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Cushing's Disease and High Dose Cabergoline Monotherapy: Rapid and Sustained Clinical and Biochemical Improvement, with Reversal of Diabetes, Hypertension and Infertility

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Authors' contributions

This work was carried out in collaboration between all authors. Authors OE and NNW designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author NH managed the literature searches, analyses of the study performed the spectroscopy analysis and authors OE and NNW managed the experimental process and identified the species of plant. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To assess the effects of high dose long term cabergoline monotherapy in a patient with Cushing's disease refusing any form of surgical intervention.
Presentation of the Case: A 32-year-old Omani female with hypertension, diabetes mellitus and secondary infertility of 10 years and amenorrhoea of 2 years duration, was referred with recurrent thigh abscesses. She was on 100 units of mixed insulin in two divided doses, metformin 1 gm bd, lisinopril 20 mg od, amlodipine 10 mg od and indapamide 1.5 mg od ."She had all the features of Cushing's syndrome, with a blood pressure (BP) of 180/110 mmHg, plethoric facies, central obesity and striae".
Investigations revealed diabetes, HBA1c 10.7% and ACTH-dependant Cushing's syndrome,

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"cortisol 720 nmol/L (normal <624) and ACTH 14.9 pmol/L. (normal 1.6-13.8)". The pituitary MRI and computerised tomographic (CT) scans from neck to pelvis " were normal"
A neuroendocrine tumour (NET) was deemed unlikely as serum cortisol levels did not "suppress during by a 72 hours trial" of octreotide 100 mcg 8 hourly and her serum chromogranin- A level (CgA) was normal. A diagnosis of Cushing's disease was made. She refused inferior petrosal sinus sampling (IPSS) and any form of surgery.
A trial of cabergoline was agreed upon. Her response was dramatic: On 1 mg daily initially, the serum cortisol was normal after one week, and by 4 months her blood sugar and blood pressure were normal off all other medications. The HBA1c had fallen from 10.7% to 5.4%. Shortly afterwards she became pregnant and on a reduced dose of cabergoline (1.5 mg/week), she delivered a healthy full term baby, echocardiography was normal in both mother and baby.
She has now been in complete remission for more than 4 years on cabergoline 0.5 mg 3 times a week without any side effects.
Conclusion: This case provides an example of successful acute and sustained primary "monotherpy" with initially high dose cabergoline in Cushing's disease. The additional positive metabolic effects and the lack of significant side effects makes high dose cabergoline monotherapy an attractive first or second line treatment for patients with Cushing's disease.

Keywords: Cushing's disease; pituitary; cabergoline; neuroendocrine tumour.

1. INTRODUCTION

"Cushing disease" is the commonest endogenous cause of "Cushing syndrome". It results in a state of chronic hypercortisolism secondary to increased ACTH production from a pituitary adenoma [1]. It has serious consequences including the aggregation of metabolic derangements such as diabetes mellitus, hyperlipidemia, hypertension and central adiposity. This results in a high cardiovascular disease risk. This in addition to the negative effects on neuropsychiatric, musculoskeletal, gonadal and other body systems. If not optimally treated it has a very high mortality [2].

Pituitary surgery constitutes the ideal treatment option. The difficult task of deciding on alternative optimal treatments arise if surgery is not possible, in refractory cases (10-40%) [3] or with recurrence (25% of successful cases) [4]. The classical second line surgical, radiotherapy or medical treatments have significant side effects and may not provide the desired response. Recently the efficacy and safety of newer medical options has been tested with promising results including dopamine agonists directed to dopamine 2 (D2) receptors on corticotroph adenomas.

Below we report details of a patient with severe Cushing's disease who responded rapidly and dramatically to high dose cabergoline monotherapy and the patient now has been in complete remission for more than 4 year on 0.5 mg three times per week.

2. CASE REPORT

A 32-year-old Omani female was referred to our unit because of poor diabetes control. Ten years before she was diagnosed with diabetes mellitus and hypertension, both of which remained poorly controlled despite treatment. Recently she had had repeated admissions because of recurrent thigh abscesses requiring drainage. Further history revealed increasing weight gain and generalized fatigue with occasional easy bruising. She was very concerned about her secondary infertility and two years amenorrhea. There was no headache or visual disturbance. She denied the use of topical or systemic steroids. Her medications at the time included 100 units of mixed insulin in two divided doses, metformin 1 gm bd and lisinopril 20 mg od, amlodipine 10 mg od and indapamide 1.5 mg od. Her BP was 180/100 "mmHg", Pulse rate of 91/minute. BMI of 31 "kg/m^2". She had a gross cushingoid appearance with central obesity, rounded plethoric face and "hirsuitism". Her skin was thin with purpurae and active abdominal striae. There was no goitre and rest of her systemic examination was unremarkable.

Investigations revealed a fasting glucose of 14 mmol/L and HBA1c "of 10.7%, The" blood count, and electrolytes, renal and liver profiles were normal. Basal hormonal testing confirmed ACTH-dependant cortisol excess with morning cortisol

of 720 nmol/L "(normal range <624)" and ACTH of 14.9 pmol/L "(normal range 1.6-13.8)". Following overnight 1 mg of dexamethasone her cortisol remained high at 523 nmol/L (normal < 50 nmol/l). Midnight sleeping cortisols were elevated at 458 and 630 nmol/l "(normal range< 128)". The pituitary MRI was normal (Fig. 1). The rest of anterior pituitary hormones were normal.

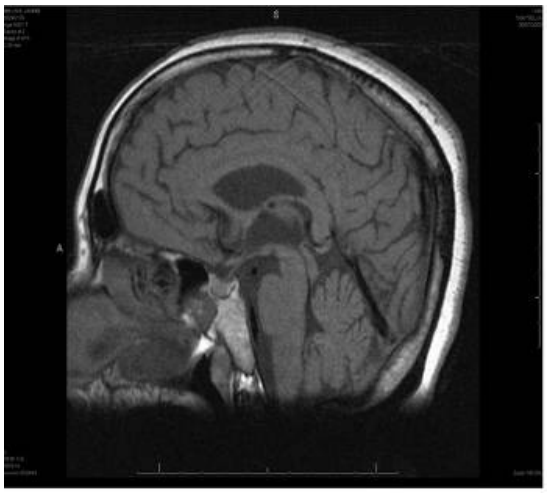

Fig. 1. MRI pituitary: Showing a normal fossa

A neuroendocrine tumour (NET) as a cause of the ACTH production was thought unlikely as her serum cortisol levels did not fall during a 72 hours trial of octreotide 100 mcg tid [5-7] and the serum chromogranin A level (Cg A) [8] and the neck, lung and abdominal CT's were normal.

A diagnosis of pituitary dependant "Cushing disease" was made. She was offered referral outside the country for inferior petrosal sinus sampling (IPSS) and possible surgery, both of which were refused.

The patient however consented to a trial of cabergoline. Her response was dramatic: On 1 mg daily, her serum cortisol levels had returned to normal after one week, and by 4 months her blood sugar and BP were normal off all other medications. The HBA1c had fallen from 10.7% to 5.4%. Shortly afterwards she became pregnant and on a reduced dose of cabergoline (1.5 mg/week), she delivered a healthy full term baby. Cabergoline was stopped after delivery but was restarted after 6 months as her disease relapsed. She has now been in complete remission for 4 years on cabergoline 1.5 mg / week without any side effects. Echocardiography was normal in both mother and baby.

This patients response was gratifying. Biochemical remission was achieved within a week and within a few months there was a complete reversal of her hypertensive and diabetic state. This has now been sustained for more than 4 years on a small dose of cabergoline (1.5 mg per week). A recent pituitary MRI remains normal.

3. DISCUSSION

To the best of our knowledge this is only the fourth time that cabergoline monotherapy has been used successfully as a first line treatment for Cushing's disease [9,10]. Its use in our patient resulted in a rapid and prolonged remission and permitted a successful pregnancy after 10 years secondary infertility. Cabergoline has been used to treat a relatively small number of patients so far and is reported to induce disease remission in up to 40% of cases over 1 year [11-15]. This is surprising as 80% of pituitary adenomas are said to express D2 receptors [16]. Perhaps the dose of cabergoline is important: we used 1 mg daily in 4 patients with Cushing's disease (including this patient) all of whom responded within one week [17] whereas in other studies the starting dose has been much smaller and responses delayed up to 6 months or more [9,10].

ACTH dependant "Cushing syndrome" is rare, roughly 90%, being due to a pituitary ACTH secreting micro adenoma and 10% a NET [1]. In those patients with a normal pituitary MRI a pituitary tumour can be confirmed or refuted by IPSS with simultaneous central and peripheral ACTH measurements [18]. Our diagnosis of Cushing's disease was arrived at indirectly: NET's usually express SS receptors and respond to octreotide [7,19]. This was not the case with our patient whose cortisol levels remained unchanged during an octreotide trial [6]. Futhermore NET's often cosecrete Cg-A [7] but our patient had normal values. These observations together with the normal CT scans favours the diagnosis of Cushing's disease. However we cannot exclude the possibility that the patient has a small NET expressing D2 receptors. We elected to use "cabergoline as the" somatostatin analogue paseriotide was not available at that time. Adrenolytic medications were not considered in view of their potential side effects [11].

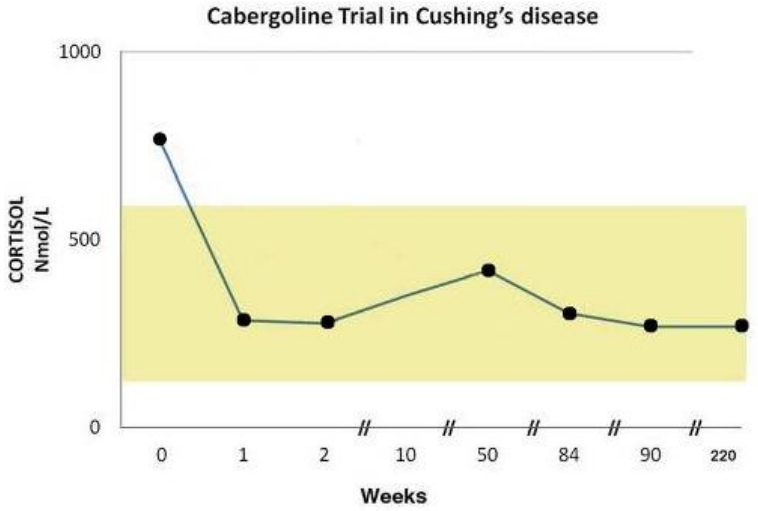

Fig. 2. Cabergoline trial in Cushing's disease: Cabergoline 1 mg daily was started initially and gradually reduced to 0.5 mg 3 times per week thereafter. She has been maintained on this dose for more than 4 years

4. CONCLUSION

This case provides an example of successful acute and sustained primary "monotherpy" with initially high dose cabergoline in Cushing's disease. The additional positive metabolic effects and the lack of significant side effects makes high dose cabergoline monotherapy an attractive first or second line treatment for patients with Cushing's disease.

CONSENT

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

Details of this patients' acute response to cabergoline have already been reported [13].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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