

Recognising and diagnosing Cushing's syndrome in primary care:

challenging but not impossible

BACKGROUND

The catalyst for this article was the experience of one of the authors whose diagnosis of Cushing's was not immediately recognised despite the presence of numerous suggestive clinical features and comorbidities. This prompted the authors to convene a group of primary and secondary care clinicians to explore how to increase awareness and simplify the process of recognising and diagnosing Cushing's syndrome (CS) in primary care.

WHY IS IT IMPORTANT NOT TO OVERLOOK CUSHING'S SYNDROME?

Endogenous CS has traditionally been considered a rare condition, with an estimated annual incidence of 1.8 to 3.2 cases per million population,¹ although a recent study suggests the true incidence may be considerably higher, especially in individuals aged <65 years.² CS can be

classified as either adrenocorticotrophic hormone (ACTH)-dependent or ACTH-independent. ACTH-dependent CS is caused by a pituitary adenoma (also known as Cushing's disease) or an ectopic ACTH-producing tumour. In the absence of exogenous corticosteroid therapy, ACTH-independent CS points to an adrenal origin. CS is an important diagnosis not to overlook because of its significant physical and psychological morbidities, associated comorbidities, and the excess mortality that complicates uncontrolled hypercortisolism (prior to effective treatments becoming available, 5-year mortality rate was 50% after symptom onset).³

WHEN SHOULD THE POSSIBILITY OF ENDOGENOUS CUSHING'S SYNDROME BE CONSIDERED IN PRIMARY CARE?

CS can present at any age, but specific subtypes are more common in certain

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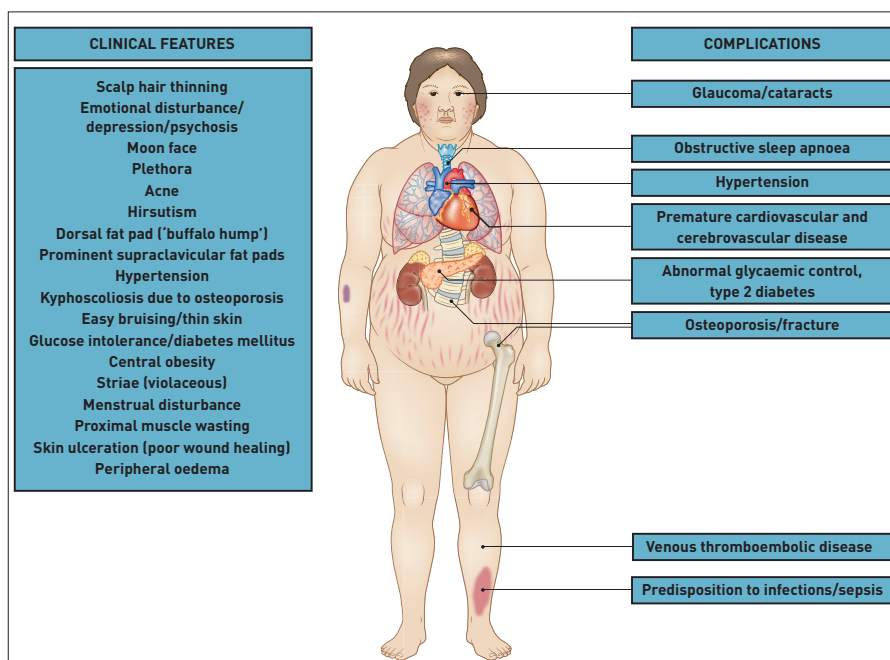
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Submitted: 8 March 2022; Editor's response: 11 May 2022; final acceptance: 14 May 2022.

©British Journal of General Practice 2022; 72: 399–401.

DOI: <https://doi.org/10.3399/bjgp22X720449>

Figure 1. Cushing's syndrome: clinical features and associated comorbidities.



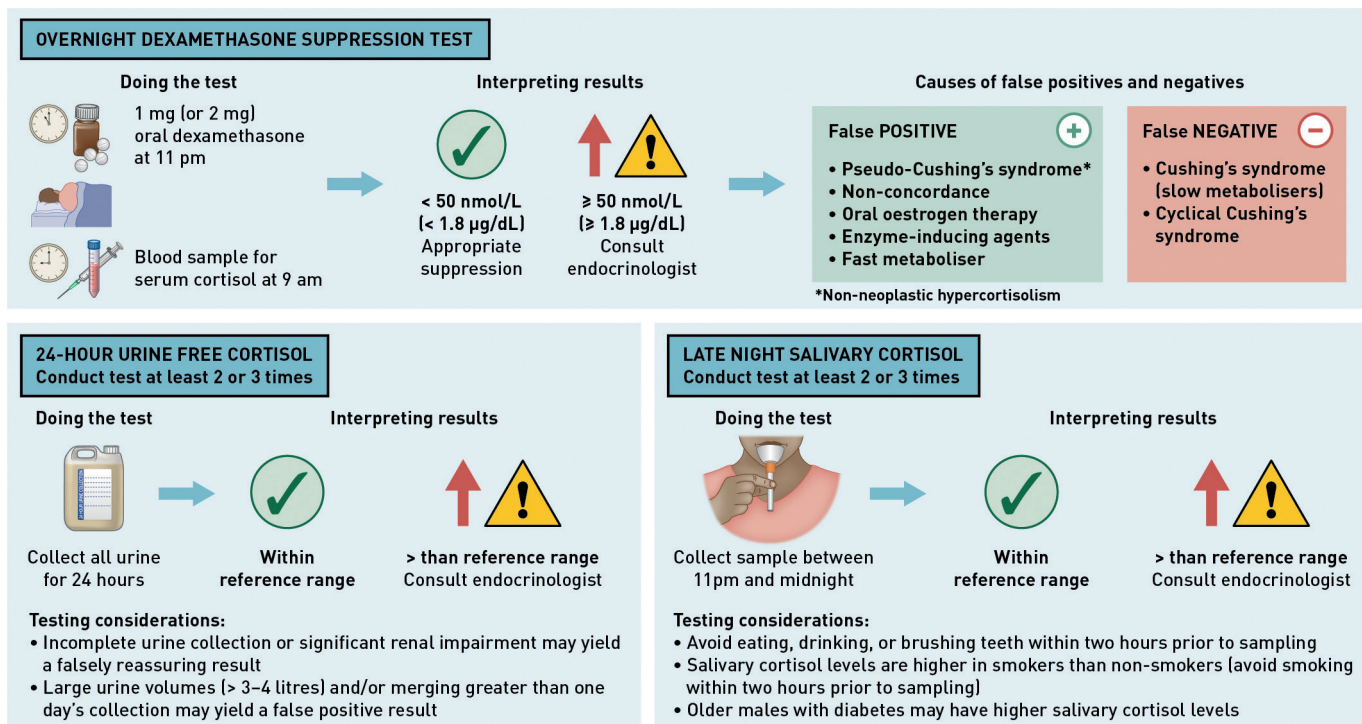


Figure 2. Screening tests for Cushing's syndrome.

patient groups, for example, a younger woman is more likely to have a pituitary origin, whereas the possibility of ectopic disease is increased in an older smoker.

The clinical manifestations of the classical Cushingoid phenotype are shown in Figure 1, together with associated complications. While this figure portrays a florid example of a patient with CS, in practice many patients will present with a more subtle constellation of features, which may only be fully appreciated once the underlying hypercortisolism has been corrected (Supplementary Figure 1). Alternatively, reviewing old photographs on a patient's phone may provide clear evidence that their appearance has changed over time.

An important factor in the delayed diagnosis reported by many patients is the failure of healthcare professionals to recognise the significance of various combinations of symptoms or signs and linked comorbidities. For example, early-onset hypertension, diabetes mellitus, venous thromboembolism (VTE), and/or osteoporosis in a young woman should prompt consideration of CS.^{4,5} Similarly, a number of discriminatory dermatological (for example, striae [especially violaceous], spontaneous bruising, thin skin, new-onset acne in adults, with facial plethora and/or moon face) and musculoskeletal (for example, muscle wasting with proximal myopathy) manifestations should also trigger the clinician to explore the possibility of hypercortisolism.⁵

WHICH INVESTIGATIONS ARE MOST APPROPRIATE TO SCREEN FOR CUSHING'S SYNDROME IN GENERAL PRACTICE?

There is no single perfect test for CS. Accordingly, guidelines often offer a menu of options, each with potential advantages and disadvantages; most commonly these are the overnight dexamethasone suppression test (O/N DST), 24-hour urine free cortisol (UFC) estimation, or late-night salivary cortisol (LNSC) measurement.⁶ Figure 2 describes how to perform and interpret these tests, and outlines some important considerations when choosing which to deploy. Importantly, although the O/N DST is sometimes viewed as challenging to conduct, it is a safe and effective investigation for use in the primary care setting and is the preferred screening investigation for many endocrinologists. The O/N DST should be distinguished from the two 48-hour dexamethasone suppression tests: 1) low-dose DST (LDDST), which may also be used to confirm or exclude a diagnosis of CS, and 2) high-dose DST (HDDST), which is used to distinguish pituitary-driven from ectopic CS.

WHEN SHOULD A PATIENT BE REFERRED TO SECONDARY CARE?

CS may be difficult to diagnose at first presentation because of the non-specific nature of some features, and frequently the diagnosis becomes more apparent as the condition evolves; as such, a period of

observation may be necessary/appropriate. When deciding whether to refer to an endocrinologist, it can be helpful to consider the probability of endogenous CS based on clinical index of suspicion (low, intermediate, or high), together with the results of an initial screening investigation, for example:

- low probability plus negative screening test = unlikely to require referral;
- low probability but positive screening test (with no explanation for false positive) = refer; and
- intermediate to high probability = arrange screening test and refer.

WHAT NEW DEVELOPMENTS ARE ON THE HORIZON TO ENHANCE THE DIAGNOSIS OF CUSHING'S SYNDROME IN PRIMARY CARE?

Rare diseases are not always front of mind for GPs and other healthcare professionals working in primary care, and it is not practical to screen every patient who presents with these common symptoms. As such, automated digital systems could play a role in identifying potential cases of CS that may otherwise be overlooked. Future tools in this regard could include the integration of sensitive algorithms into patient record systems such as EMIS (EMIS Group, Leeds, UK) and SystmOne (TPP, Leeds, UK), providing red flags when a certain pattern of clinical features is recorded. Others have advocated the use of computer software to analyse photographs collected over time to identify morphological changes of the head and face that may suggest CS, although it could be argued that in this setting the key step of considering the possibility of CS has already occurred.⁷

REFERENCES

1. Hakami OA, Ahmed S, Karavitaki N. Epidemiology and mortality of Cushing's syndrome. *Best Pract Res Clin Endocrinol Metab* 2021; **35(11)**: 101521.
2. Broder MS, Neary MP, Chang E, *et al*. Incidence of Cushing's syndrome and Cushing's disease in commercially-insured patients <65 years old in the United States. *Pituitary* 2015; **18(3)**: 283–289.
3. Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. *Am J Med* 1952; **13(5)**: 597–614.
4. Nieman LK. Recent updates on the diagnosis and management of Cushing's syndrome. *Endocrinol Metab* (Seoul) 2018; **33(2)**: 139–146.
5. Pivonello R, Isidori AM, De Martino MC, *et al*. Complications of Cushing's syndrome: state of the art. *Lancet Diabetes Endocrinol* 2016; **4(7)**: 611–629.
6. Fleseriu M, Auchus R, Bancos I, *et al*. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol* 2021; **9(12)**: 847–875.
7. Popp KH, Kosilek RP, Frohner R, *et al*. Computer vision technology in the differential diagnosis of Cushing's syndrome. *Exp Clin Endocrinol Diabetes* 2019; **127(10)**: 685–690.

KEY TAKEAWAY MESSAGES

A potential diagnosis of CS should not be overlooked given the ramifications of uncontrolled hypercortisolism. Although investigation for possible CS is frequently perceived as challenging, the initial steps are more straightforward than often anticipated, and entirely feasible to conduct in the primary care setting.

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Funding

HRA Pharma facilitated the initial convening of the group of primary and secondary care clinicians and provided funding for the development of this article but did not have any editorial input into the content.

Patient consent

Patient consent was obtained.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

Kate Scoffings, Damian Morris, Andrew Pullen, Sharon Temple, Anna Trigell, and Mark Gurnell served on the HRA Pharma Advisory Group that proposed the development of this article. Mark Gurnell has previously served on an Advisory Board for Recordati. David McMinn, PhD, of Lay Summaries Ltd provided medical writing support under the direction of the authors.

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