\mu\text{IU}/\text{mL}$ . Following the oral dose of bromocriptine, serum ACTH fell from 106 to 50 pg/mL at 240 minutes, while serum  $\beta$ -endorphin decreased slightly from an elevated value of 14 to 12.6 fm/mL.



Figure—Biochemical response to bromocriptine (BC) therapy. The stippled areas represent reference ranges. The asterisk indicates a period of symptomatic relapse during therapy.

## Response to Bromocriptine Therapy

Eighteen weeks after delivery and six weeks after stopping the second course of aminoglutethimide, bromocriptine therapy was introduced beginning with 5 mg/day for one week, increasing to 7.5 mg/day for nine weeks, and then gradually reducing the dose over the next four weeks. During this period of therapy, serum cortisol, urinary cortisol, and serum ACTH levels were consistently within the normal reference ranges (Figure), and another computed tomography examination of the sella was within normal limits. The patient felt well, scalp hair regrew, all physical signs of Cushing's syndrome disappeared, and regular menses returned. Despite presumption that the remission of Cushing's disease had been induced by bromocriptine, the possibility that the patient had had a transient form of the disorder merited consideration, and bromocriptine therapy was withdrawn after more than three months of treatment. Within four weeks, facial swelling recurred. Moreover, there was convincing biochemical evidence for recurrent hypercorticism (Figure). Accordingly, bromocriptine therapy was reinstated and continued without interruption for 17 months. During this continuous therapy, the patient reported four episodes of weight gain and facial swelling accompanied by insomnia and overactivity. During the most severe episode, which occurred after five months of continuous therapy, urine-free cortisol was elevated to 557  $\mu\text{g}/\text{dL}$  (Figure). However, the clinical abnormalities rapidly abated without change in bromocriptine treatment, and the markedly increased urinary cortisol subsided. On another occasion, when the patient neglected to take bromocriptine for



ten days, she reported weight gain, weakness, and nocturia, symptoms which resolved within five days after restarting bromocriptine. After a six-month period during which urinary cortisol values were continuously normal and the patient experienced no hypercortical symptoms, bromocriptine therapy was discontinued. The total duration of therapy had been 22 months. To date, more than two years later, her condition has remained in remission. At no time were there any side effects attributed to bromocriptine treatment.

## Discussion

This unusual case of Cushing's disease presented in a fulminant manner suggestive of an ectopic neuroendocrine tumor, but with the passage of time displayed an indolent course and completely resolved following a period of bromocriptine therapy. Since the rapid onset of her disease occurred within a few days after a normal, term pregnancy, some relationship merits consideration. Remission of hypercorticism during pregnancy, followed by postpartum relapse, has been previously documented (14-16). During normal pregnancy, ACTH levels are suppressed, possibly through the direct suppressive effect on the pituitary of placental estrogens and progesterone (17). Cortisol levels in serum are strikingly elevated because of the threefold to fourfold elevation in the cortisol-binding globulin. Conceivably, physiologic adjustment in the immediate postpartum period could release large quantities of cortisol bound to cortisol-binding globulin, while the termination of ACTH suppression could be conducive to the development of Cushing's disease. Possibly of even greater importance is the known development of the intermediate lobe of the pituitary during pregnancy (18).

Based upon animal and human studies, Krieger (2) suggested that Cushing's disease in man may originate from corticotroph cells in either the anterior pituitary or the intermediate lobe, and that the two disorders may present different functional characteristics and responses to different therapeutic maneuvers. A distinct intermediate lobe, present in the human fetus in rudimentary form, disappears after birth (19). However, the corticotroph cells residing in the zona intermedia may proliferate during pregnancy (18). Corticotrophs in the anterior lobe produce a 16 K protein, ACTH, and  $\beta$ -lipotropin from the precursor molecule proopiomelanocortin (20). In the intermediate lobe, further proteolytic cleavage yields  $\alpha$ -melanocyte-stimulating hormone derived from ACTH, and  $\beta$ -endorphin derived from  $\beta$ -lipotropin. The factors regulating ACTH production are also different in the two lobes. In the anterior lobe, ACTH synthesis is increased by corticotropin-releasing hormone, antidiuretic hormone, and insulin-induced hypoglycemia, but is decreased by glucocorticoids. Intermediate lobe corticotrophs are little affected by these stimuli, and have a low concentration of the cortisol receptor (21). However, ACTH synthesis in the intermediate lobe is apparently inhibited by dopamine (2,21).

These experimental data have prompted investigations designed to identify Cushing's disease patients with hypothalamic dysregulation who might be treated with chemotherapeutic agents (2). Lamberts et al (3) have provided substantial evidence supporting the hypothesis that Cushing's disease may arise in

corticotrophs of intermediate lobe origin. In six of 15 Cushing's disease patients who had transsphenoidal surgery, histological analysis after argyrophilic staining revealed neural tissue in the midst of the adenomas. Compared to cases lacking neurofibers, these six subjects responded to a single oral dose of bromocriptine with a reduction in serum ACTH, had reduced responsiveness to dexamethasone, were more likely to have hyperprolactinemia, and were less likely to attain a remission following pituitary surgery. In two instances, the adenomas were situated adjacent to the pars nervosa in the region of the zona intermedia. Our case was similar to these six cases in that there was failure of cortisol suppression by high-dose dexamethasone, hyperresponsiveness of prolactin to thyrotropin-releasing hormone stimulation, and a reduction in ACTH titers following a single dose of bromocriptine. Our patient did not demonstrate an ACTH response to thyrotropin-releasing hormone, but it is disputed whether such a response occurs in patients with Cushing's disease of intermediate lobe origin (22). Indeed, the very concept of intermediate lobe origin for Cushing's disease continues to be disputed (23).

The efficacy of bromocriptine in the management of Cushing's disease both in the short and long term has been evaluated by many investigators with variable results. In about 50% of 49 cases reported in six different series, a single dose of 2.5 mg of bromocriptine resulted in lower ACTH levels (3-7,24). It is uncertain whether the acute response to dopamine agonists relates to the outcome of long-term therapy, but certainly the response to long-term treatment has not been favorable. Reported remissions are usually incomplete and temporary (4-10). One reported patient with prolonged remission required continuous therapy (11). Our patient, with a complete remission achieved following a prolonged course of bromocriptine therapy, is unique. However, her course was marked by four brief relapses even while taking bromocriptine. We speculate that our patient had self-limited hypothalamic dysfunction, which was responsive to dopamine repletion but which periodically escaped therapeutic control.

This case report testifies to the complex nature of Cushing's disease, consistent with recent insights into the control of ACTH synthesis in the pituitary. Dopamine agonists should be considered as a means of medical therapy in the management of the disorder, particularly in cases associated with hyperprolactinemia and reduced responsiveness to dexamethasone. If a favorable biochemical response is observed in the short term, a trial of therapy should be instituted. Apparently, if surgery becomes necessary in a bromocriptine responder, total hypophysectomy is required to secure a remission (3).

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