Clinical Endocrinology (2011) **75**, 27–30 doi: 10.1111/j.1365-2265.2011.04033.x

CLINICAL QUESTION

What is the best approach to suspected cyclical Cushing syndrome? Strategies for managing Cushing's syndrome with variable laboratory data

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Summary

Cyclical Cushing's syndrome is a pattern of hypercortisolism in which the biochemistry of cortisol production fluctuates rhythmically. This syndrome is often associated with fluctuating symptoms and signs. It is now being increasingly recognized. The phenomenon is important because it can, if not recognized, lead to errors in diagnosis and differential diagnosis of the syndrome and in assessment of therapeutic outcomes. The techniques and criteria, protocols and dynamic biochemical tools to detect cycling in patients with hypercortisolism are discussed as are the strategies for diagnosing and managing this important subgroup of patients with hypercortisolism.

(Received 20 December 2010; returned for revision 6 January 2011; finally revised 23 February 2011; accepted 23 February 2011)

Introduction

Cyclical Cushing's syndrome (CS) is a pattern in hypercortisolism in which the biochemistry of cortisol production fluctuates rhythmically. This can also be associated with fluctuating symptoms and signs. This type of case was initially thought to be rare.[1–3] However, it has recently been recognized as occurring much more frequently.[4–6] The phenomenon is important because, if not recognized, it can lead to errors in diagnosis and differential diagnosis of the syndrome and in assessment of therapeutic outcomes. All of these can have very serious clinical consequences.

As a result of reading this article, it is hoped that readers will be better able to consider more carefully the risks associated with too wide a diagnostic trawl for the diagnosis of CS and the associated chances of finding some abnormality of steroid biochemistry.

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In cases where the diagnosis is being strongly considered, the risks of not considering episodic secretion when laboratory results are discordant are discussed. Readers should be able to plan strategies to assess for variable and cyclical secretion and to use these in diagnosis, differential diagnosis and treatment assessments.

Strategies for diagnosis, therapy and management

Diagnosis of CS

For a detailed discussion of this, readers are referred to the recent Endocrine Society guidelines.[7] These recommend biochemical testing in adult patients with (i) unusual features for age (ii) progressive features particularly those which are more predictive of Cushing's syndrome and (iii) adrenal incidentalomas.

The three commonly used diagnostic tests are urinary-free cortisol, dexamethasone suppression testing and midnight salivary cortisol. The guidelines emphasize the fact that these commonly used diagnostic tests can lead to differing outcomes. See also the review of Elamin *et al.*[8] The guidelines suggest that those with an abnormal result should be referred to an endocrinologist and should undergo a second test. It therefore is important that practising endocrinologists have strategies to use when such patients either present to them or are referred on to them by other doctors.

Decisions as to how far to progress testing has then to be made in the light of the results when set alongside the clinical picture. All patients with discordant or positive tests do not need further extended testing if there are not sound clinical reasons. If, however, the initial results are discordant or if the patient appears very likely to have hypercortisolism clinically and yet has negative results then further specialized testing is needed.

In every case where possible Cushing's syndrome is being assessed, a clinical decision has to be made at some point as to how far to take investigation as no one test is infallible. The decision should be based on the clinical index of suspicion plus enough tests for the experienced endocrinologist to be confident that, in all probability, Cushing's syndrome has been excluded. In some cases, the assessment should include testing for cyclical disease.

It is important to point out that most patients do not require this type of testing, and it should only be ordered by endocrinologists with extensive experience in managing hypercortisolism.

Diagnosis of cyclical Cushing's syndrome

Patients with strongly suggestive features of hypercortisolism de novo or after surgery or other therapy for the syndrome and unconvincing or variable biochemistry may be considered by tertiary specialists as possibly having cyclical disease.

In the literature on cyclical Cushing's syndrome, there are unfortunately many cases where cycles have actually not been established. In my opinion, at least three peaks and two troughs (not necessarily to normal range) have to be demonstrated and this requires continuous sequential and not sporadic biochemical assessment. Cycle lengths between 12 h and 85 days have been reported.

This diagnosis often requires prolonged study, and hence, detecting cyclical Cushing's syndrome has been a significant challenge to endocrinologists as 24-h urinary-free cortisol sampling is time-consuming and laborious for the patient. Therefore, when we first began to study the cyclical phenomenon, we performed a study comparing the 24-h urinary cortisol to creatinine ratio with the early-morning ratio on samples from 46 patients and a correlation of 0·93 was found.[3] To confirm that sending samples at ambient temperature in the mail led to no loss of cortisol, a fresh urine sample was left at room temperature for 7 days. Each morning, an aliquot was removed and frozen. After the 7 days, the samples were analysed for urinary cortisol concentrations. No differences were found. These validation experiments allowed us to follow patients for prolonged periods with the patient posting in daily urine samples from home.

Since the above study, our usual strategy has been to assess using sequential first voided early-morning urines measured for cortisol to creatinine ratios. We usually ask patients to collect for 28 consecutive days realizing that this may miss some patients with long cycle intervals if their ratios become normal at trough. Sporadic single repeated estimations will not lead to a clear diagnosis. We are dubious of true cyclicity if only one value is high at peak instead looking for 'shoulders' beside the peak. Each specialist laboratory has to establish its own normal range that will depend on assay used.

More recently, we have compared these urinary results to sequential late-evening salivary cortisol and results have correlated fairly well (see Fig. 1 below) so the latter testing may ultimately prove to be easier for patients.[9–11]

Our own Belfast studies have shown cyclical CS to be relatively common in a variety of situations and this reflects a detailed approach to diagnosis and use of the above diagnostic approach.[3–6,12]

Differential diagnosis and assessment of therapy

If hypercortisolism has been confirmed and excretion has been shown to be variable, it then becomes obvious that the differential diagnosis must be established very carefully indeed so that a precise therapy plan can be put into place.[12]

Cyclical Cushing's syndrome has been reported mostly in pituitary-dependent Cushing's syndrome. However, it has also been described in primary adrenal disease including PPAND, in carcinoid tumours and in other tumours producing ACTH ectopically.

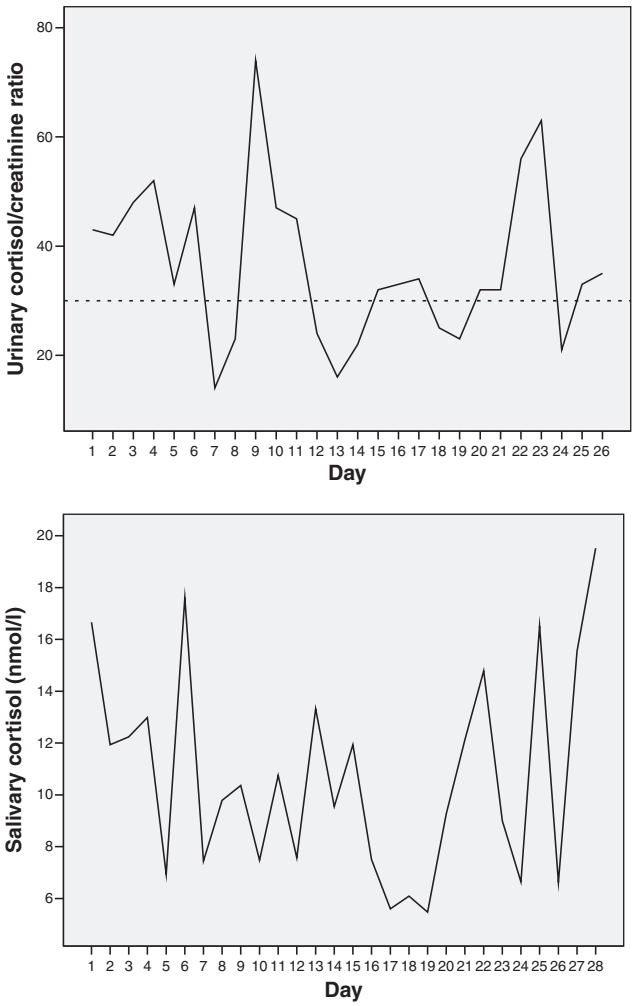

Fig. 1 Cyclical Cushing's syndrome confirmed with a cyclical pattern of 4 days using sequential early-morning urine (top) and late-night salivary (below) samples.

The increased reports in pituitary disease may simply reflect the fact that most cases of endogenous hypercortisolism are pituitary in origin. The aberrant adrenal receptor syndromes should always be considered as in these the baseline fasting cortisol is frequently normal.

High-dose dexamethasone testing can give misleading results although the general value of this test in the differential diagnosis of hypercortisolism is now much disputed. Some believe that patients with cyclical and episodic CS are more likely to have paradoxical responses to that drug.[13,14]

Perhaps more importantly, bilateral inferior petrosal sinus sampling can be unreliable unless performed when the syndrome is active. Testing directly before the sampling is mandatory and close cooperation with the laboratory is essential. A morning serum cortisol or a late-evening salivary cortisol should be measured and shown to be raised before the test proceeds. Even then there is the possibility that cyclical disease of other causes than pituitary may be associated with a lack of suppression of corticotrophs and hence false positives on sampling though as yet this has not been reported in the literature.

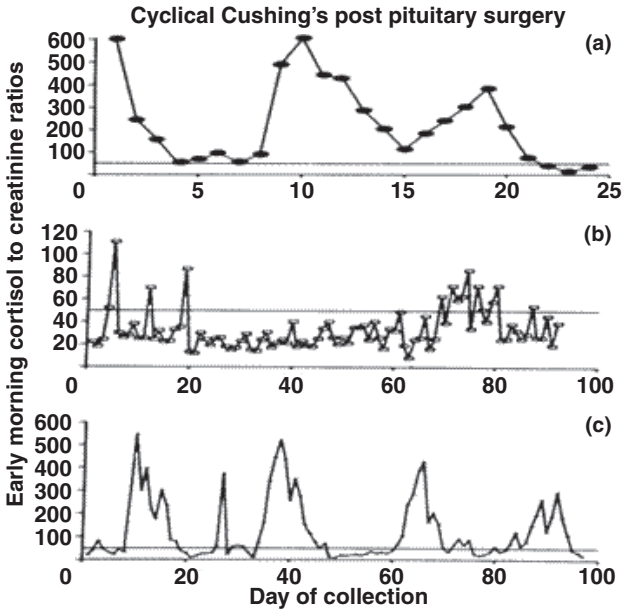

Fig. 2 Early-morning urinary cortisol (nM) to creatinine (mM) ratios in three patients diagnosed with cyclical disease after surgery (see ref [5]). Note that the ordinate and abscissa axes vary from patient to patient. The normal value is <50.

In testing after surgical procedures, variability should be considered. We consider it if biochemistry results are discrepant or variable, or if clinical features are slow to resolve or recur while results remain normal. In assessments of surgical success or failure after pituitary surgery, we have found cyclical Cushing's syndrome to be very common although the reason for this is obscure (Fig. 2). In our report of the long-term outcome in 63 patients who had pituitary surgery for the treatment of Cushing's disease between 1979 and 2000, we described our detailed follow-up of the 45 patients who achieved apparent remission after surgery.[6] Of these 45 patients, 10 had had late relapses, and of those 10, six demonstrated definite cyclical cortisol production. Relapses can be missed in such cases until a much later stage if there is not astute clinical observation and a readiness to do more extensive testing.

Similarly, in the assessment of response to drugs in hypercortisolism, remission can be wrongly attributed to drug therapy because of the variability of the laboratory data. This concern is likely to become much more important as new medical therapies become available possibly for primary therapy.

There is no literature on how best to follow up patients diagnosed with cyclical CS prior to any therapy, but it seems intuitively correct to be suspicious of single results after treatment and to repeat consecutive daily tests at appropriate intervals.

Conclusions

Many cases of Cushing's syndrome are easily diagnosed when fully developed. However, clinical manifestations are broad and the milder case can be difficult diagnostically. Laboratory tests should not be performed unless there are strong additional features present. If the clinician tests patients without salient other features, they will end up with many difficult to interpret biochemical results. A better recommendation is to have a review consultation in 6 months for reassessment and laboratory testing can be performed thereafter if necessary.

When appropriately selected patients have diagnostic tests and these are discordant, assessment for variability should be performed at a centre experienced in the management of the syndrome. This should also be the case if tests are normal in a patient with clear features of Cushing's syndrome. These assessments should be with daily sequential assessment of urinary or salivary cortisol as described above.

Differential diagnosis has to be made very carefully in cyclical disease. Cortisol should be raised when inferior petrosal sampling is performed. A late-night salivary or early-morning serum cortisol should be measured on the planned day of testing before it proceeds.

Finally, many of the cases of recurrent hypercortisolism after initially successful pituitary surgery have been shown to be cyclical and a high index of suspicion for this possibility is required so that prompt additional measures to control hypercortisolism can be undertaken. Follow-up of cyclical disease should be even more extensive than that performed in other cases of the disease.

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