Aberrant expression of serotonin receptors in an aldosterone- and cortisol-producing adenoma

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INTRODUCTION

Aberrant expression of serotonin receptors has been described to be involved in the pathophysiology of both aldosterone-producing and cortisol-producing adrenal adenomas.

CASE REPORT

A 46-year-old woman was referred for evaluation of severe hypertension associated with hypokalemia. No clinical features of overt hypercortisolism were present. The initial hormonal work-up after discontinuation of interfering antihypertensive drugs and correction of hypokalemia showed:

		Reference range	
Aldosterone (pg/ml)	213	40-310	Positive aldosterone/renin ratio
Renin (µU/ml)	< 2.0	3.0-45	
Aldosterone/renin [(pg/ml) / (µU/ml)]	> 40	< 24	
Cortisol (ng/ml)	142		
ACTH (pg/ml)	< 5	10-48	Suppressed ACTH
DHEA-s (ng/ml)	200	900-3500	Low DHEA-s concentration
Morning cortisol post 1-mg dexamethasone suppression test (ng/ml)	28	<18	Abnormal LDDST

Subsequent confirmatory tests were performed:

Saline infusion test			
Time of infusion	0'	2h	4h
Aldosterone (pg/ml)	67	118	99
Renin (µU/ml)	< 2.0	< 2.0	< 2.0

→ Confirmation of hyperaldosteronism

Midnight serum cortisol test			
	22h	0h	2h
Cortisol (ng/ml)	49	43	36
ACTH (pg/ml)	< 5	5.0	< 5

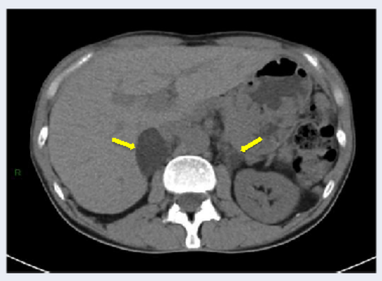
→ Elevated nocturnal nadir of cortisol

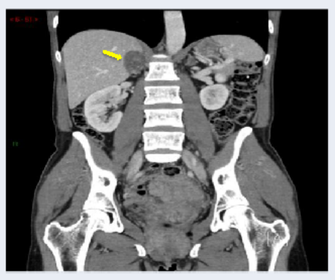
8-mg Dexamethasone suppression test	
Cortisol (ng/ml)	32

→ Insufficient suppression of cortisol

Based on the conjunction of these results, primary hyperaldosteronism with concurrent subclinical Cushing's syndrome was diagnosed.

A CT-scan demonstrated a lesion of 4 cm in the right adrenal gland and a second lesion of 1 cm in the left adrenal gland, both displaying an adenoma imaging phenotype.





Abdominal CT scan showing bilateral adrenal masses. Both lesions have unenhanced attenuation values < 10 HU.

We then explored the potential aberrant expression of serotonin receptors in the adrenal cortex by intravenous (IV) administration of metoclopramide, a serotonin type 4 receptor (5-HT_4-R) agonist, following dexamethasone (DXM) suppression of adrenal steroidogenesis.

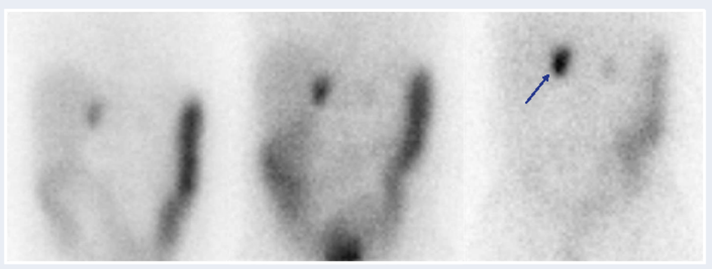
Abnormal cortisol increase after injection of metoclopramide, under DXM suppression

We noted a clearly abnormal cortisol increase in peripheral blood after metoclopramide injection. An increase of aldosterone was also observed. This latter increase occurs in normal individuals but no cut-off of supra-physiological response exists.

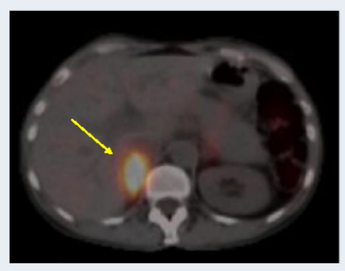
CASE REPORT

In order to localize the source of autonomous secretions, we proceeded to a bilateral sequential adrenal venous sampling (AVS) after DXM suppression, in basal conditions and after IV stimulation by metoclopramide. Results were difficult to interpret due to technical difficulties in cannulation of the right adrenal vein, but an abnormal increase in cortisol after stimulation was observed in the left adrenal vein.

In view of the inconclusive results of the AVS, we then performed a ^{131}I-19-Iodocholesterol scintigraphy under DXM suppression. This showed intense radiotracer uptake in the right adrenal mass and weak uptake in the left adrenal mass.



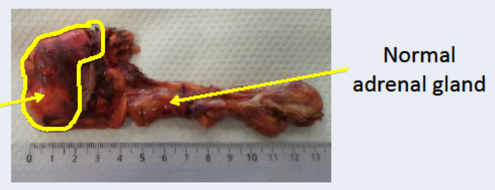
Day 3 post injection | Day 4 post injection | Day 7 post injection



Fused SPECT/CT image

Based on tumoral size and uptake pattern on scintigraphy, right laparoscopic adrenalectomy was performed.

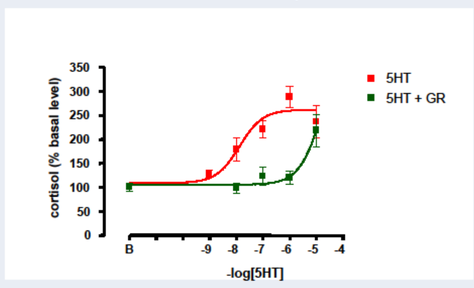
Histological examination revealed an adrenocortical adenoma.

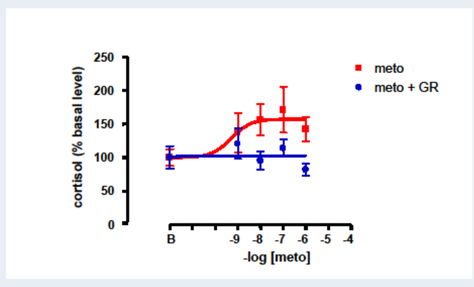


Postoperatively, blood pressure, aldosteronemia and free urinary cortisol returned to normal values.

IN VITRO STUDIES

Adrenocortical cells derived from the tumor tissue were cultured as previously described (1). They exhibited aldosterone and cortisol co-secretion. Administration of 5-HT or metoclopramide induced a dose-dependent increase in cortisol production. These effects were inhibited by concomitant administration of the 5-HT_4-R antagonist GR113808.





Incubation of tumor tissue fragments with 5-HT induced a significant increase in aldosterone production which was abolished in the presence of GR113808.

These data were suggestive of aberrant expression of 5HT_4-R in the tumor tissue.

CONCLUSIONS

We report a rare case of an aldosterone- and cortisol-co-producing adenoma in a patient with severe hypertension and bilateral adrenal masses exhibiting an abnormal plasma cortisol response to metoclopramide. *In vitro* studies revealed enhanced sensitivity of the tumour tissue to 5-HT indicative of illicit expression of 5-HT_4 receptors.

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