Response of ACTH to octreotide in a probable corticotropic adenoma associated with Addison's disease

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Abstract

BACKGROUND: Our patient was a 65-year-old woman previously diagnosed with Addison's disease. She presented an empty sella turcica and, at the age of 47, was discovered to have autonomous hypersecretion of adrenocorticotropic hormone (ACTH), suggesting a corticotropic adenoma secondary to Addison's disease, with a lack of response to high levels of dexamethasone. She maintained high ACTH levels despite corticosteroid treatment.

METHODS: The patient underwent a CRH stimulation test using an intravenous bolus (100 μg) with samples every 30 minutes for 3 hours and, the day after, an octreotide infusion (0.1 mg/200 cc saline) for 2 hours with measurements every 30 minutes for 3 hours. The following month she received subcutaneous octreotide 0.1 mg tid., and samples were taken every week.

RESULTS: Thirty minutes after the corticotropic-releasing-hormone (CRH) stimulation test, baseline ACTH levels (1 063 pg/ml) increased to 1530, the other values lying between 1 020–862. After octreotide infusion, baseline ACTH (1 212 pg/ml) was 946-643-1 630-4 600-1 730 at 30-60-90-120-180 minutes. The following month, with octreotide treatment, serum ACTH levels were 454-768-1233-429 pg/ml each week.

DISCUSSION: Octreotide acts mainly on somatostatin type 2 receptors (SSTR2) and has no effect in Cushing's syndrome, although a suppressor effect in some ACTH ectopic hypersecretions and in Nelson's syndrome has been demonstrated. It has been observed that SSTR5 appear more frequently than SSTR2 in corticotropic adenomas and corticosteroids downregulate octreotide sensitivity.

CONCLUSIONS: Octreotide did not suppress secretion of ACTH in suspected corticotropic adenoma. Newer somatostatin analogues, acting mainly on SSTR5, may be able to control ACTH hypersecretion in cases such as this.

CASE REPORT

Abbreviations

ACTH	- adrenocorticotropic hormone
CRH	- corticotropic releasing hormone
tid	- three in day
iv	- intravenous
sc	- subcutaneous
im	- intramuscular

INTRODUCTION

At present, the treatment of choice for adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas is surgical removal, the alternatives being radiotherapy or steroidogenesis inhibitors. These therapeutic options have been used in the absence of any really effective treatment for this type of tumour [19]. The discovery of dopaminergic agonists and the somatostatin receptors (SSTR) in ACTH-hypersecreting pituitary adenomas has been followed by somatostatin analogues such as octreotide or lanreotide (with a preferential action on type 2 SSTR) [7].

Somatostatin inhibits the release of several hormones in the adenohypophysis, although its action on ACTH is questionable. Up to five types of SSTR (SSTR1, SSTR2, SSTR3, SSTR4, SSTR5) have been discovered in pituitary adenomas; octreotide acts mainly on SSTR2 [23,26,10,20]. However, no significant responses have been obtained to date with this drug on ACTH-secreting tumours, except in patients with Nelson's syndrome and in some ectopic tumours [7,26,6,17]. It has recently been observed that SSTR5 (and not SSTR2) are the most frequent receptors in corticotropic tumours [11], and a decrease in the activity of SSTR2 has been observed when corticosteroids are administered [26,8,27]. Consequently, new therapeutic options are becoming available, and these use new somatostatin analogues acting on other receptor subtypes, such as SSTR5.

We present a case in which octreotide was not efficacious in a probable ACTH-secreting adenoma. The patient was a woman with Addison's disease treated with hydrocortisone and fluorohydrocortisone, who presented autonomous ACTH secretion with clinical manifestations including mucosal and cutaneous hyperpigmentation, and an empty sella turcica in imaging tests. This suggested a probable corticotropic adenoma secondary to Addison's disease [13], as occurs in other parts of the pituitary axis, such as the thyroid [16]. ACTH suppression tests were performed with an octreotide infusion (0.1 mg in saline for 2 hours) after a CRH stimulation test (100 μg iv), and octreotide was given for one month (0.1 mg sc tid). However, this therapy failed to inhibit secretion of ACTH.

PATIENT DETAILS

Our patient, born in 1928, first presented symptoms of adrenal insufficiency at age 14 and was diagnosed with Addison's disease with a probable tuberculous origin at age 18. She presented several episodes of adrenal crisis coinciding with the withdrawal of corticosteroids. At age 30, she began suffering from headaches, and a cranial x-ray revealed a sella turcica with a double floor. A pneumoencephalogram was performed, and a partially empty sella turcica was diagnosed [14].This was later confirmed by magnetic resonance imaging (MRI); soft tissue volume was estimated to be 844 mm^3 and total sella turcica volume to be 1287 mm^3. A suspected nodule in the remaining pituitary tissue was never found (Figure 1).

The patient remained in good general health during treatment with oral hydrocortisone (20 mg daily) and fluorohydrocortisone (0.05 mg every two days). When hydrocortisone was increased to 40 mg daily, she presented episodes of perspiration, swelling, and general discomfort. The patient always presented cutaneous

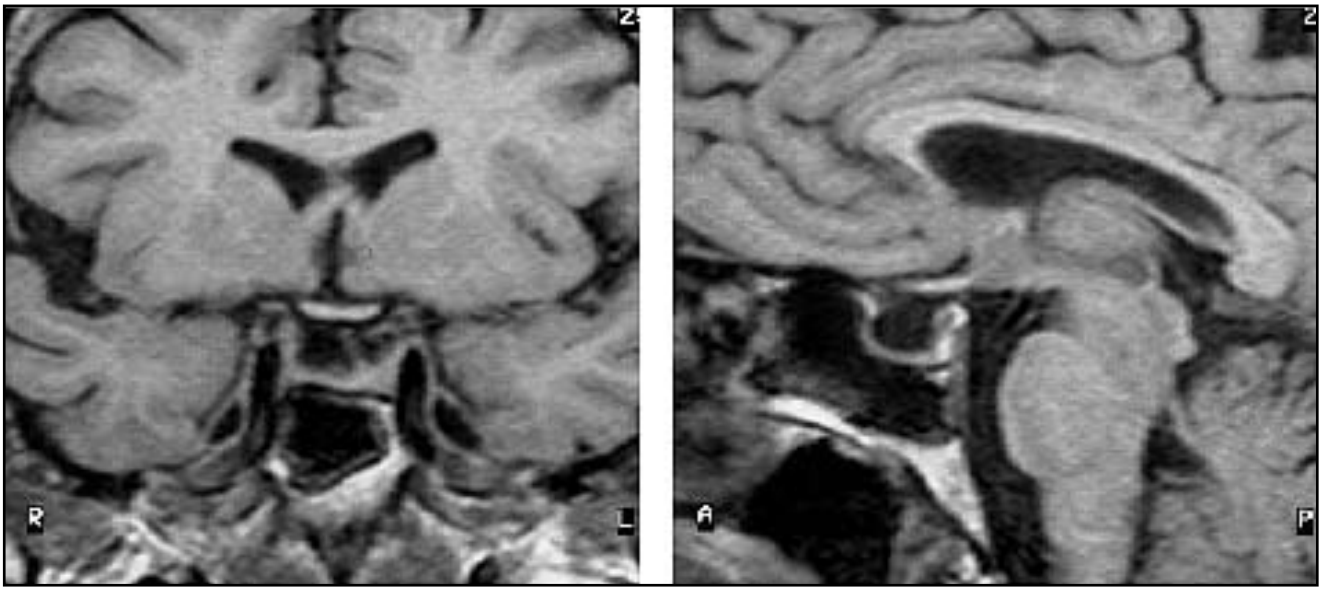

Figure 1. MRI showing empty sella turcica.

hyperpigmentation in the knuckles, tongue (Figure 2), and shoulders, and maintained ACTH levels of between 700 and 1500 pg/ml. Furthermore, she presented plasma cortisol levels <1 μg/dl, dehydroepiandrosterone sulfate (DHEA-S) <30 μg/dl, androstenedione 0.1 ng/ml, with normal levels of prolactin, thyrotropin (TSH) and free thyroxine (f-T4), and a growth hormone (GH) <0.1 ng/ml that did not respond to growth-releasing-hormone (GRH) stimulation or L-dopa/benserazide, although she subsequently presented a basal level of 1.7 which increased to 21.0 ng/ml after the hypoglycemia stimulation test.

In 1978, ACTH suppression tests were performed with 2 mg of dexamethasone daily (0.5 mg/6h) for two days, and with 8 mg daily (2 mg/6h) for the following four days. Her baseline ACTH levels varied from 2 000 pg/ml to around 1 000 pg/ml after the first two days, before stabilizing at around 900 pg/ml while she was taking the 8 mg of dexamethasone daily. Other dynamic tests were performed, such as the insulin hypoglycemia test (0.10 U/kg iv) and the lysine-vasopressin test (10 U im), which produced increases over baseline levels of 65% and 30%, respectively. She also received 250 μg iv of native somatostatin and subsequently a similar quantity by infusion for 60 minutes, which led to a 12% decrease in ACTH after 30 minutes. Furthermore, after a prolonged suppression performed with 60 mg of hydrocortisone (20 mg/8h) for two months, cushingoid features appeared while ACTH levels remained high (720–800 pg/ml). ACTH rhythm was studied during the third month by taking plasma ACTH samples on two consecutive days at 08:30 and 21:30: values of 700–750 pg/ml on the first day and 1 000–1 150 pg/ml on the second confirmed the loss of her circadian rhythm [13].

In 1983, the patient was diagnosed with sigma carcinoma, which went into complete remission after surgical removal. She entered the menopause at 46 years of age, developing osteoporosis in 1991. Treatment with bisphosphonates and oral calcium resulted in a subsequent improvement as demonstrated by successive bone densitometry tests. In 1992 she was diagnosed with type 2 diabetes mellitus, and presented glycosylated haemoglobin A1c below 6% with dietetic treatment. No more tests were performed or therapy with somatostatin analogues acting on SSTR5 administered as the patient died in a traffic accident in August 2002.

MATERIALS AND METHODS

ACTH was measured by radioimmunoassay, with an N-terminal antibody, according to Berson and Yalow's technique (the detection limit was 10 pg/ml) [4].

The patient was given a CRH stimulation test with an intravenous bolus of 100 μg with samples every 30 minutes for three hours. On the following day, an octreotide infusion (0.1 mg/200 cc. saline) was administered for two hours, and samples were taken every 30 minutes for three hours. Throughout the following month she received octreotide subcutaneously at 0.1 mg tid, and samples were taken every week. The patient remained asymptomatic during the testing period (1 month).

RESULTS

After an initial CRH stimulation test (100 μg iv in bolus), basal ACTH levels (1 063 pg/ml) increased, reaching a peak of 1 530 pg/ml thirty minutes after administration, with the other values ranging from 983 to 862 pg/ml. As mentioned above, a subsequent infusion was performed for two hours with 0.1 mg of octreotide diluted in 200 cc of saline solution. The initial ACTH level (1 212 pg/ml) changed to 946-643-1630-4 600 pg/ml at 30-60-90-120 minutes, and one hour later it was 1 230 pg/ml (Figure 3).

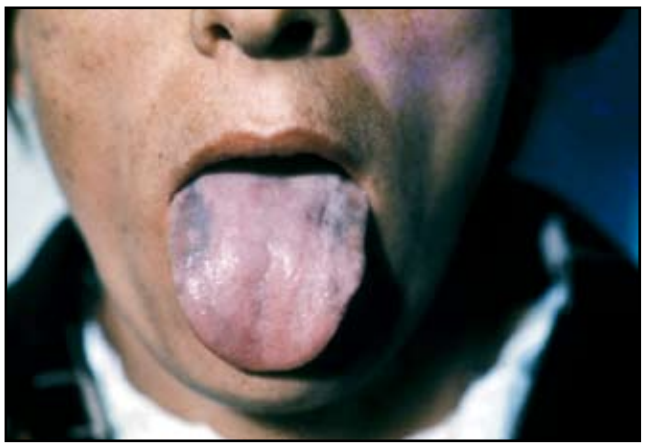

Figure 2. Tongue hyperpigmentation.

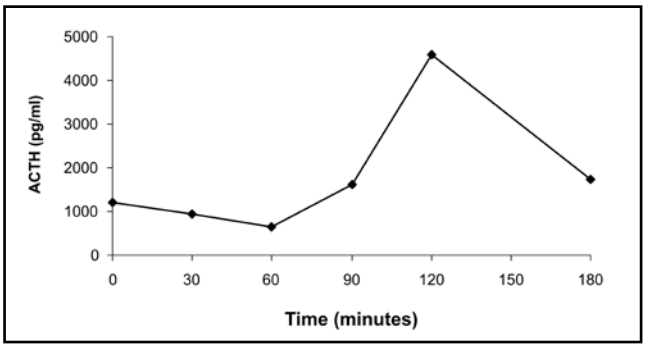

Figure 3. ACTH response to octreotide infusion test (0.1 mg) for 2 hours.

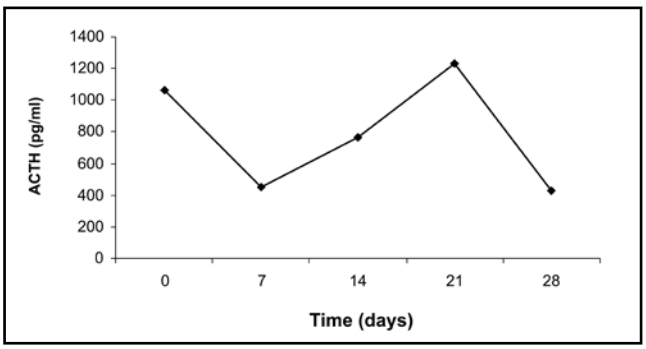

Figure 4. ACTH response to octreotide monthly treatment (0.1 mg tid).

During the following month the patient was treated with subcutaneous octreotide at 0.1 mg tid, with ACTH samples at 7, 14, 21, and 28 days. Serum ACTH levels were 454, 768, 1 233, and 429 pg/ml, respectively (Figure 4).

DISCUSSION

Although rare, there have been reports of ACTH-secreting pituitary adenoma in patients with Addison's disease receiving substitution therapy with corticosteroids [18,5]. There have also been reports of similar cases affecting other pituitary axes, such as the thyroid, in which patients with hypothyroidism can develop thyrotropin-secreting tumours due to the lack of inhibitory effect by the peripheral hormone [16].

Our patient presented very high ACTH levels which were not suppressed by the different suppression tests performed and did not present their typical rhythm of circadian secretion. The data showed autonomous ACTH hypersecretion suggestive of a corticotropic adenoma.

Attempts to increase the corticosteroid dose to suppress corticotropin activity in our patient resulted in negative tolerance, and she immediately developed cushingoid features. Consequently, octreotide was administered to stop autonomous secretion of ACTH. However, the patient developed mucocutaneous hyperpigmentation [26] with ineffective suppression in both short tests followed by treatment for one month with a subcutaneous dose of 0.1 mg/8h and a paradoxical increase in ACTH between the second and third week. Similar cases of this paradoxical ACTH effect have been reported in the literature, although their significance is uncertain [21,9].

ACTH secretion in vitro has been widely studied in the removal of murine pituitary corticotrope AtT-20 cells [26,27,3,12]. Here, inhibition of ACTH secretion with octreotide is dose-dependent, while the downregulation of these receptors produces an increased secretion of the hormone [3]. Therefore, ACTH-secreting tumours were treated with octreotide, which was not effective and thus did not agree with in the vitro results [27,12,24]. Other studies have already observed this scant effect of somatostatin on ACTH hypersecretion in Addison's disease [15,1].

It has recently been observed that diminished expression of SSTR2 occurs when AtT-20 cells are subjected to corticosteroids [26,8,27], which to a certain extent explains the ineffectiveness of octreotide on ACTH-secreting tumours, except in the case of Nelson's syndrome and some ectopic tumours. Consequently, in untreated Cushing's disease, scintigraphy with 111-diethylenetriaminepentaacetic acid (DPTA)-octreotide is of little use, except in Nelson's syndrome [7,6,17]. The effectiveness of octreotide in certain ACTH-secreting ectopic tumours and its visualisation using octreotide scintigraphy is believed to be due to the resistance of these tumours to corticosteroids, unlike pituitary adenomas [12,25].

When corticotropic adenomas have been examined in humans (a very short series) [12], a greater presence of SSTR5 than SSTR2 (on which octreotide acts) has been observed, thus contributing to the ineffectiveness of octreotide in these tumours [26]. A certain resistance has been found in the expression of SSTR5 with corticosteroids, as was also observed with attempts at suppression using dexamethasone. This drug acts on these receptors as a new objective in the treatment of ACTH-secreting pituitary tumours [26,27].

As a result, tests are being conducted on the effectiveness of new somatostatin analogues that act on SSTR5: BIM-23268 presents selective action against these receptors, and multiligands such as SOM230 present 30, 5, and 40 times more affinity for SSTR1, SSTR3, and SSTR5, respectively, and have 2.5 times less effect on SSTR2 than octreotide [23,26,11,27,12,22,2]. These new analogues were not tested in our patient due to her unfortunate death in a traffic accident [14].

CONCLUSIONS

In this case, octreotide did not control ACTH hypersecretion. As neither octreotide nor lanreotide have a significant effect on SSTR5, future studies of corticotropic adenomas and other secreting pituitary tumours should examine the new somatostatin analogues, especially multiligands. If the desired results are obtained, therapy for this type of tumour will probably change, in that medical treatment, rather than surgery, can be offered in many cases.

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