

Challenges in the investigation and management of a patient with cyclical Cushing's disease and insulin requiring diabetes.



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Clinical History

- 40 year old nurse initially referred in 1999 for investigation of weight gain, fatigue, easy bruising and hypertension.
- A screening 24hr urinary cortisol was raised at 3998nmol/24hr (normal range <320)
- Low and high dose dexamethasone suppression tests were within normal range. CT imaging was also normal
- She was lost to follow up
- She subsequently developed rheumatoid arthritis, requiring intermittent courses of corticosteroid therapy.
- Other extensive medical history included Sjogren's syndrome, steatohepatitis, coeliac disease, AF and osteoporosis.
- She was diagnosed with Type 2 diabetes in 2001 and was treated with metformin, gliclazide and liraglutide.
- In 2013 she was referred to secondary care diabetes outpatients for initiation of insulin and at this point her clinical appearance raised concerns regarding Cushing's syndrome.
- HbA1c remained raised at 96mmol/mol and patient reported unexplained considerable variation in insulin requirements.

Investigations

- Overnight 1mg dexamethasone suppression test : serum cortisol 1226nmol/L
- 24hr Urinary free cortisol normal range on multiple occasions

Dexamethasone suppression test

Time	Dose	Cortisol (nmol/L)
0800	0.5mg qid	146
0800	0.5mg qid	19
0800	2mg qid	15
0800	2md qid	18
0800		20

- Dynamic MRI Pituitary – 1.5mm nodule in pituitary gland. CT adrenals normal.

- ACTH suppressed but measurable intermittently

- CRH test

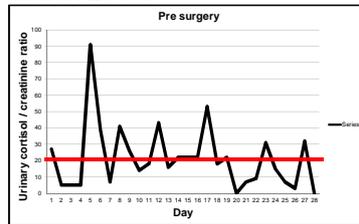
Time (mins)	ACTH (ng/L)	Cortisol (nmol/L)
-15	10	115
-5	<10	106
0	<10	99
5	23	101
10	35	193
15	38	389
30	31	475
45	26	475
60	24	445

Petrosal sinus sampling (ACTH ng/L)

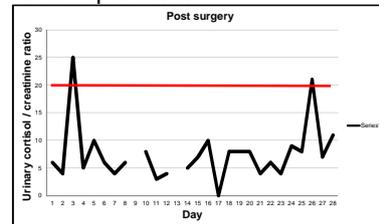
Time (mins)	0	1	2	3
R petrosal	67	118	700	591
L petrosal	<10	<10	15	32
Peripheral	<10	<10	13	27

28 day early morning urines for cortisol to creatinine ratio

March 2016.



Post operative.



- Post operative results:
- Day 5 serum cortisol 567nmol/L
- 24hr Urinary free cortisol 107nmol/L
- 3 month post op low dose dexamethasone suppression test:

Time	Dose	Cortisol	ACTH
2300		221	
0800	0.5mg qid	470	22
0800	0.5mg qid	22	
0800	2md qid	21	

Management

- Transphenoidal surgery December 2016
- Histology did not confirm adenoma. Immunohistochemistry: no ACTH predomination.
- Post operative 28 day early morning urine cortisol improved.
- Improvement in symptoms post op – sweating disappeared and mood improved however symptoms had returned at review.
- Glycaemic control has improved with reduced insulin requirements.

- In cases such as this cure and remission is challenging and she has had mixed postoperative results to date with a high day 5 cortisol but normal urinary free cortisol and low dose dexamethasone suppression test.

Conclusion

- This case illustrates the challenges in investigation, diagnosis and management of patients with cyclical Cushing's disease. Routine biochemical screening for Cushing's in the diabetes clinic is not useful but rather clinical evaluation remains key. During elective admissions variability in insulin requirements were noted by up to 50% reflecting the added challenge of achieving good glycaemic control in this setting.