INVITED COMMENTARY

The diagnosis of Cushing’s syndrome: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective

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Abstract

Cushing’s syndrome is considered a rare disease and its diagnosis can be challenging. Establishment of evidence-based recommendations is difficult. In 2008, several national and international consensus recommendations for the diagnosis or management of Cushing’s syndrome were reported. The Endocrine Society, with the participation of the European Society of Endocrinology, has developed a task force to update recommendations for the diagnosis of Cushing’s syndrome. The main aspects of these recommendations are presented in this article and discussed in the context of current research efforts in Europe focusing on the improvement of diagnosis and management of rare diseases including adrenal disorders such as Cushing’s syndrome.

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Early diagnosis of Cushing’s syndrome is crucial, as the natural history of the condition is marked by significant excess of mortality and morbidity (e.g. in particular cardiovascular disorders, infection, psychiatric disorders, osteoporosis and growth arrest, and subsequent short stature in children). In keeping with the dynamic nature of the corticotroph axis physiology, biological investigations for the diagnosis of Cushing’s syndrome are complex by comparison with those of other endocrine disorders. Furthermore, Cushing’s syndrome is a rare disease, despite recent reports suggesting a higher frequency than usually assumed. For these reasons, the diagnosis of Cushing’s syndrome can be challenging, and establishment of evidence-based recommendations is difficult.

The Endocrine Society, with the participation of the European Society of Endocrinology, has recently organized a task force to update recommendations for the diagnosis of Cushing’s syndrome. The previous consensus on diagnosis and complications of Cushing’s syndrome, also a joint venture with the participation of American and European specialists, was published in 2003 in the Journal of Clinical Endocrinology and Metabolism (1). The consensus achieved by the current American-European Working Group has been published in the May 2008 issue of the Journal of Clinical Endocrinology and Metabolism (2). The year 2008 seems to be the year of Cushing’s syndrome, as in July 2008 a summary consensus of an international workshop on the treatment of adrenocorticotropin-dependent Cushing’s syndrome was published (3). At the national level in France, two guidelines dealing with Cushing’s syndrome were also produced in 2008: the first one is the recommendations on adrenal incidentalomas which is an expert consensus on behalf of the French Society of Endocrinology (4); the second one is the National Diagnosis and Treatment Guideline (NDTG) for Cushing’s syndrome (5). This NDTG was requested by the Higher Health Authority (HAS, a public authority in France which oversees the scientific evaluation of medical practice) to the Reference Centre for Rare Adrenal Diseases as part of the National Rare Diseases Plan (2004–2008), and discussed with many participants, including endocrinologists, biologists, surgeons, radiologist, medical societies, and the patients’ association, as well as with health insurance organizations. The main goal was to provide a guide for physicians but also to establish a list of procedures and services validated by the national health insurance funds.

The Endocrine Society Diagnosis of Cushing’s Syndrome Task Force included a chair, five additional experts, a methodologist, and a medical writer.
They followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group, an international group with expertise in the development and implementation of evidence-based guidelines (6). The guidelines were reviewed and approved sequentially by the Endocrine Society’s Clinical Guidelines Subcommittee and Clinical Affairs Core Committee, members responding to a web posting, and the Endocrine Society Council. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available current scientific evidence about two questions: who should be tested and how to test for Cushing’s syndrome? The main points of the consensus are discussed below and summarized in Tables 1 and 2. For further and in-depth analysis, we refer to the original text of the consensus, which contains helpful tables and algorithms.

The guideline recommends looking for Cushing’s syndrome in patients with multiple and progressive features suggestive of hypercortisolism, in patients with unusual features for age, in children with decreasing growth contrasting with increasing weight and in patients with adrenal incidentaloma. A two-step investigation is recommended.

i) First-line tests for establishing the diagnosis of Cushing’s syndrome are expected to be highly sensitive, simple to carry out, possibly for an outpatient if the patient is compliant, and not costly. A recent meta-analysis (7), commissioned by the Endocrine Society Cushing’s Syndrome Task Force in preparation of the guideline, found that 24-h urine cortisol, 1-mg overnight dexamethasone (Dex) suppression test and midnight cortisol, and combined strategies based on these tests have similar accuracy. These recommendations are further supported by the recent demonstration that the diagnostic performance of salivary cortisol is similar between inpatients and outpatients (8). Interpretation of these screening tests are based on cut-offs with urinary cortisol and/or late night salivary cortisol above the normal values validated in a large population of normal subjects and serum cortisol after overnight 1-mg Dex suppression test above 50 nmol/l (18 ng/ml or 1.8 μg/dl) considered to be suggestive of Cushing’s syndrome.

ii) The guideline reminds us of the important fact that intermittent Cushing’s syndrome should be considered if the clinical impression contrasts with normal laboratory tests or even transient cortisol deficiency. The simplest way to make this diagnosis is to ask patients to collect a 24-h urine sample or bedtime saliva at the time they feel symptoms have recurred.

iii) The guideline recommends against the use of random serum cortisol or plasma ACTH levels, urinary 17-ketosteroids and tests designed to determine the cause of Cushing’s syndrome (e.g. pituitary and adrenal imaging and 8-mg Dex suppression test) as the first-line tests for the diagnosis of Cushing’s syndrome.

iv) The second step is to confirm Cushing’s syndrome. When hypercortisolism is severe, the diagnosis is easily confirmed by repeating the first-line tests. Certain second-line tests are useful if doubts persist between Cushing’s syndrome and a functional hypercortisolic state, the pseudo-Cushing state, e.g. in patients suffering from major depression and chronic alcoholism. The Endocrine Society guideline avoids the term ‘pseudo-Cushing’ and replaces it by ‘hypercortisolism in the absence of (true) Cushing’s syndrome’. This rewording will allow inclusion of the conditions associated with overactivity of the hypothalamic–pituitary–adrenal axis such as hypothalamic amenorrhea or intense chronic exercise.

As expected, the different consensus or guidelines are similar on major aspects of the diagnosis of Cushing’s syndrome. In particular, the first step of the diagnosis is rather similar in all consensus and guidelines. However, as often for a disease with a low incidence limiting the size of the published series, there are few but distinct differences. This reflects the need for further studies, but might also result from regional differences and healthcare systems. Among these differences, the following could be discussed:

i) Cushing’s syndrome can be misdiagnosed for a long time in patients with apparently isolated psychiatric, rheumatologic, or cardiologic symptoms. To avoid that, the existence of ‘multiple and progressive features compatible

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**Table 1** Diagnosis of Cushing’s syndrome: who should be investigated?

<table>
<thead>
<tr>
<th>The table lists the main points of the guideline for the diagnosis of Cushing’s syndrome. The points of discussion or divergence from a European perspective (see text) are in italics. Testing for Cushing’s syndrome, after excluding exogenous glucocorticoid use, is recommended in:</th>
</tr>
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<tbody>
<tr>
<td>Patients with <strong>multiple and progressive features</strong> compatible with the syndrome, particularly those with a high discriminatory value (e.g. facial plethora, easy bruising, striae, and proximal myopathy);</td>
</tr>
<tr>
<td>Patients with unusual features for age (e.g. osteoporosis, hypertension, and type 2 diabetes);</td>
</tr>
<tr>
<td>Patients with adrenal incidentaloma;</td>
</tr>
<tr>
<td>Children with decreasing height percentile and increasing weight.</td>
</tr>
</tbody>
</table>
Table 2 How to investigate for Cushing’s syndrome?

The table lists the main points of the guideline for the diagnosis of Cushing’s syndrome. The points of discussion or divergence from a European perspective (see text) are in italics.

The initial use of one of the first-line tests is recommended, based on its suitability for a given patient with high diagnostic accuracy:
- at least two measurements of 24-h urine cortisol;
- two measurements of late night salivary cortisol (at bedtime or between 2300 and 0000 h);
- 1-mg overnight dexamethasone suppression test (administration of dexamethasone at 2300 or 0000 h with measurement of blood cortisol at 0800 or 0900 h) or, in certain populations, 2-mg 48-h dexamethasone suppression test.

Some tests might be more appropriate in special populations:
- urine cortisol in pregnant women;
- urine cortisol and late night cortisol in patients receiving drugs known to enhance dexamethasone clearance (e.g. antiepileptic drugs);
- 1-mg overnight dexamethasone suppression test in patients with severe renal failure;
- urine cortisol and late night salivary cortisol in suspected cyclic Cushing’s syndrome;
- 1-mg overnight dexamethasone suppression test in case of an adrenal incidentaloma.

An endocrinologist’s advice is recommended for patients:
- with an adrenal mass;
- with an abnormal result;
- with initially normal responses but who are suspected of cyclic hypercortisolism or accumulate additional features over time;
- with familial disease that puts them at risk of Cushing’s syndrome (e.g. Carney complex and multiple endocrine neoplasia-1).

The endocrinologist has to choose second-line tests:
- either one or two of the above
- or a serum midnight cortisol
- or a dexamethasone–corticotropin-releasing hormone (Dex–CRH) test. The interest of this test and its value by comparison with the CRH test or the desmopressin test to differentiate Cushing’s syndrome from pseudo-Cushing’s syndrome is debated. Note that usually ovine CRH is used in the US, and human CRH is used in Europe.

with the syndrome’ might not be considered as a necessary condition, especially in the presence of more specific symptoms, which are catabolic features and centripetal obesity.

ii) The search for Cushing’s syndrome might not be restricted to unusual features for age, but could be extended to atypical features for severity (e.g. resistant hypertension, osteoporosis without explanation despite comprehensive testing for secondary causes, depression resistant to drugs, etc.).

iii) The potential severe consequences of Cushing’s syndrome in children and pregnant women justify that both are addressed to experienced endocrinologist’s teams.

iv) In the French NDTG, the 2-mg 48-h Dex suppression test is not considered as a first-line test because it is not often simple to carry out in an outpatient even if adequate written instructions are provided. It is recommended as a second-line test, after referring to an endocrinologist.

v) Since 2006 several studies (9–13) have shown a lower specificity of the Dex–corticotropin-releasing hormone (CRH) test for differentiating real Cushing’s syndrome from pseudo-Cushing states than the initial publication by Yanovski and colleagues (14), suggesting that this test gives no better results than the repeated assessment of the other screening tests. The cut-off currently applied to Dex–CRH tests carried out with ovine CRH, common practice in the US, cannot be automatically superimposed for those employing human CRH, widely used in Europe. Human CRH stimulates less ACTH and cortisol secretion than ovine CRH. Furthermore, there are differences in the timing of the test and diagnostic threshold between authors (11, 14). Lastly, human CRH is expensive, similar to the 48-h hospitalization often needed when strictly adhering to the protocol of the classic Liddle’s test in some centers.

vi) A recent Italian study, provided by Arnaldi and colleagues (15), attempts to rehabilitate the CRH test in the differential diagnosis between ACTH-dependent Cushing’s syndrome and pseudo-Cushing states, first described by the NIH group (16). They found that the two distinct parameter combinations of basal or peak cortisol and plasma ACTH peak during the human CRH test are each independently informative in diagnosing and excluding ACTH-dependent Cushing’s syndrome vs pseudo-Cushing states (15).

vii) The Endocrine Society guideline restricts the desmopressin test to research studies only. However, in several publications mainly from Italy, the desmopressin test had a better diagnosis accuracy (10, 17, 18), than that of Dex–CRH test, even in patients with mild hypercortisolism. In addition, desmopressin is cheaper than CRH, and the test procedure is less cumbersome than that of the Dex–CRH test. Furthermore, the desmopressin test may be useful in the differential diagnosis of ACTH-dependent Cushing’s syndrome, and in the post-surgical survey of Cushing’s disease (19). Like Dex–CRH test and perhaps CRH test, the desmopressin test may prove useful for patients with mild hypercortisolism and normal ACTH levels, in whom the differential diagnosis has narrowed to Cushing’s disease or pseudo-Cushing states (18).
Recognition of Cushing’s syndrome is easy in cases of severe cortisol excess, but diagnosis is challenging in mild cases that tend to be more frequent than in the past in countries with an effective health care system. Because of the escalating incidence of obesity, diabetes mellitus, of the population aging, and of the large use of computed tomography and densitometer, the clinicians are faced with increasing numbers of patients to screen for Cushing’s syndrome. They can rely on the support of the current Endocrine Society consensus guideline, which provides useful practical recommendations. This consensus extensively reviews laboratory shortcomings and interfering conditions that may complicate the diagnosis of Cushing’s syndrome. The Journal of Clinical Endocrinology and Metabolism and the European Journal of Endocrinology are extensively read by endocrinologists who might consider Cushing’s syndrome when confronted with a diabetic or obese patient or when working up a patient with an adrenal incidentaloma. General practitioners and non-endocrinologist specialists are probably more often faced with telltale signs and complications of Cushing’s syndrome common to other disorders. Yet, it might be difficult for a family physician or for a non-endocrinologist specialist to be aware of Cushing’s guidelines or other rare diseases, in a context where knowledge is evolving rapidly. Rare diseases raise the need to learn to recognize the exception and to have access to up-to-date recommendations. The endocrinologists have to use effective means to point out major points of diagnosis of Cushing’s syndrome to health professionals, in order to improve the effectiveness of diagnosis of Cushing’s syndrome and obtain clinical benefits for patients. The Internet-based information server Orphanet, developed by France initially in 1997, is a key player and important partner of health professionals and patients (www.orpha.net). This tool is probably underused. Training professionals to better identify rare diseases, and organizing screening and access were the two strategic priorities of the French National Rare Diseases Plan.

In Europe, efforts are being developed for rare diseases in order to overcome the various issues facing patients, their families, and physicians. A first result of these European efforts is the development of research programs to study the pathophysiology or the epidemiology of these disorders. Two main initiatives have been supported in the field of Cushing’s syndrome. The ERCUSYN project is supported by the public health program, and is dedicated to the development of a register of Cushing’s syndrome and headed by Susan Webb from Spain (www.lohmann-birkner.de/ercusyn). This program has a specific interest in the investigation of the Quality of Life of patients with Cushing’s syndrome. The European Neuroendocrine Association is also performing a worldwide study on the mortality of Cushing’s disease (www.eneasoc.org) coordinated by Ana Maria Colao from Italy. The European Network for the Study of Adrenal Tumors (www.ensat.org) chaired by Felix Beuschlein from Germany currently runs a program headed by Xavier Bertagna from France supported by the European Science Foundation. This program has a specific interest in the development of European databases in order to develop new classifications and therapies and to progress in the understanding of the pathophysiology of adrenal tumors. In the long run, these research programs will help to set up European standards for management of the various causes of Cushing’s syndrome. At the national level, programs for patient management through national health care systems have been also developed in European countries that might in the long run help to define a similar transnational approach at the European level. For instance in France, the National Program for rare disease in its first period (2004–2008) has defined for more than 100 groups of rare diseases reference centers (including seven in the field of endocrinology) and networks to cover all the countries and promote homogeneous excellent standard of care, patients’ and physicians’ information and clinical research.

Improving recognition is an important goal of the Community strategy, defined on November 2008 by the European Commission (European Commission Communication on Rare Diseases and The Proposal for a Council Recommendation on a European action in the field of rare diseases, 11th November 2008). It is also a priority for EURORDIS, a European collective of more than 200 rare disease associations. For various reasons, the European dimension should be well adapted to progress on rare disorders. Let’s hope that future European and National plans will efficiently face these challenges!

Declaration of interest
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