Limitations of dexamethasone suppression tests for Cushing's disease – a reminder!

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Introducation:

Establishing the diagnosis of Cushing's disease is a well recognised challenge when symptoms are subtle and investigations lead to discordant results. Differentiation from pseudo-Cushing's and other causes of apparent hypercortisolism is not always straight-forward[1]. The Endocrine Society gives clear guidelines on the pathway of investigations of Cushing's disease[2]. Many cases present themselves with equivocal findings and attention to detail is necessary in clinical practice to avoid misinterpretation. We present a reminder of the challenges of co-prescribed medications activating CYP3A4 pathway which will interfere with the sequence of investigations for Cushing's disease.

Case 1. A 70 years old man with longstanding resistant hypertension on five antihypertensive agents, type 2 diabetes and raised BMI at 35.6 was investigated for exclusion of possible Cushing's disease. Clinically he had truncal obesity with plethoric face but no other Cushingoid features. His medication list included Phenytoin and Phenobarbitone for epilepsy treatment. DEXA scan showed normal bone density.

Case 2. A 78 years old male was found to have a 2.2cm adrenal incidentaloma of benign appearance on imaging (Hounsfield Units 1). His comorbidities included hypertension well controlled on single agent. Clinically he had no Cushingoid features except for thin skin with limited areas of bruising. His medication included Carbamazepine as mood stabiliser, with no exogenous steroids.

Investigations:

	24H UFC	ODST	LDDST	Midnight cortisol	ACTH	K
Case 1	82 nmol/L & 152 nmol/L (<270 nmol/L)	132 nmol/L	0' 396 nmol/L 48' 111 nmol/L	39 nmol/L	11.6 (midnight) 33.7 (am)	4.4
Case 2	581 nmol/L & 402 nmol/L (<270 nmol/L)	585 nmol/L	0' 490 nmol/L 48' 366 nmol/L	Not done	17.3	4.0

Comments:

- Well recognised causes of false positive results for dexamethasone suppression tests: reduced dexamethasone absorption, drugs enhancing CYP3A4 hepatic dexamethasone metabolism, liver and renal failure, pseudo-Cushing states.
- No data on length of withdrawal from anti-epileptics when test interference ceases. Risk-benefit assessment of stopping antiepileptics for patients with controlled epilepsy.
- Carbamazepine has also been reported to cause false elevations of urinary free cortisol levels[2] (Case 2).
- Role of DHEA to support exogenous corticosteroid effect.
- A case for increasing the availability of salivary cortisol measurements, specially for day profile including midnight levels with potential role in avoiding hospitalisation for further investigations.
- Role of dexamethasone-CRH test in differentiating pseudo-Cushing states[3,4].

Selected drugs that may interfere with the evaluation of tests for the diagnosis of Cushing's syndrome[2]

Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4	*Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4*
• Phenytoin • Carbamazepine • Rifampin • Phenobarbital • Pioglitazone	• Itraconazole • Ritonavir • Fluoxetine • Diltiazem • Cimetidine
Drugs that increase CBG and may falsely elevate cortisol results	*Drugs that increase UFC results*
• Estrogens • Mitotane	• Carbamazepine (increase) • Fenofibrate (increase if measured by HPLC) • Some synthetic glucocorticoids (immunoassays) • Drugs that inhibit 11b-HSD2 (licorice, carbenoxolone)

Learning points:

Careful history remains the starting point of patient evaluation. Alcohol and exogenous steroids were excluded in both patients' case histories.

While current antiepileptic agents include Lamotrigine, Levetiracetam, Topiramate, some patients are still well controlled on older agents as Phenobarbitone and Phenytoin. A good clinical history including drug history (see table) is still a necessity before enrolling on complicated dynamic function tests which are not without patient inconvenience and financial burden to a department.

Conclusion:

Definitive confirmation of hypercortisolic state has not been achieved in our case and interval re-evaluation is the planned strategy at follow up with repeated 24H UFC at two monthly intervals. We can only rely on 24 hours urine free cortisol levels and midnight cortisol as screening tests for such cases and we need to bear in mind their limitations too.

References:

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