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ACTH Dependent Cushing's Syndrome: A 72-Hour Trial of Octreotide will Identify Patients with Pituitary Dependent and Ectopic ACTH Overproduction

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors have seen all the patients and managed them, perform the 72-hour octreotide suppression test, writing the paper and reviewing the literature. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine whether the use of an octreotide suppression test will reliably distinguish pituitary from ectopic ACTH overproduction. Somatostatin receptors are expressed in NETs, but are downgraded in the pituitary as the result of hypercortisolaemia. Octreotide should therefore lower ACTH and cortisol levels in patients with NETs but not in patients with Cushing's disease and pituitary tumors.
Methodology: A cross sectional study was performed in 13 patents with ACTH dependent Cushing's (8 women, 5 men) with ages ranging between 21 to 40 years were studied. Serum cortisol concentrations were measured at 0800 hrs before and during the administration of. Octreotide at a dosage of 100 mcg subcutaneously every 8 hours for 72 hours.
Results: The serum cortisol concentrations returned to normal in 4 patients who were later documented to have ectopic disease, two with typical bronchial carcinoids and two with pancreatic NETs and metastatic disease. The other 9 patients had no suppression in serum cortisol concentrations and were documented later to have pituitary tumours.

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Conclusion: These results indicate that a short trial of octreotide will identify patients with ectopic disease as evidenced by a fall in serum cortisol levels whereas in those with Cushing's disease and pituitary tumours serum cortisol levels remains unchanged.
Recommendation: We recommend all patients with ACTH dependent Cushing's syndrome have an octreotide suppression test, even if the MRI shows an adenoma, so as to exclude the possibility of a pituitary incidentaloma in a patient with ectopic disease, or false localization from IPSS to the pituitary gland due to ectopic CRH secretion.

Keywords: ACTH dependent Cushing's syndrome; somatostatin receptors, octreotide suppression test; inferior petrosal sinus sampling; bronchial carcinoid.

1. INTRODUCTION

Adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome (CS) is uncommon. Approximately 90% of cases are caused by an ACTH-secreting pituitary tumour; 40% of these small pituitary tumours cannot be seen on pituitary-directed head MRI scans. Approximately 10% of patients with ACTH-dependent CS have ectopic ACTH secretion by neuroendocrine tumors (NETs). To distinguish between these 2 causes of ACTH-dependent CS the gold standard procedure is inferior petrosal sinus sampling (IPSS). However, because IPSS is not available in our center we have been using a 72-hour trial of the somatostatin analogue (octreotide) to distinguish between the eutopic and ectopic ACTH syndromes. NETs have receptors for somatostatin and respond with a fall in serum cortisol concentrations, whereas cortisol levels remain elevated in patients with pituitary-dependent CS.

Our decision to use octreotide in patients with ACTH dependent (CS) was prompted when we suspected a patient with a pulmonary nodule to have ectopic ACTH production. With octreotide treatment, he made a rapid clinical and biochemical improvement with normalization of his serum cortisol and ACTH concentrations. This state of affairs persisted for a year until he finally agreed to surgery. His tumour was typical bronchial carcinoid and he recovered completely (Fig. 1).

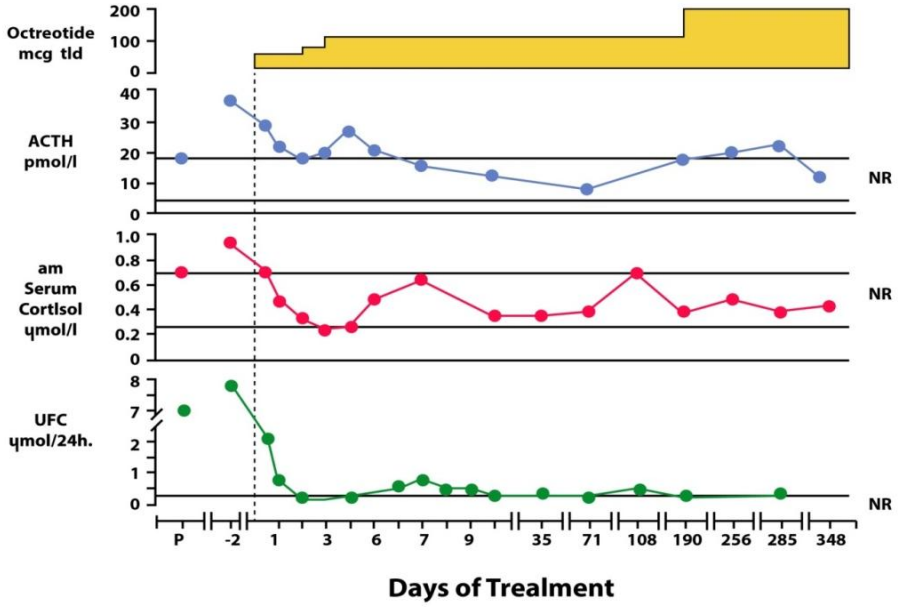

Fig. 1. Lung carcinoid and ectopic ACTH secretion: long term response to octreotide (index case) with permission reference 6. Normal Range (NR)

2. METHODOLOGY

We studied 13 patients (8 women, 5 men) with ages ranging between 21 to 40 years with ACTH dependent Cushing's syndrome. All presented with classical disease and their presenting details are shown in Table 1. Five patients had CT/MRI evidence of a pituitary tumour and in 7 the scans were normal. Octreotide was administered at a dosage of 100 mcg subcutaneously every 8 hours for 72 hours. Serum cortisol concentrations were measured daily at 0800 hrs before and during the administration of Octreotide.

3. RESULTS AND DISCUSSION

3.1 Results

The serum cortisol concentrations returned to normal in 4 patients who were later documented to have ectopic disease, two with typical bronchial carcinoids and two with pancreatic NETs and metastatic disease. The other 9 patients had no suppression in serum cortisol concentrations and were documented later to have pituitary tumours (Fig. 2).

3.2 Discussion

ACTH dependent Cushing's syndrome is a rare disorder [1-3]. The diagnostic challenge is to differentiate pituitary versus ectopic ACTH production. The gold standard procedure is to carry out inferior petrosal sinus sampling (IPSS) with ACTH measurements [4,5]. This procedure is not available in our center and over the years we have developed an alternative approach using a 3-day octreotide suppression test [6,7]. Most neuroendocrine tumours (NETs) express somatostatin (SS) receptors and respond to treatment with octreotide whereas the SS receptors in Cushing's disease are downgraded by hypercortisolaemia [8] and do not respond with a reduction in cortisol levels.

Table 1. Fasting serum cortisol and ACTH levels in 13 patients with ACTH induced Cushing's syndrome at presentation

ACTH Dependent Cushing's Syndrome (13 patients)

Patient	Cortisol*	ACTH*	MRI	TSS
1	675	25	N	-
2	826	9	N	-
3	856	27	N	-
4	1200	36	N	-
5	612	13	+	Y
6	812	4	+	Y
7	900	20	+	Y
8	923	24	+	Y
9	700	16	+	Y
10	1100	6	+	Y
11	752	14.4	N	Remission on Cabergoline for 9 years
12	1054	23	N	Bilateral Adrenalectomy
13	750	84	+	Y

MRI: (N) Normal, (+) Micro adenoma, (-) Not done

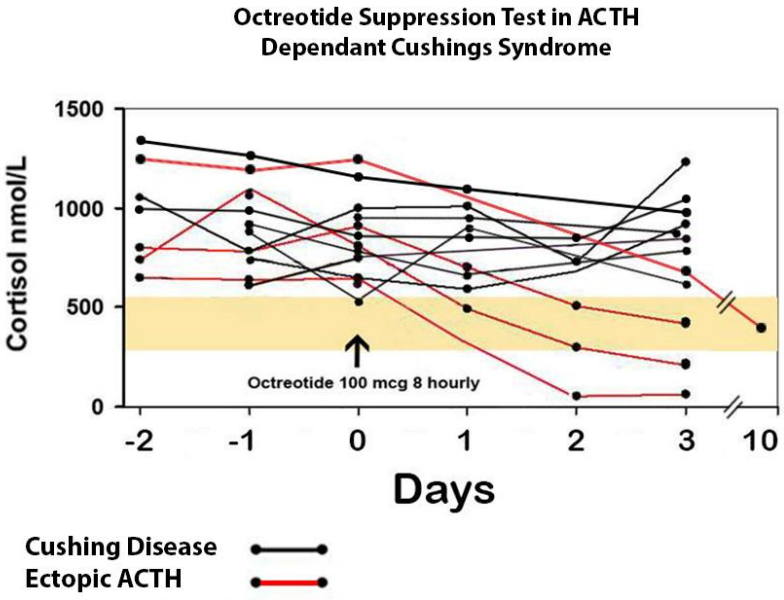

Fig. 2. Octreotide suppression test in 13 patients with ACTH dependent Cushing's syndrome (administered at a dosage of 100 mcg subcutaneously every 8 hours for 72 hours). Serum cortisol concentrations were measured daily at 0800 hrs

Tumours secreting ACTH are most commonly found in the lung and pancreas but may occur anywhere [9-11]. Their location may be identified by scintigraphy using labeled octreotide (Fig. 3 a,b), or preferentially 68 Galium-DOTANOC PET/CT.

The use of octreotide as a treatment for ectopic ACTH production has occasionally been reported [6,7,9], but in most other reports metyrapone and ketoconazole were used to control adrenal corticosteroid overproduction as they inhibit steroidogeneisis [11-13]. These medications do work but are potentially quite toxic, particularly to the liver. In our experience, octreotide is without significant side effects and should be used in every patient who responds to octreotide suppression test before surgery, or long term if surgery is not an option for any reason. Even if the MRI reveals a microadenoma octreotide suppression test should still be carried out to exclude the rare possibility of a pituitary incidentaloma [14]. This occurrence has previously been reported [15].

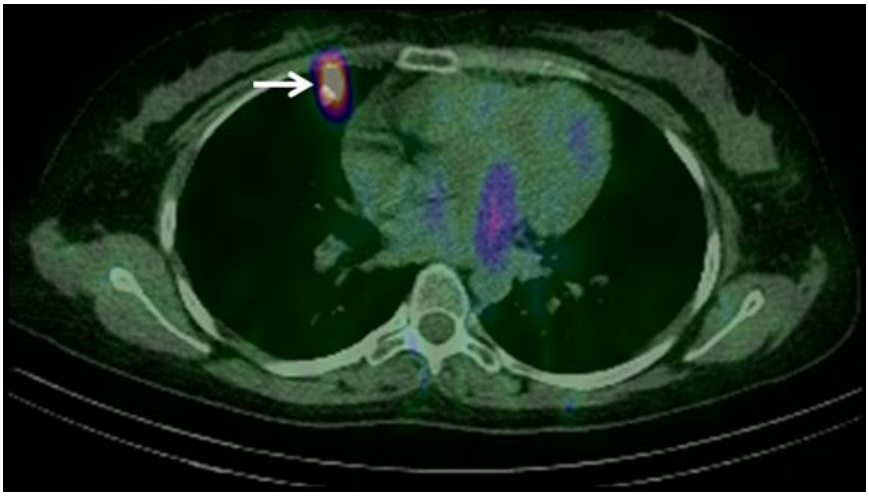

Fig. 3a. Patient 4: Octreotide scan: Focal tracer uptake in the right middle lobe

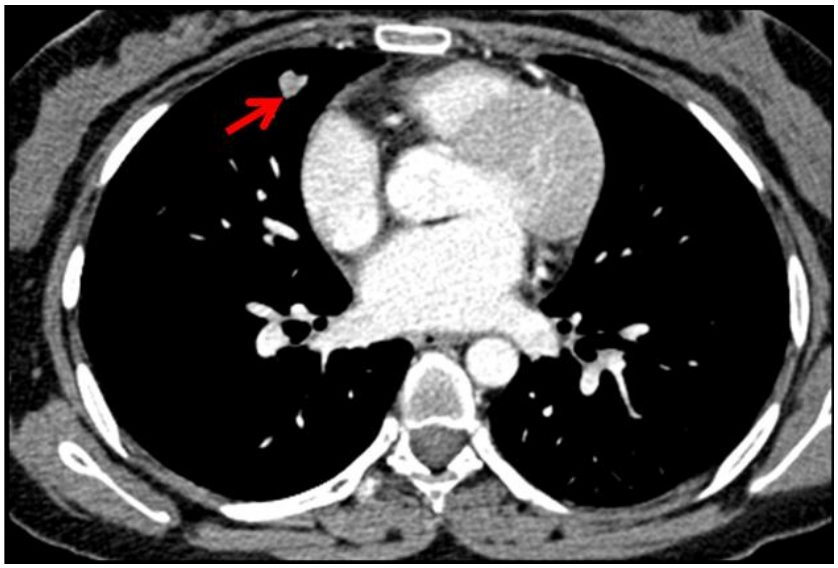

Fig. 3b. Patient 4: CT chest: Right nodular lesion corresponding to octreotide scanning

We did not encounter any patients with ectopic Cushing's due to small cell lung cancer, so cannot speculate on what their response to octreotide suppression might have been. This procedure is simple and safe and in our opinion should replace the use of IPSS in countries where it is not available.

In those patients with Cushing's disease who do not respond to octreotide suppression test, it is our policy to give a trial of high dose cabergoline which in our experience induces remission in most patients prior to surgery. In fact, we have one patient, refusing any surgery who has been in clinical and biochemical remission for 10 years on twice weekly cabergoline therapy [16].

4. CONCLUSION

We recommend that a 72-hour octreotide suppression test be given to all patients with ACTH-dependent CS. In our experience this test is safe, simple and reliably distinguishes pituitary from ectopic ACTH overproduction. Patients with NETs who respond to octreotide may then be controlled before surgery or in the long term with long acting octreotide if surgery is declined or not practicable.

5. RECOMMENDATION

We recommend all patients with ACTH dependent Cushing's syndrome have an octreotide suppression test, even if the MRI shows an adenoma, so as to exclude the possibility of a pituitary incidentaloma in a patient with ectopic disease, or false localization from IPSS to the pituitary gland due to ectopic CRH secretion [14].

CONSENT

Written informed consent was obtained for publication of the submitted article and accompanying images from the patients.

ETHICAL APPROVAL

Written informed consent was obtained and signed by our ethical committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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