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Mini-review

A Simple Complex Case: Restoration of Circadian Cortisol Activity

Ragini C Bhake [1,] *, Stafford L Lightman [1]

[1] Henry Wellcome Laboratories for Integrative Neurosciences and Endocrinology, Dorothy Hodgkin Building, University of Bristol, Bristol, UK

*** Correspondence:** Email: mdzrb@bristol.ac.uk; Tel: (0)-117-331-3167; Fax: (0)-117-331-3169

Abstract: A 38-year-old librarian with confirmed Carney complex (PRKAR1a mutation) was referred for further evaluation of ACTH-independent Cushing's syndrome. Previously, she was known to have schwannoma (excised), adenomyoepithelioma and normal annual echocardiograms. Over three years prior to current presentation, she had become aware of coarse hair on her chin and abdomen, as well as centripetal weight gain. She had noticed subtle but definite reduction in her girdle muscle strength. She had acquired some mood changes atypical of her personality, and had developed an interrupted sleep pattern. To our knowledge, this is the first published report of circadian RU486 therapy for PPNAD in a patient with Carney complex. It may have been possible to restore low levels surrounding the midnight hours using other agents, but the side-effect profile and lack of significantly elevated levels of cortisol made them less favorable options.

Keywords: carney complex; cushing's; mifepristone; PRKAR1a; RU486

1. Case History

A 38-year-old librarian with confirmed Carney complex (PRKAR1a mutation) was referred for further evaluation of ACTH-independent Cushing's syndrome. Previously, she was known to have schwannoma (excised), adenomyoepithelioma and normal annual echocardiograms. She had a borderline high prolactin of 789 mIU (normal range < 500 mIU) with regular menstrual cycle and magnetic resonance imaging of the pituitary suggestive of 4 mm microadenoma. Over three years prior to current presentation, she had become aware of coarse hair on her chin and abdomen, as well as centripetal weight gain. She had noticed subtle but definite reduction in her girdle muscle strength. She had acquired some mood changes atypical of her personality, and had developed an interrupted sleep pattern.

On examination she had the classic dermatological signs associated with the Carney complex. Her BMI was just over the normal Caucasian range, with minimal increase in abdominal girth (relative to her), small amount of dorsocervical fat and mild hirsutism. She did not however show evidence of a typical cushingoid phenotype. Her blood pressure was 158/108.

2. Investigations:

Twenty-four hour urinary free cortisol measurements on three occasions six months apart were 63, 176 and 96 nmol/L (normal range < 120 nmol/L). Serum total cortisol prior to and after low dose dexamethasone suppression was 292 and 357 nmol/L, and after high dose dexamethasone suppression test was 321 and 457 nmol/L, respectively (normal < 50 nmol/L post suppression). Adrenocorticotropic hormone (ACTH) prior to dexamethasone administration was undetectable. Salivary cortisol levels on three separate mornings on waking were all 4 nmol/L, and on the preceding nights were 4, 3 and 4 nmol/L. Computed tomography performed for ACTH-independent Cushing's syndrome was reported to show two normal adrenal glands.

3. Literature Review:

Carney complex or Swiss syndrome [1], a rare condition of autosomal dominant inheritance, has a varied presentation that involves tumours of multiple organ systems including the skin, heart, usually more than one endocrine organ including the adrenal, pituitary and thyroid glands; male and female reproductive organs, breast tissue and neural tissue [2]. Classically it was known as a complex of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas [3]. The presence of specific diagnostic criteria in a given patient must prompt consideration of the condition [4]. Most of the individual tumors appear to be benign on histopathological examination [2], although recently a case of adrenal cancer has been described [5]. Cutaneous manifestations may include pigmented lesions unrelated to sun exposure and/or myxomas usually involving the face and upper trunk but may occur elsewhere and tend to develop early in life [2]. Cardiac myxomas may be single or multifocal and may have fatal consequences if left untreated [2]. The endocrinopathies associated with this condition are often multiple, and include non-ACTH dependent hypercortisolism, growth hormone- or prolactin- secreting (usually asymptomatic) pituitary adenomas, thyroid adenomas and rarely carcinomas, large-cell calcifying Sertoli cell tumours of the testes and ovarian cysts [4]. The genetic defect in PRKAR1a located on chromosome 17 is seen in approximately 40% of kindreds studied in a large case series [4].

Primary pigmented nodular adrenocortical disease (PPNAD) most commonly seen in this context, describes the histologic appearance of adrenal glands with small-pigmented nodules interspersed between usually atrophic cortex [2] and is believed to be almost universal [2,4]. It manifests as autonomous ACTH-independent hypercortisolism, which may remain subclinical, be cyclic, or present with the Cushing phenotype [2] and rarely, may regress spontaneously [6]. It generally manifests in the second decade of life, rarely diagnosed after the fifth. Laboratory diagnosis can be challenging as it takes years to develop. Tests used conventionally may be confirmatory as in any other non-ACTH dependent Cushing's syndrome, such as elevated urinary free cortisol, failure of dexamethasone to suppress cortisol, with no response of cortisol or ACTH to corticotropin-releasing hormone. 6-day Liddle test leading to a paradoxical increase of 50% or more

in urine free cortisol excretion has been recommended as the preferred test in this group of patients, although the mechanism is poorly understood [7]. Imaging of adrenal glands is often unhelpful.

The classic pattern of HPA activity in PPNAD is complete loss of circadian rhythm of cortisol, with the absolute levels generally within or just over the normal range [8]. Hence a physiological approach to treatment would be to lower cortisol levels in the hours immediately surrounding sleep in an effort to restore normality of the circadian rhythm. The recommended treatment for PPNAD is bilateral adrenalectomy [8], but although it can remit physical features [9], it has significant morbidity and mortality [10]. Of the therapeutic agents available, a relatively short-acting option to reduce cortisol levels or block its effects during the latter part of the evening and early sleep hours would potentially be able to achieve this. The likely candidates are adrenal inhibitors (e.g. Ketoconazole, Metyrapone, Aminoglutethimide, Mitotane) or the glucocorticoid receptor antagonist Mifepristone. Adrenal inhibitors are not without significant side effects [9]. Mifepristone (RU38486 or RU486) is a promising alternative that has been used less frequently in the treatment of Cushing's syndrome and although it has fewer side effects [11], biochemical monitoring of cortisol levels during treatment is unreliable [12].

4. Case Resolution:

We chose to treat our patient with low dose Mifepristone (200 mg) in the evening, which she has been taking for the past 6 months. Within weeks, her sleep pattern had normalised. She used to be wide-awake after 2–3 hours of sleep resulting in fatigue and lower productivity during the day. She now has more energy and interest in day-to-day activities. Her irritability has abated, and her calm persona restored. She has lost 6kg in weight within these 6 months without any lifestyle modification, and more importantly for her the fat around her abdomen has reduced. There is a marked subjective improvement in the strength of shoulder and hip muscles. Her blood pressure at the last clinic visit had fallen to 140/91. She has reported no side-effects during subsequent visits. She has been counselled to avoid pregnancy whilst on treatment, and she has no current plans.

To our knowledge, this is the first published report of circadian RU486 therapy for PPNAD in a patient with Carney complex. It may have been possible to restore low levels surrounding the midnight hours using other agents, but the side-effect profile and lack of significantly elevated levels of cortisol made them less favourable options. With Mifepristone, it was possible to switch-off the glucocorticoid receptor mediated transcriptional activity at night to mimic the normal nocturnal fall in HPA activity. It is the lack of this nocturnal nadir of glucocorticoid activity with continuous activation of the glucocorticoid receptor throughout the 24 hours that is a major factor in the aetiology of glucocorticoid-mediated symptoms [13]. Monitoring the efficacy of treatment is by clinical review including history and clinical examination. Since daytime glucocorticoid activity is not compromised due to the short half-life of mifepristone, there is little danger of hypoadrenal complications. We propose this circadian therapy with mifepristone as a novel approach to treatment of PPNAD with autonomous ACTH-independent hypercortisolism, by restoring circadian rhythm with low dose RU486 administration in the evening. Its potential effectiveness in other secretory adrenal incidentalomas may also be worth considering.

Conflict of Interest

The authors claim no conflict of interest.

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