European Society of Endocrinology

ESE Clinical Update on Cushing's Syndrome 2021

A series of webinars held on 7–9 April 2021

Welcome

Cushing's syndrome constitutes an area of intense research and discovery. This report provides summaries of three dynamic webinars in April 2021 that addressed the diagnosis, management, challenges and future landscape of this condition.

The European Society of Endocrinology (ESE) was delighted to welcome experts in the field, who shared their knowledge and experience over the course of three, 2-hour webinar sessions that examined:

- approaches in diagnosis, spanning blood tests, imaging and potential future methodologies using metabolomics
- management, including options additional to surgery, and the care of patients with mild autonomous cortisol secretion, bilateral adrenal hyperplasia or ectopic Cushing's
- current and future challenges, such as emerging treatments, Nelson's syndrome, anticoagulation therapy and what 'remission' means
- a wide range of interesting cases, illustrating the experiences of endocrinologists at the forefront of patient care.

We are grateful to all who took part and contributed important experience, research outcomes and insights.

Cushing's Awareness Day takes place on 8 April each year (the anniversary of Harvey Cushing's birth), and the ESE Clinical Update on Cushing's Syndrome 2021 was timed to coincide with this event. It is an important part of the efforts that are necessary to increase awareness of rare diseases, such as Cushing's.

The content of the webinars is available to attendees at **www.eseondemand.org**.

Eystein Husebye, Niki Karavitaki and **Darko Kastelan**
Scientific Programme Committee

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ESE thanks all faculty members for their valuable contributions to the ESE Clinical Update on Cushing's Syndrome 2021.

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Diagnostic dilemmas in Cushing's syndrome

Chairs: **Eystein Husebye** *(Norway)* & **Carmina Fuss** *(Germany)*

Overview of the diagnostics of Cushing's

Stelios Tsagarakis *Athens, Greece*

Cushing's syndrome is a rare endocrine disorder due to cortisol hypersecretion. The broad clinical spectrum extends from severe cases to individuals who appear almost normal, many of whom present after an adrenal abnormality is incidentally discovered on imaging.

Populations with increased risk for Cushing's syndrome include patients with obesity, diabetes, osteoporosis and polycystic ovary syndrome. Various attempts have been made to screen at-risk populations, but it has generally been concluded that the syndrome's rarity precludes any special screening programme. This has clearly been stated in guidelines since 2008.[1]

Investigative tests

Urinary free cortisol has been the most commonly used screening test. It reflects daily cortisol production by measuring the unbound free cortisol in urine, which is independent of changes in corticosteroid-binding globulin. The estimated sensitivity of the test is 90% and the specificity is 80%. But it has many drawbacks, including false positives and false negatives.

Administration of dexamethasone suppresses adrenocorticotrophin (ACTH) and cortisol secretion, and forms the basis of the dexamethasone suppression test (DST) used to test for excess cortisol. In normal individuals, the cortisol levels following dexamethasone administration are very low. There are two versions of the test: the simple 1-mg overnight test, and the classic 2-mg 2-day low dose DST. A serum cortisol below 50nmol/l or 1.8µg/dl is considered a normal response. The test has a 95% sensitivity and an 80% specificity, so a negative result strongly predicts absence of Cushing's syndrome.

A loss of circadian rhythm is a critical feature of Cushing's syndrome, but can be difficult to ascertain. In the past, midnight serum cortisol measurement was used, but this requires hospitalisation. Late night salivary cortisol is a practical alternative, as it can be collected in ambulatory patients at home. The sensitivity of the test is 95% and the specificity is 93%. Some caveats relate to the effects of age and co-morbidities, and there is also variability in patients with Cushing's syndrome. Assessment of 24-hour profiles of cortisol secretion may be a more effective and robust way to detect abnormalities.

Thus all currently available investigative techniques have pitfalls, and require careful interpretation. This is particularly true when one needs to differentiate between Cushing's syndrome and the (formerly incorrectly termed) 'pseudo-Cushing's states'. The pathophysiology is that of a functional non-neoplastic (rather than neoplastic) hypercortisolism. It is driven by corticotrophin-releasing hormone (CRH) activation of the pituitary-adrenal axis.

In recent years, the desmopressin test has been increasingly used. The rationale for its use is that normal corticotrophs express V3 vasopressin receptors, but not V2 receptors, which are a marker of many neoplastic corticotroph cells. Desmopressin is a specific V2 receptor agonist, and normal individuals do not respond to desmopressin. When compared with the dexamethasone-suppressed CRH test, the desmopressin test has a much higher specificity but a lower sensitivity. The relevant studies are summarised by Findling & Raff.[2]

More than one test is usually required in the diagnosis of Cushing's syndrome. Diagnostic precision is compromised by false positive and false negative results, particularly in cases of functional hypercortisolism. Mild forms of the disease are not reliably diagnosed. It is therefore essential to investigate the diagnosis in stages, beginning with a test that is simple to use and has very high sensitivity.[1] No single test is perfect, and, occasionally, repeated tests may be required to avoid missing mild or periodic cyclic disease.

Underlying causes

As regards the aetiology, the majority of cases are ACTH-dependent.[3] Approximately 20% of patients have an adrenal source, and these can be confirmed with a 09.00 plasma ACTH measurement and imaging of the adrenals by computed tomography or occasionally magnetic resonance imaging (MRI).

In cases of ACTH dependence, the more common diagnosis of pituitary ACTH secretion should be differentiated from the less common ectopic ACTH source. Such ectopic sources may not be obvious, and the classic ectopic ACTH syndrome due to small cell lung carcinoma, presenting in older patients with severe metabolic defects and obvious malignancy, is now less common in practice than small bronchial, thymic, pancreatic or other endocrine tumours.

There are a range of diagnostic approaches to determine the cause of excess ACTH (see the Table below).[4] A high resolution pituitary MRI scan is the imaging method of choice to detect a pituitary adenoma. However, up to 40% of patients with Cushing's disease have a negative MRI. The high dose DST is rarely performed nowadays. The peripheral CRH stimulation test is still in use where available, with a positive response indicating probable pituitary ACTH secretion. Bilateral inferior petrosal sinus sampling remains the gold standard for discriminating between pituitary and ectopic sources.

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The diagnostic means for determining the cause of excess ACTH.
High-resolution MRI
8-mg dexamethasone suppression test
Peripheral CRH stimulation test
Bilateral inferior petrosal sinus sampling

Pitfalls of bilateral inferior petrosal sinus sampling

John Newell-Price *Sheffield, UK*

Inferior petrosal sinus sampling (IPSS) is a procedure to measure adrenocorticotrophin (ACTH) levels in the veins adjacent to the pituitary gland. It is a highly invasive and technical procedure which needs to be done in experienced centres. This description of the performance of the test also discusses some of the pitfalls.[1] It is worth emphasising that the ratios mentioned are all empirically derived; none of them have any inherent legitimacy.

Approximately 30% of patients with Cushing's disease have a negative magnetic resonance imaging scan of the pituitary, whereas some patients with ectopic ACTH syndrome (EAS) can have pituitary abnormalities. It is for these reasons that IPSS has become an important test. The idea, of course, is to avoid inadvertent pituitary surgery in patients who have EAS. A positive gradient in ACTH levels from the pituitary to the periphery is found in patients with Cushing's disease, but not in patients with EAS.

How is the procedure carried out?

A catheter is placed by an interventional radiologist via a groin approach, and then the catheter wires are placed up into the petrosal sinuses. The position is confirmed by venography. Central and peripheral samples are taken for plasma ACTH measurement, and then the central to peripheral (IPS:P) ratio of plasma ACTH is calculated. The Table (right) shows petrosal sinus and peripheral ACTH levels obtained from a patient with Cushing's disease at different times after stimulation with corticotrophin-releasing hormone (CRH).

How well does this test perform?

A meta-analysis was published last year of 1249 patients with Cushing's disease and 152 patients with EAS.[2] The baseline IPS:P gradient in this analysis was >2 and the stimulated IPS:P gradient was >3. The overall sensitivity for Cushing's disease diagnosis was 86% in the unstimulated measurements, with the specificity at 98%. Regardless of the secretagogue used, the sensitivity after stimulation increased to 97% and the specificity to 100% (though in reality no test will be 100% accurate).

Pitfalls and issues with secretagogues

Ovine sequence CRH has recently become unavailable in the USA and probably worldwide. Human sequence CRH is available, but it is less stimulatory than ovine CRH. Arginine vasopressin is used in some centres but, of course, arginine vasopressin binds all the vasopressin receptors, including the V1a receptors that are particularly present in the gut, and that can cause side effects such as vasoconstriction in the gut and nausea and vomiting.

Desmopressin is cheaper and more widely available than CRH. In addition to its actions at the V2 receptor, desmopressin is able to activate the V1b or V3 receptors in pituitary corticotroph cells; these are rarely found in ectopic tumours. One study compared the performance of desmopressin and CRH in a group of patients where both secretagogues were being used. The two showed a very similar overall performance.[3]

Technical and anatomical pitfalls

There are technical pitfalls in placement of the catheter. Unilateral cannulation cannot rule out Cushing's disease on the contralateral side. There are also anatomical variants which need to be identified during the procedure. It is important to work carefully with the radiologist to understand what anatomy has been demonstrated.

Other causes of false negatives for Cushing's disease include lack of response to the chosen secretagogue. Additionally, if there is cyclical disease and the patient is assessed during the trough period there may be a lack of an IPS:P gradient.

Prolactin has been proposed as a way of working around some of these false negatives, to assess whether there was correct catheter placement and/or abnormal venous drainage. If the IPS:P ratio for ACTH is <2 unstimulated or <3 stimulated, one should check the venogram and calculate the IPS:P ratio for prolactin. If it is >1.3 stimulated or >1.8 unstimulated then cannulation was successful. If not, the prolactin value can be used to apply a correction and determine whether the underlying cause is Cushing's disease or an ectopic tumour. While this is an attractive option for analysis, the number of patients who have negative IPSS but genuine Cushing's disease will be relatively few.

Note that these corrections are not needed when the ACTH gradients are positive, especially considering that there is now some evidence for dominance of prolactin drainage.[4]

Physiological pitfalls

IPSS cannot be used to distinguish between individuals with and without Cushing's: it is important to know the patient has Cushing's hypercortisolaemia before sampling. Any cortisol-lowering medication has to be withdrawn before the procedure. There are occasional cases of cyclical EAS associated with a positive IPS:P gradient. Other rare examples of false positives include an olfactory neuroblastoma, and an ectopic corticotroph adenoma in the sphenoid sinus, both of which led to positive gradients. These emphasise the need for a careful assessment of the pituitary and the surrounding tissues by radiology.

Concluding comments

Care is needed in interpreting the results of IPSS. False negatives for Cushing's disease are more likely than false positives. Overall, the complication rates are low. Groin haematoma is the most common, venous thromboembolism is a possibility, and stroke is a very low risk.

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ACTH levels (ng/l) consistent with the presence of Cushing's disease, in samples taken from a patient at different times after administration of 100µg human sequence CRH. There is a clear gradient between levels in the right IPS and those in the periphery.

Time (min)	Right IPS	Left IPS	Peripheral
0	78	65	57
+3	420	110	70
+5	251	130	113
+10	225	142	129
+15	180	136	122

Imaging in ectopic Cushing's syndrome

Anju Sahdev *London, UK*

Imaging has evolved in the last decade, so what used to be specialist imaging is now standard practice. We still face three main challenges when looking for ectopic tumours in Cushing's syndrome.

- They may be anywhere in the body (60% in the chest, remainder in the abdomen and pelvis).
- They are generally small, so imaging must be of high resolution and sensitivity.
- Multiple imaging modalities are available, and there is a very significant overlap with neuroendocrine tumours (NETs).

Unless you design your study to find what you are looking for, the protocols can be so variable that they miss lesions.

First-line imaging

Most of the adrenocorticotrophin (ACTH)-producing tumours are overt (>80%). They can be detected on routine first-line imaging with computed tomography (CT) or magnetic resonance imaging (MRI). These tumours are usually seen clearly enough using standard portal venous imaging or arterio-portal venous phase imaging of the neck, chest, abdomen and pelvis (see Figure, below). This can allow localisation, staging and the planning of surgery.

There are a few minor modifications that will improve the sensitivity and thus the detection rate in first-line CT acquisition. Thin slice scans (1–3mm) are now generally routine. Multiplanar reconstruction allows you to look at the same structure from different angles. In addition, 500ml water orally, just before scanning, helps us to increase detection rate.

We begin with a precontrast image of the entire abdomen, and proceed to arterial phase imaging of the liver and pancreas (25–30s), and then a portal venous scan through the chest, abdomen and pelvis (60s). This protocol allows the detection of small NETs in the stomach, duodenum and pancreas, as well as lung lesions, thymic carcinoids and bowel NETs, and also examination of the adrenals. Oral water distends the stomach and duodenum and the contrast enhancement identifies lesions in the wall.

Triphasic CT (1-mm, multiplanar scans) is an important requirement for detecting smaller pancreatic lesions. Most typical NETs in the pancreas (70–85%) will show arterial enhancement (40% will only have arterial enhancement). We must include the portal venous phase because 15% of tumours will only enhance in this phase and would otherwise remain undetected.

We generally tend to use MRI for first-line imaging only when CT is contraindicated. We use standard morphological/anatomical sequences, including the T2-weighted sequence where the islet cell tumours have a very high signal intensity. Furthermore, diffusion-weighted sequences allow us to look precisely at the pancreas and liver (by improving MRI sensitivity from 70% to close to 90%). The MRI sequences also include chemical shift imaging, which helps to characterise any causal lesions in the adrenal glands.

Second-line imaging

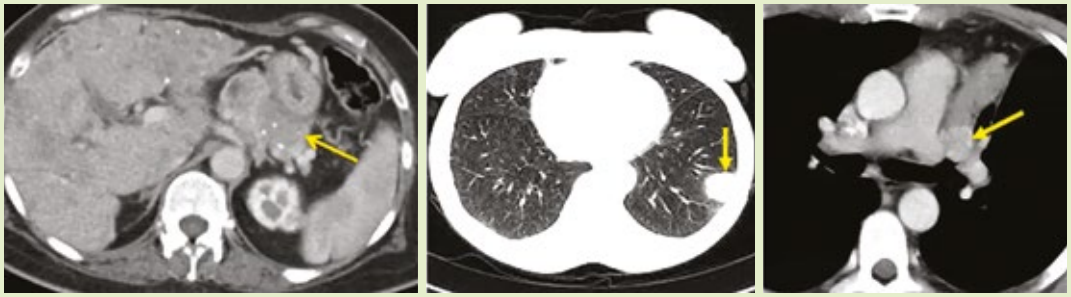
When first-line imaging fails to show an obvious ACTH-producing tumour, second-line imaging identifies another 15–20% of tumours. MRI of the pelvis is frequently used. This is targeted at unusual sites, such as rectal carcinoids, seminal vesicle disease or prostate disease.

Before moving on to second-line imaging, particularly nuclear medicine imaging, a second read of the scans is important. This is particularly the case if the first imaging was performed without good close correlation with the clinical details. One site where very small lesions are almost inevitably overlooked is the lungs. It can help to scan the patient prone.

In normal practice, second-line imaging really means the nuclear medicine modalities. These will identify about 80% of the tumours undetected after first-line imaging. ^{68}Ga-DOTA scans offer the best sensitivity, followed by ^{18}F-fluorodeoxyglucose (FDG), then ^{111}In-octreotide and finally ^{123}I-MIBG. Nuclear medicine studies have much better specificity than CT or MRI, which is very useful in problem solving with regard to lesions in cross-sectional imaging, such as those in bone and liver, and borderline lymph nodes.

Unfortunately, there is no one 'best test' when it comes to nuclear medicine. We can divide nuclear medicine scans into two main categories. Those using metabolic markers (such as FDG-positron emission tomography (PET)/CT) generally perform better for more aggressive tumours, since somatostatin receptor expression is lost. Conversely, where the tumours retain receptor expression, ^{68}Ga-DOTA scans are much more sensitive than FDG.

Aside from performance, there are other things to consider regarding nuclear medicine imaging. Availability is probably the most important: very few institutions will have access to all the modalities that could be used to identify ectopic ACTH production. Consideration should also be given to factors such as radiation exposure, cost, and time taken for the investigation.



Examples of tumours that are readily detected by first-line imaging: (left) a neuroendocrine tumour (NET) within the tail of the pancreas. with flecks of calcification, which is large enough, and easy enough, to see using standard portal venous phase CT; (centre) a small cell lung cancer; (right) a central carcinoid tumour in a typical location.

Steroid metabolomics and cortisol excess

Wiebke Arlt *Birmingham, UK*

The study of steroid metabolomics in cortisol excess provides a diagnostic test that is not yet used in clinical practice.

The steroid metabolome consists of mineralocorticoids, glucocorticoids, active sex steroids and the precursors of each of these groups (see Figure below). These are all metabolised in the liver and excreted in the urine, and all these metabolites together comprise the urine steroid metabolome. We can measure multiple metabolites in the urine using gas chromatography-mass spectrometry (GC-MS). This enables us to undertake multisteroid profiling.

Analysis of urinary steroid metabolite excretion in 24-hour urine from 88 healthy adults has shown that most of what humans produce and excrete comprises glucocorticoids, followed by active androgens. There are much smaller amounts of androgen precursors, mineralocorticoids and glucocorticoid precursors.

Urine steroid metabolomics in adrenal tumours

Steroid metabolomics can be applied to the differentiation of benign and malignant adrenal tumours.[1] The majority of the adrenal tumours are discovered incidentally. They are found during 5% of cross-sectional imaging procedures.

When we encounter an adrenal nodule, we need to answer some important questions.

- Does the adrenal mass overproduce hormones?
- Is the adrenal mass an adrenocortical carcinoma (ACC)?

ACC is a malignant tumour with poor prognosis and accounts for 2–11% of adrenal masses undergoing diagnostic work-up. Imaging is very sensitive in detecting adrenal nodules but its specificity in differentiating between benign and malignant tumours is very poor: 80% at best. This means that we have delayed diagnosis of ACC and unnecessary surgery.

Urine steroid metabolomics provides a novel biomarker approach to improve upon this. In our proof of principle study 10 years ago, we asked 150 patients with confirmed benign and malignant tumours to collect 24-hour urine samples.[2] These samples underwent GC-MS analysis for steroid metabolite profiling. This was then followed by machine learning analysis. A special machine learning method was developed to learn in detail about the difference between benign and malignant tumours and to produce an algorithm that could differentiate between the two. Amazingly, by applying this approach, we found that there was an ACC-specific steroid fingerprint that provided a much higher specificity than the current imaging procedures.

We used this method in a prospective study. We determined that we needed 2000 adrenal tumours to have sufficient prospective validation for our test and that this would need 5% ACCs. To achieve this, the largest study ever (EURINEACT), we collaborated across the European Network for the Study of Adrenal Tumors (ENS@T).

Then we looked at the accuracy of these tests. If you compare tumour diameter with Hounsfield units and with urine steroid metabolomics (USM), USM is better as a single test and also better as a dual test, consecutively reducing the false positives. And if you combine tumour diameter with Hounsfield units and USM, you get the best performance.[3]

In implementation of this assay, we are reducing the analysis to only eight steroids, but we now have a multisteroid profiling assay that we can run rapidly.

Steroid metabolomics for diagnosis of Cushing's

We applied this approach to the analysis of patients with Cushing's syndrome: 88 patients with confirmed adrenal Cushing's syndrome, 29 patients with Cushing's disease and 127 healthy controls. They underwent high-throughput analysis with a 27-steroid panel using tandem mass spectrometry of 24-hour urine. It yielded some interesting first results.

We looked at the steroid metabolome. You can analyse whether the group you are looking at has significantly increased or decreased metabolites in comparison with the healthy controls. In Cushing's syndrome, the metabolome showed significantly increased glucocorticoid metabolites and decreased androgens and androgen precursors. In comparison, in Cushing's disease, there were significantly increased glucocorticoid metabolites but also increased androgens and androgen precursors.

We have identified four glucocorticoid metabolites that differentiate best between healthy individuals and those with Cushing's. Similarly, we have identified four precursors that differentiate best between Cushing's syndrome and Cushing's disease. Using 11 patients with overt Cushing's syndrome and 28 healthy controls we also looked at the diurnal profile, splitting urine samples into day-time and night-time collections. A diagnostic test might be much more sensitive and specific using overnight urine.

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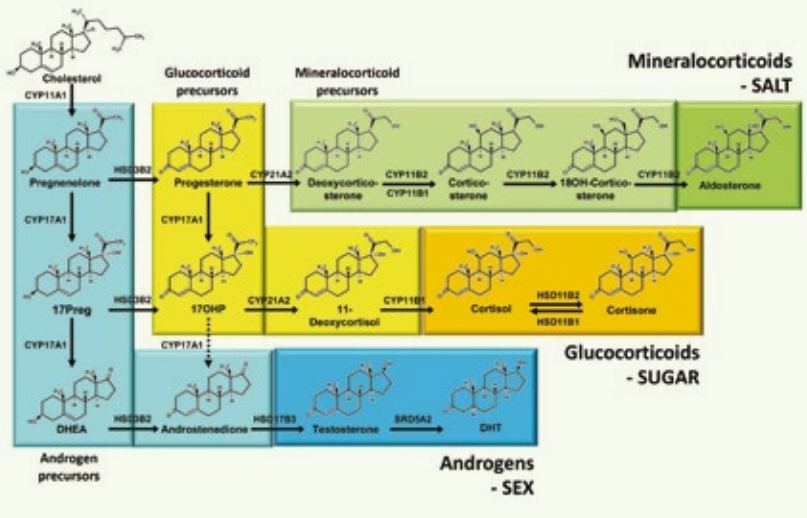


Components of the steroid metabolome.

Case presentations

Case 1. Cushing's disease with psychosis and profound weight loss

Tara McDonnell *Dublin, Ireland*

This case highlights the neuropsychiatric manifestations of Cushing's syndrome. A 22-year-old female presented with a first episode of psychosis, requiring an involuntary admission to the psychiatric department. She had notable anorexia, having lost 18% of her body weight. She had delusions which were paranoid in nature. The patient believed that, if she ate, she would cause harm to her family or herself. She also had passivity phenomena, insomnia and generalised anxiety. Polycystic ovary syndrome (PCOS) had been diagnosed 12 months previously.

The patient was not on any medications and was high-achieving at college. Her mental status exam revealed poor eye contact, blunted affect and psychomotor retardation. Physical examination revealed proximal myopathy and her Cushingoid features prompted endocrinology input.

History-taking revealed she had secondary amenorrhoea and increased hirsutism over the preceding months. Her family had noticed increased irritability within the last 2–3 months. Medical investigation showed that she had hypokalaemia, suppressed gonadotrophs and mild elevation of prolactin and testosterone. Tests showed that 24-hour urine free cortisol was elevated, over 25 times the upper limit of the reference range. Midnight salivary cortisol and cortisone were also elevated, confirming hypercortisolaemia.

Her adrenocorticotrophin (ACTH) level was high, and further investigations were required to determine if the ACTH source was pituitary or ectopic. Magnetic resonance imaging of the pituitary was not significant and did not reveal any adenoma. A corticotrophin-releasing hormone test and bilateral inferior petrosal sinus sampling both supported the diagnosis of Cushing's disease.

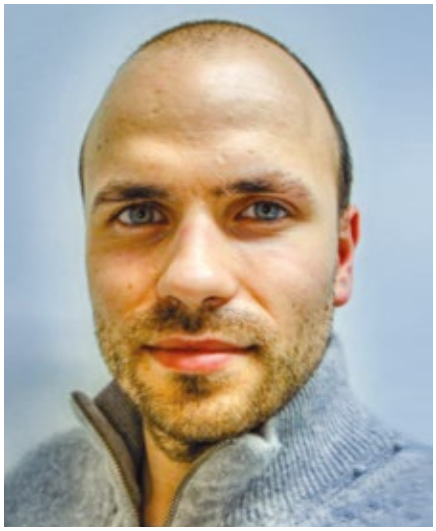
The patient was transferred to an inpatient medical ward, with ongoing psychiatric support for management of her psychosis, utilising olanzapine. She also required caloric supplementation via a nasogastric tube. We utilised steroidogenesis inhibition to help stabilise her condition, using ketoconazole and metyrapone pre-operatively.

She proceeded to transsphenoidal surgery. Exploration identified a central abnormality which was excised, and histology revealed a corticotroph adenoma. Low morning cortisol level indicated early remission of Cushing's disease. Post-operatively, her mood improved and she was eating better. She remains hypocortisolaemic 6 months after surgery. Her menses have returned and her psychosis has resolved. Her antipsychotics were discontinued.

Neuropsychiatric complications are severe co-morbidities in Cushing's syndrome and can persist into the remission phase. Major depression is described in 50–80% of Cushing's, followed by anxiety, mania and, rarely, psychosis. This case highlights these neuropsychiatric manifestations and the significant morbidity associated with these symptoms, with severe impact on quality of life and functionality. Remission improves these manifestations but they may not be completely reversible.

Case 2. Ectopic Cushing's syndrome: a unique case of exhaustive work-up

Diogo Ramalho *Oporto, Portugal*



This challenging case of ectopic Cushing's syndrome concerns a 51-year-old woman with a history of multiple cardiovascular risk factors, depression and chronic hypokalaemia.

The patient was diagnosed with adrenocorticotrophin (ACTH)-dependent Cushing's syndrome in 2009. She had very high levels of ACTH and cortisol. At that time, pituitary magnetic resonance imaging was performed, which showed a 6-mm pituitary nodule compatible with microadenoma. The nodule was removed by transsphenoidal surgery, but after surgery the hormone levels did not decrease and the lesion did not stain on histochemical analysis. Thus, the lesion was a pituitary incidentaloma.

When she was admitted to our hospital in 2010, we started her on ketoconazole and a search was performed for the probable ectopic source. Computed tomography (CT) of the chest revealed mediastinal lymphadenopathies and a thoracic biopsy was performed. It was compatible with small cell lung carcinoma stage 3b. Initial staging of the tumour did not reveal any other lesions and tumour therapy was proposed for the patient. She experienced partial remission of the carcinoma. However, 3 months later, ACTH, cortisol and urinary free cortisol increased again and the patient suffered a clinical relapse of hypercortisolism.

She was hospitalised with decompensated diabetes, hyperactive delirium and refractory hypokalaemia. Chest CT and fluorodeoxyglucose positron emission tomography (PET) did not show any

progression of the pulmonary disease, but an abdominal CT scan found a new cystic lesion in the pancreas. A DOTANOC PET scan was undertaken, and the pancreatic mass stained positive for ACTH in the biopsy sample, suggesting an ectopic source. In line with that, doubts emerged about whether the lesions originated in a primary small cell lung carcinoma and a core biopsy was performed. This time immunohistochemical analysis was in favour of a neuroendocrine tumour of pancreatic origin.

The patient was discharged 1 month later. She was refused for surgical treatment of the primary tumour and started on lanreotide in association with ketoconazole. After 5 months, the patient died of severe sepsis and pneumonia.

So, with such high levels of both cortisol and ACTH, and with chronic hypokalaemia, an ectopic source of ACTH would be considered first. This would avoid unnecessary surgery. In such a context a PET scan can be helpful in identifying a neuroendocrine tumour. Before the correct diagnosis, ketoconazole alone can be used to control hypercortisolism, and lanreotide has been shown to improve control of neuroendocrine complications and prolong lifespan. A high level of suspicion and critical judgement are required to obtain earlier diagnosis and treatment, in order to avoid complications and improve quality of life and survival.

Case 3. How frequent is cyclical Cushing's syndrome?

Kristina Isand *Oxford, UK*

This case dates back to 2011, when a female patient aged 68 was referred to an endocrine clinic.

She had had symptoms of weight gain and hirsutism over a period of 2 years. She had two major co-morbidities: osteoporosis and hypertension. Her 24-hour urinary free cortisol was high (over 700nmol/l) and she also had non-suppressed cortisol levels on dexamethasone suppression test (DST). Her random cortisol at that time was also high (over 900nmol/l). But her hormonal profile was otherwise fine, as were her electrolytes. Magnetic resonance imaging of her pituitary showed a 5-mm microadenoma in the centre of the gland.

She had an adenomectomy in February 2012. Initially, it seemed to be successful, because her post-operative cortisol value was low at 36nmol/l. The pathology report showed an atypical corticotroph adenoma with an MIB-1 index of 3–5%, but reaching 15% in the areas with increased mitotic count. She was put on hydrocortisone replacement for 2 years and was followed up annually with an overnight DST and measurement of urinary free cortisol and late-night salivary cortisol.

Initially, her cortisol tests were normal but, after 7 years, she developed weight gain symptoms again. She complained that her appetite was increased, she had reduced exercise tolerance, she felt fatigued and her mood was altered. It seems as though she had a mild clinical recurrence of Cushing's.

Looking at her investigations, over time the 24-hour urinary free cortisol levels had been elevated three times but normal twice. Similarly, the midnight salivary cortisol levels had been elevated four times but normal on three occasions. We also saw one mildly elevated overnight DST and one occasion when suppression was observed. Clearly the abnormal cortisol responses were cyclical.

What actions were taken? In May 2020, a positron emission tomography scan showed a small recurrence on the site of the original adenoma. From July to November, she was treated with metyrapone, but it was stopped because she felt even more unwell. This is something seen more frequently in cyclical (compared with non-cyclical) Cushing's patients. The patient now is scheduled for repeat surgery.

What are the take-home messages? This case highlights the importance of cyclical changes in cortisol secretion when we are investigating patients with Cushing's syndrome. The frequency of this is largely unknown and it can cause a delay in diagnosis. A multicentre study is needed to look at these patients prospectively in order to give them their diagnosis earlier.

Cushing's disease has a negative impact on patients' physical and emotional well-being, and also their survival. But is it even worse when it is cyclical?

Management of Cushing's syndrome

Chairs: **Darko Kastelan** *(Croatia)* & **Katja Kiseljak-Vassiliades** *(USA)*

When surgery for Cushing's disease fails

Frederic Castinetti *Marseilles, France*

If a patient has recurrent Cushing's after surgery, a decision must be made regarding further treatment.

Repeat surgery

If anything is visible by magnetic resonance imaging (MRI), you might contemplate further surgery. A 2019 study analysed 62 patients who underwent repeat transsphenoidal surgery for Cushing's disease by the same expert surgeon, which was effective in 50–80% of cases.[1] You should first consider which surgeon performed the original procedure, and whether your own surgeon believes they can cure the patient, based on the MRI.

Radiation techniques

Gamma knife radiosurgery offers roughly 50–80% remission, with a delay before remission of usually 2–5 years (when hypercortisolism must be controlled by medical treatment).[2] Modern techniques are highly accurate; it is important to clearly define the target on the MRI, so that nothing is missed by the radiosurgeon. Recurrence can be observed in 15–20% of patients after a mean time in remission of 3 years. Hypopituitarism is observed in 20–50% of patients; other side effects include secondary tumours, cognitive impairment, and stroke.

Alternative options

Repeat surgery and radiation techniques are the two main options if something is visible by MRI, though bilateral adrenalectomy and medical therapy can also be considered in this situation. You are, however, less likely to see anything on pituitary MRI if your patient was operated on in an expert centre (or what you see will not be accessible to surgery). Long term medical treatment or bilateral adrenalectomy should be discussed in this instance.

Drugs to lower cortisol

Drugs including osilodrostat, pasireotide, ketoconazole, mifepristone, metyrapone, mitotane and cabergoline can control cortisol secretion in 30–80% of cases, depending on which is used. Each has its own side effects.

Many studies have a short follow-up. In terms of long term efficacy, there are two main retrospective studies. Our 2014 French multicentre study on ketoconazole in Cushing's disease included 51 patients who had been treated for more than 24 months (mean 108 months).[3] We found that 33 patients (65%) had normalised urinary free cortisol (UFC) at the end of the study, and UFC was decreased by more than 50% in a further 12 patients. The greatest risk of liver enzyme increase is seen on initiation of treatment and when changing the dose during the first month. This treatment leads to hypoandrogenism and so may be best in females.

A second study of 195 individuals, including 115 with Cushing's disease, concerned metyrapone.[4] Here, 48 patients were treated for a mean of 22 months. Normal hormone evaluations were found in 83% of patients at the end of the study, with criteria for remission that included mean cortisol levels during the day. The main side effects of hypokalaemia and hypertension appear rapidly after drug initiation. In the long term, hyperandrogenism appears in many females.

The titrating approach

The titrating approach is one of two ways to deliver medical treatment and aims to achieve a physiological situation. You give medical treatment during the day to try and normalise UFC, but you will not perfectly reproduce the rhythm of cortisol. This is why some investigators give a high dose in the evening and a lower dose in the morning, to try to reach a normal value at midnight.

How can we know if a patient is well controlled? The best profile in terms of co-morbidities (systolic and diastolic blood pressure and blood glucose level) and major improvements was found when UFC and late night salivary cortisol were both normalised. In a recent study of pasireotide, only 17.4% of patients had normalised mean UFC and mean late night salivary cortisol.[5] So, to determine whether your patient is well controlled, you must obtain several measurements of UFC and late night salivary cortisol, and ideally have both normalised to have optimal control of secretion.

When using metyrapone or osilodrostat, levels of precursors that are cross-reactive with cortisol will rise. Depending on how you measure cortisol, you may get the impression that it is less controlled than is actually the case.

Block and replace

In this approach to treatment, you give a maximal dose of steroidogenesis inhibitor to ensure you have no residual cortisol secretion, and then replace with hydrocortisone.

Bilateral adrenalectomy

This option is rapidly effective with a low morbidity and mortality. A 2013 literature review examined the outcome of bilateral adrenalectomy in Cushing's disease or ectopic Cushing's syndrome.[6] Nelson's syndrome may develop following bilateral adrenalectomy for Cushing's disease, with a prevalence of 43% (28–53%) and mean delay of 5.3 years (2 months–27 years). Expert consensus recommendations for follow-up and treatment have recently been published.[7]

Totosellar radiation

One final possibility is totosellar radiation, or whole sellar stereotactic radiosurgery. In 68 patients with a mean endocrine follow-up of 5.3 years, the remission rate was 75.9% and median time to remission was 12 months.[8] There was a higher remission rate with higher volumes irradiated. You might think this would lead to a higher rate of pituitary deficiencies, but this was not so obvious from the results, which showed a 25% increase in new hormone deficiencies over 5 years. The 25% recurrence rate perhaps indicates that the whole region had not actually been irradiated.

In conclusion

There are multiple approaches to manage recurrence after failed transsphenoidal surgery, which occurs in 20–30% of cases. The choice of procedure should be made using a multidisciplinary approach, considering the risks and benefits of each.

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Management of autonomous cortisol secretion

Martin Fassnacht *Würzburg, Germany*

Autonomous cortisol secretion (ACS) is the term used for patients with an adrenal tumour (usually an incidentaloma) and some kind of hypercortisolism, but no signs of Cushing's syndrome. It should replace the term subclinical or preclinical Cushing's, because these patients are not at high risk of developing overt Cushing's syndrome.

Diagnostic criteria

A 2012 review of 29 studies (3075 patients) using 19 different diagnostic criteria gave a prevalence of 5–60% (which is not very helpful).[1] During the ESE–European Network for the Study of Adrenal Tumors (ENS@T) guideline panel discussion, we therefore decided to simplify diagnosis by just using the 1-mg overnight dexamethasone suppression test (DST).[2] A cortisol level after DST of <50nmol/l excludes ACS, whereas a level >140nmol/l confirms ACS. Between these levels, ACS is 'possible'.

Association with disease

It is not yet clear whether ACS is really a disease. Many studies, including a meta-analysis,[3] suggest an association between cortisol excess and several diseases, such as hypertension, type 2 diabetes, obesity and osteoporosis. However, most are retrospective, too small or without hard endpoints.

Unpublished work as part of the EURINE-ACT study focused on 1308 patients with benign adrenocortical adenomas. A 1-mg DST showed that half had a non-functioning tumour, one-third had cortisol after DST of 50–140nmol/l (possible ACS), 10% had cortisol after DST >140nmol/l (ACS) and 5% had adrenal Cushing's syndrome. There was a clear downward shift in adrenocorticotrophin (ACTH) levels from non-functioning tumours through ACS to overt Cushing's, and a clear increase in the risk of co-morbidities such as hypertension (which was increased even in patients with non-functioning tumours).

The ENS@T-NAPACA Outcome Study provides an unpublished retrospective analysis of 3659 patients with adrenal incidentalomas from 29 ENS@T centres who were followed for at least 3 years. Patients were divided into three groups following a 1-mg DST: 57% had non-functioning tumours, 36% had possible ACS and 7% had ACS. Almost 10% of patients died during the minimum 3-year follow-up. Cox analysis showed that those with cortisol excess clearly did worse; a greater percentage with cortisol excess experienced major cardiovascular events, both before detecting the tumour and afterwards.

Evidence to support the idea that these effects are associated with cortisol is now very strong, though not yet sufficient to prove that ACS is a disease.

All these patients are at high risk for cardiovascular disease, so my first message is that you should perform a 1-mg DST in all patients with an adrenal incidentaloma. If we find an elevated result from DST, we measure the plasma ACTH to demonstrate that this is ACTH-independent (adrenal origin). My second message is that all patients with an incidentaloma (particularly those with ACS) should be screened for different diseases: at least hypertension and type 2 diabetes, but also dyslipidaemia and osteoporosis. These conditions should be treated according to the relevant guidelines.

Management

Does surgery benefit these ACS patients? Here the data are less convincing. A review considered eight studies;[4] each compared a conservative approach with adrenalectomy. The control groups showed no improvement in co-morbidities. In the surgical patients, there was a reduction in hypertension in 61%, weight loss in 39% and improvement of impaired glucose metabolism in 34%. But the numbers are small and the definitions of response are not consistent, so I am not yet completely convinced.

We need a randomised trial: the CHIRACIC trial is a prospective trial which includes 50 hypertensive patients with incidentaloma and ACS. Use of a standardised blood pressure treatment means it will be easier to compare patients receiving anti-hypertensive drug treatment only and those also undergoing adrenalectomy. Results will not be available before 2022.

The data on possible drug therapy are even more limited. One prospective pilot study in 2017 included six patients with ACS and two control groups matched for age, sex and body mass index, including six patients with a non-functioning adenoma and six healthy individuals.[5] They measured serum cortisol hourly for 24 hours. When ACS patients received metyrapone (500mg at 18.00 and 250mg at 22.00), the cortisol curves became almost identical across the groups.

Given the limited evidence, my third message is more my personal approach. We consider surgery only in patients with ACS and low ACTH, so we are sure of an adrenal origin. There must also be at least one significant co-morbidity (preferably hypertension or diabetes, as the data here are strongest). Lastly, the patient must have a clear interest in surgery. An alternative is what we call 'diagnostic treatment' with an antiglucocorticoid drug for 6 months. If treatment is successful and co-morbidities improve, we might reconsider surgery. If not, then surgery will not help.

The approach to management outlined in the 2016 guidelines[2] remains valid and is summarised in the Figure below.

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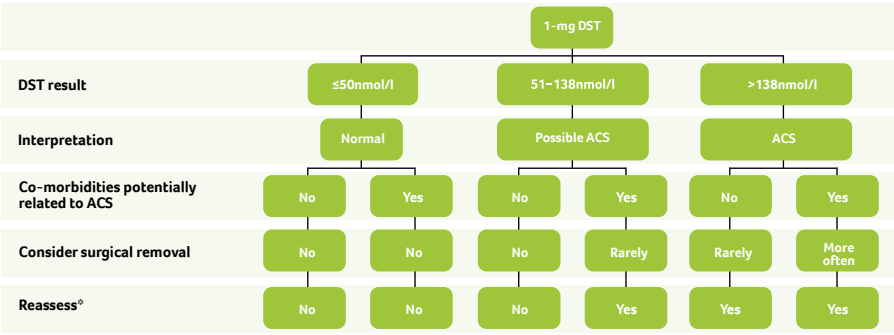

Outline approach to patient management. Reproduced in adapted form by permission from *European Journal of Endocrinology* **175** G1–G34.[2] *Reassess cortisol excess and co-morbidities during follow-up in patients without surgery.

Cushing's due to bilateral adrenal hyperplasia

Jérôme Bertherat *Paris, France*

Bilateral adrenal hyperplasia includes two subgroups of benign bilateral adrenocortical tumours: primary pigmented nodular adrenocortical disease (the most common form of micronodular hyperplasia) and primary bilateral macronodular hyperplasia (PBMAH). The latter is encountered more often in the clinic and will be the focus of this discussion. It is usually found in patients between 45 and 60 years of age.

Spectrum of disease

A computed tomography (CT) scan of patients investigated for obvious clinical signs of Cushing's reveals very large adrenals (see Figure, right). Upon surgery, adrenal weight appears to be 10–20 times normal. The two adrenals are completely autonomous. You will find multiple nodules which, by definition, are larger than 1cm in both adrenals, and can reach 3–4cm in diameter in severe cases. This situation is rare.

Increasingly often, we see patients with mild forms of the disease. The adrenals are larger than normal (see Figure), but patients usually do not present with specific clinical signs of Cushing's, although they may have co-morbidities. These cases are often found during investigation of an incidentaloma.

Adrenal masses can be bilateral adenomas or macronodular hyperplasia.[1] A significant proportion of these masses are macronodular hyperplasia in patients that do not present overt Cushing's.

A meta-analysis of different studies on incidentaloma compared the level of cortisol after dexamethasone suppression. It appears that, overall, the level is higher in bilateral than in unilateral incidentalomas.[2]

So there is a broad spectrum. On one hand we have the rare situation with overt Cushing's and high urinary free cortisol. These patients can sometimes be problematic to manage.

The more common situation is a mild form of the disease with no overt Cushing's. Urinary cortisol is usually still perfectly normal, but a dexamethasone suppression test (DST) shows no suppression and adrenocorticotrophin (ACTH) is low.

We know now that 20–25% of patients with PBMAH have a mutation in *ARMC5*. Cases with such a mutation present with overt Cushing's much more often than wild type patients, as well as hypertension and diabetes. So this might be one explanation for the heterogeneity of the disease.

Medical therapy

In some selected cases of PBMAH it has been useful to control cortisol in the short term by targeting the illegitimate receptor, for instance with somatostatin analogues and beta blockers.

With regard to anti-cortisolic drugs, good results are reported with metyrapone and ketoconazole. Four cases showed good results on blood pressure and diabetes after a few months of treatment with mifepristone.[3] Interestingly, the ACTH level was completely suppressed before mifepristone and clearly increased on treatment, demonstrating an impact on blockage of the glucocorticoid receptor.

Surgical management

There are very good results from surgery in terms of correcting the clinical signs of Cushing's syndrome. The morbidity of adrenalectomy carried out using a laparoscopic approach is low and the mortality in recent series is zero.

There has been a move towards unilateral adrenalectomy. Clearly, in patients with only mild autonomous cortisol secretion, bilateral adrenalectomy is not a good option.[1] In selected patients, unilateral adrenalectomy of the dominant side can be considered, taking into account the patient's age, degree of cortisol excess, co-morbidities and, of course, their preference.

What evidence supports unilateral adrenalectomy? In a review of the literature of 117 cases, the initial remission rate based on hormone criteria was 93%, and adrenal insufficiency was observed in a third of these patients. The recurrence rate was 15%, leading to completion of a bilateral adrenalectomy in 14% of this whole series of patients. The median time between first and second surgery was about 6 years. To consider unilateral adrenalectomy, you probably need to take into account the level of cortisol excess and the volume of each adrenal, looking at any type of asymmetry.

It is good to normalise cortisol, but it is even better to improve the patient's co-morbidities. For bilateral incidentaloma, the answers are unknown, but one series from Greece is interesting.[4] The outcome was compared between 12 patients who underwent unilateral adrenalectomy and 11 patients who were not operated upon. Improvement of hypertension and diabetes was seen in two-thirds of the surgical group but in none of the other group. So this approach may not only normalise cortisol, it may also improve a patient's situation.

In conclusion

There is no doubt that you have to treat patients with overt Cushing's. For patients with subclinical Cushing's, you must decide based on co-morbidities. The options include medical treatments which target illegitimate receptors, and anti-cortisolic drugs. You would discuss unilateral or bilateral adrenalectomy, depending on the severity of Cushing's and the adrenal morphology.

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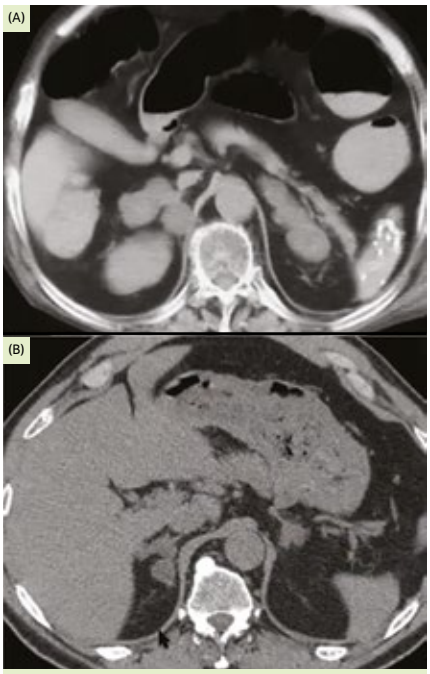

CT scans from (A) a patient who was investigated for typical and obvious signs of Cushing's and (B) a patient with more mild disease.

Management of ectopic ACTH syndrome

Ashley Grossman *Oxford, UK*

Case study
A 35-year-old woman presented with an 8-week history of hirsutism, male pattern hair loss, amenorrhoea and acne. She had a Cushingoid appearance.

Her serum cortisol was 2003nmol/l. She was hypokalaemic, had elevated glucose and a slightly high white cell count. She also had high urinary free cortisol and did not suppress on an overnight dexamethasone suppression test. Adrenocorticotrophin (ACTH) was grossly elevated, so clearly she had ACTH-dependent Cushing's syndrome. With a short history, a very high cortisol, a very high ACTH and hypokalaemia, we thought it was probably ectopic.

Pituitary magnetic resonance imaging (MRI) did not show an adenoma, nor was there anything obvious on a computed tomography (CT) scan of the chest, abdomen and pelvis. While she clearly had ACTH-dependent Cushing's syndrome, the source of ACTH was uncertain. Bilateral inferior petrosal sinus sampling (BIPSS) also implied an ectopic source of ACTH.

^{18}F-Fluorodeoxyglucose positron emission tomography (PET) showed mild uptake in the carinal region but, most interestingly, a node had moderate uptake on the octreotide scan. Bronchoscopy and fine needle aspiration of this lymph node showed a neuroendocrine neoplasm. We optimised her metabolic state and started her on cortisol blockade.

The subcarinal node was removed by mediastinoscopy and had, as anticipated, a lung carcinoid. It was clearly metastatic; it was positive for the normal markers, and had a low Ki-67, so it was a grade 1 neuroendocrine tumour (NET). Surprisingly, despite not having located the primary tumour, post-operative cortisol was <50nmol/l. The patient did well on hydrocortisone replacement. She is regularly reviewed by ^{68}Ga-dotatate PET because, at some point, we expect the ectopic source to reveal itself. Currently, she remains completely cured of Cushing's syndrome.

Tumours causing ectopic ACTH
Studies have included a number of large series, such as one from St Bartholomew's Hospital and another from the National Institutes of Health (NIH). Most of these tumours are actually intrathoracic, bronchial carcinoids being the most common. The data from the two centres overlap considerably, although occult ACTH was less common at St Bartholomew's (12.5% versus 19%), probably because we had 5 years of follow-up rather than 2 years.

What is meant by overt, covert and occult?[1] Overt ectopic ACTH syndrome (EAS) is defined by prompt identification of the tumour. Covert applies when tumour identification takes some time, usually using special imaging techniques. We talk about occult ACTH when, even after many years of follow-up, no source is found.

These patients in general present with severe metabolic upsets such as hypokalaemia, hypertension and diabetes.[2] So, this is a much more severe syndrome than, for example, ACTH-dependent syndrome due to Cushing's disease or a primary adrenal abnormality, but there is considerable overlap. A short history of a very severe disorder indicates that EAS is more likely.

Looking at it the other way round, if we consider a series of 918 patients with NETs, 3.2% had EAS (with most in the lung or the thymus).[2] Again, 15% were occult. In this series, the overall survival was only just over 3 years, but we tend to see longer survival nowadays.

Locating the source
How do we find the source when it is difficult? A survey of 231 patients found that 52% were overt, 29% were covert and 19% were occult.[3] CT was amongst the most useful modalities, detecting 66% of cases. ^{68}Ga-dotatate PET scanning detected 82% (100% of the covert cases) and is probably the most useful, ideally with co-registration with CT or MRI.

One can assume that patients with ACTH-dependent Cushing's syndrome have a 14% prevalence of EAS. If a positive central gradient is seen on BIPSS (>3 after stimulation), then the diagnosis is very likely to be Cushing's disease. If there is no gradient and no obvious source for ectopic ACTH, undertake a corticotrophin-releasing hormone test: a positive response might indicate Cushing's disease, whereas a lack of response suggests EAS.

Florid Cushing's syndrome
The clinical features of florid Cushing's syndrome include florid features, cortisol >1000nmol/l, and probably diabetes, hypokalaemia, low albumin and leucocytosis. ACTH should be measured.

An NIH study looked at two groups of patients with Cushing's syndrome. The first did not present with any serious infection, while the second had nasty infections that were difficult to treat.[4] The cut-off between the groups was again around 1000–1200nmol/l. These very severely unwell patients can also have a Cushing's coagulopathy.[5]

Patient management
It is important to act quickly, treating hypokalaemia, diabetes and hypertension within the first 24 hours. Low molecular weight heparin is used for anticoagulation and clinicians should search out sepsis. Many patients can be difficult to handle because they can become psychotic: drugs like haloperidol or olanzapine may be needed.[6]

Major drugs used in the short term are ketoconazole, metyrapone and etomidate. With metyrapone, about half achieve normalisation of cortisol and 80–90% show a dramatic improvement. Ketoconazole is also associated with a very marked improvement. Remember to recheck metabolic parameters once cortisol has been lowered.

Etomidate can be used when a patient is 'in extremis'. A 54-year-old female patient had a metastatic pancreatic tumour but was intolerant of somatostatin analogues (the normal first-line treatment) and was being considered for peptide receptor radionuclide therapy. She became extremely unwell and confused. She was diabetic and hypokalaemic, although she was not overtly Cushingoid, despite a serum cortisol of 4700nmol/l and a very high ACTH (450ng/l). ^{68}Ga-dotatate PET/CT scan revealed multiple uptake in metastases. Etomidate works very similarly to metyrapone but has a rapid effect parenterally. Over a few days after starting treatment, her cortisol fell dramatically, allowing her to undergo bilateral adrenalectomy. Virtually undetectable serum cortisol resulted.

Bilateral adrenalectomy should generally be considered in the long term, if the source of ACTH cannot be identified or removed.

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Case presentations

Case 1. Medical management of ectopic Cushing's

Bhavna Sharma *London, UK*

A 65-year-old man had COVID-19 symptoms of cough, fever, abdominal pain and agitation. In the past year, he had been diagnosed with diabetes, hypertension, chronic obstructive pulmonary disease, schizophrenia and depression. He was severely hypertensive (175/110mmHg), but systemic examination was unremarkable, except that he was aggressive, combative and confused. He had no overt Cushingoid features. He had hypokalaemic metabolic alkalosis; this hypokalaemia was extremely refractive.

Full body computed tomography (chest, abdomen and pelvis) revealed a non-specific abnormality on the right side of his lung and his adrenals were non-specifically bilaterally enlarged.

We found a very raised 24-hour urinary cortisol. His midnight plasma cortisol was raised, as well as his adrenocorticotrophin. Neither a 1-mg overnight dexamethasone suppression test (DST) nor a low dose 48-hour DST showed any suppression. We would have liked to move on to fluorodeoxyglucose positron emission tomography, a bronchoscopy or perhaps bilateral inferior petrosal sinus sampling, but the patient refused.

Since the main problem was hypercortisolism, we started him on metyrapone. Because of his hypokalaemia, we began eplerenone as well. We planned to titrate the cortisol to a mean of 300nmol/l (at least for the 09.00 measurement).

He was transferred to another team to assess possible infection. When we saw him 2 weeks later, he had been on metyrapone and eplerenone for 2 weeks and had developed hypocortisolism. We switched to a block and replace regime, on prednisolone 5mg.

This acute management of ectopic Cushing's, enabled us to correct his electrolytes. His diabetes and hypertension were normalised and the only antihypertensive he needed was eplerenone. His sugar control did not require any insulin. He had been extremely combative and aggressive but, with normalisation of cortisol, his confusion resolved. Most importantly, the advantage of this acute management was that it gave us time to undertake further diagnostic measures.

Refractory hypokalaemia in the context of metabolic alkalosis is a typical presentation of ectopic Cushing's. Medical management of Cushing's should also be considered when diagnosis is delayed.

With thanks to my supervisor Mushtaqur Rahman for his support.

Case 2. Diversity in macronodular hyperplasia

Mirsala Solak *Zagreb, Croatia*

The first patient was a 48-year-old man who had had Cushingoid features for 1 year, hypertension and anxiety. In a 1-mg overnight dexamethasone suppression test (DST), his cortisol was very high, as were his midnight plasma cortisol and urinary free cortisol (UFC); his adrenocorticotrophin (ACTH) was low.

The second patient, a 59-year-old woman, had adrenal masses, some typical signs of Cushing's syndrome, chronic cellulitis of the left leg (treated for some time without success) and a history of osteoporosis with multiple fractures and type 2 diabetes. Her hormone work-up was similar to that of the first patient. They both had ACTH-independent Cushing's syndrome.

Their computed tomography (CT) scans were similar, showing bilateral macronodular hyperplasia. We referred them for endoscopic surgery of the larger adrenal gland. After 4 months, the first patient showed no improvement in Cushingoid features or blood pressure control. His hormone work-up still revealed Cushing's syndrome. The other patient also had no improvement in Cushingoid features and her cellulitis was still problematic. Her hormone work-up was similar to that of the first patient. We referred them for laparoscopic surgery of the other adrenal gland, which led to improvement in the clinical signs of Cushing's and better control of co-morbidities in both patients.

The third patient was a 56-year-old woman with incidental bilateral adrenal masses. She had no Cushingoid features but was obese, with type 2 diabetes and hypertension. Cortisol was unsuppressed with a 1-mg overnight DST, her UFC was normal and her ACTH was low.

The final case was a 52-year-old female, referred for incidental bilateral adrenal masses. She had no Cushingoid features, but was overweight, with a history of hypertension and osteoporosis. She had unsuppressed cortisol secretion on an overnight DST, normal UFC and low ACTH. So they both had autonomous secretion of cortisol, formerly known as subclinical Cushing's syndrome.

Both these last two patients were referred for laparoscopic surgery of the larger adrenal gland. At 4 months after surgery, the third patient had an improvement in her diabetes. She had unsuppressed cortisol in an overnight DST, but it was better than before surgery. The fourth patient showed improved hypertension. Cortisol was not completely suppressed on overnight DST, but was much better than before surgery. We followed these patients for a few years and both had a stable clinical picture, with co-morbidities that did not worsen.

Presenting four patients shows the diversity in clinical presentation and treatment of macronodular hyperplasia, even when CT scans are quite similar.

Case 3. Bilateral incidental tumours in the adrenals

Grethe Ueland *Bergen, Norway*

Adrenal tumours are common in the population. Most are non-secreting, but at least 20% show some cortisol overproduction, termed autonomous cortisol secretion. Furthermore, in 15% of incidentaloma cases, there are bilateral adrenal tumours.

Bilateral tumours and hormone over-production can lead to difficult treatment decisions, as it is hard to know whether hormone overproduction is unilateral or bilateral. This problem is overcome in primary aldosteronism by adrenal venous sampling (AVS) to decide the laterality of hormone overproduction. There has not been so much progress in the analysis of hypercortisolism.

A 60-year-old man with type 2 diabetes and osteoporosis had experienced weight loss of 25kg in the previous year, and developed pronounced sarcopenia, so he had to walk with sticks. A computed tomography (CT) scan of the abdomen and thorax showed that the right adrenal measured 65mm; it had microscopic fat and was radiologically most likely to be a myelolipoma. The left adrenal showed macronodular hyperplasia, with no distinct tumour.

The patient had suppressed adrenocortico-trophin (ACTH) in a basal morning sample, and inadequate suppression of cortisol after a 1-mg dexamethasone suppression test (DST) and the conventional DST. He had two elevated late night salivary cortisol measurements and two elevated 24-hour urinary free cortisol (UFC) measurements.

We had a dilemma: the right-sided tumour could be the source of the cortisol excess or, alternatively, the hyperplastic left adrenal might be responsible for the hormone overproduction. We performed AVS; it indicated a right-sided overproduction of cortisol that perhaps suppressed cortisol secretion from the left adrenal.

The patient's right adrenal gland was removed and he needed cortisol replacement for 3 months post-operatively. Renewed biochemical testing showed normalisation of all parameters. He gained musculature and 8kg of weight in the first year, and was able to walk again without sticks. His diabetes had also been cured at 6 months post-operatively. He had annual follow-up, with normal biochemical testing. In November 2020, he unfortunately died from another cause.

This case was one of the first patients where we used AVS to assess lateralisation of autonomous cortisol secretion. We have now performed the procedure in 60–70 patients. Comparison of the results with cholesterol scintigraphy using SPECT CT and with post-operative biochemical results shows a very good match.

If adrenalectomy is planned in patients with bilateral tumours and autonomous cortisol secretion or Cushing's syndrome, it is crucial to decide if cortisol overproduction is unilateral or bilateral. AVS is a safe and feasible method to decide laterality in this setting.

Case 4. Ineffective hypophysectomy in a child with Cushing's

Eda Yanar *Moscow, Russia*

This is a case of Cushing's disease after hypophysectomy. The patient first presented at 6 years of age with progressive truncal obesity and growth retardation. From 8 years of age she had headaches, fatigue and emotional lability. Her first evaluation was at the age of 9 and a half, when her height was 110cm (which is −4SD) and her weight was 28kg.

Clinical signs showed facial plethora, moon face and dorsal hump; high blood pressure was detected. Hypercortisolism was diagnosed based on 24-hour urinary free cortisol and lack of circadian rhythm of cortisol secretion. Magnetic resonance imaging (MRI) failed to find an adenoma. Bilateral inferior petrosal sinus sampling (BIPSS) gave a pituitary:peripheral adrenocorticotrophin (ACTH) ratio of 9.5. We found signs of osteoporosis but there were no signs of hyperglycaemia or coagulopathy on first examination.

During transsphenoidal surgery, an adenoma was identified. Total hypophysectomy was performed. Histology confirmed an ACTH-secreting adenoma. After surgery, she developed adrenal insufficiency. Secondary hypothyroidism, growth hormone deficiency and diabetes insipidus were also identified. After discharge from hospital, she experienced loss of weight and improved height. Unfortunately, this did not last long.

Her next evaluation was 18 months later, at the age of 13 years. Her height was 119cm (−5.8SD). Her puberty characteristics had not changed from her first evaluation and her Cushingoid features persisted. We also found hyperglycaemia and diabetes, and there were signs of fracture.

The laboratory confirmed ACTH-dependent hypercortisolism, again without any signs of adenoma on MRI. Again we performed BIPSS, and for the second time we confirmed pituitary ACTH excess. Radiation therapy was suggested.

At the age of 13 years, she underwent gamma knife stereotactic radiosurgery and, at the same time, started on ketoconazole therapy to reduce hypercortisolaemia. After 7 months, remission has still not been achieved. She is still receiving ketoconazole therapy.

Early diagnosis of Cushing's disease remains a major challenge in children. Manifestation was at a very young age, and she showed emotional lability which is not a common symptom of paediatric Cushing's disease. Even after initially successful treatment, and even after total hypophysectomy, it is necessary to continue lifelong follow-up for these patients, because of the risk of disease recurrence.

Challenges and the future of Cushing's management

Chairs: **Niki Karavitaki** *(UK)* & **Susan Webb** *(Spain)*

Emerging treatments for Cushing's

Rosario Pivonello *Naples, Italy*

A number of new medical treatments for Cushing's have either already been approved or are still in phase II or phase III trials.[1]

Pasireotide

Pasireotide targets the somatostatin type 5 receptor, expressed in corticotroph pituitary tumours. Many studies have demonstrated its remarkable efficacy in normalising urinary free cortisol (UFC) when given s.c. twice daily. More recently, a phase III study has looked at the long-acting formulation (given monthly i.m.) in 150 patients.[2] At doses of 10 and 30mg, it demonstrated similar efficacy and safety compared with conventional pasireotide administration. At month 7, UFC was normalised in 41.3% of patients. There was also a ≥20% decrease in tumour volume in almost half these patients and improvement in many clinical parameters, such as blood pressure, lipid profile, body weight and quality of life. Hyperglycaemia was the most commonly associated adverse event, requiring monitoring and treatment.

An important extension study demonstrated that, if treatment continues for many months or years, patients who are initially controlled by the treatment continue to maintain their UFC in a high percentage of cases, with further improvement in the clinical profile and fewer adverse events.[3]

Osilodrostat

In contrast to pasireotide, osilodrostat acts on the adrenal. It has recently been approved for all types of Cushing's syndrome. This steroidogenesis inhibitor acts on 11β-hydroxylase with a higher potency for lowering cortisol and a longer half-life than other adrenally active steroidogenesis inhibitors, such as metyrapone. This allows twice daily administration.

The phase III, multicentre, open label LINC 3 study is the most important clinical trial of osilodrostat in Cushing's disease.[4] It studied 137 patients with Cushing's disease for 24–48 weeks. After 24 weeks, around 68% had normalised UFC. During the randomisation phase after 24 weeks, osilodrostat maintained UFC normalisation in 86.1% of patients compared with placebo (29.4%). Osilodrostat showed good efficacy in terms of improved systolic and diastolic blood pressure, body weight, lipid profile and glucose profile, but had a variable effect on tumour volume. Adverse effects were mostly associated with hypocortisolism or accumulation of adrenal hormone precursors. The drug was effective in Cushing's disease and also in other forms of Cushing's syndrome.[5]

Levoketoconazole

Levoketoconazole is a stereoisomer of ketoconazole, and seems to have higher potency at lower doses compared with the racemic mixture. The phase III, multicentre, open label SONICS study included 94 patients with Cushing's syndrome.[6] Between 300 and 1200mg levoketoconazole were given daily for 26–47 weeks. Normalisation of UFC at 6 months was seen in 31–36% of patients, but this rose to 62% when only patients completing the 6-month maintenance phase were included. After 6 months, there was significant improvement in body weight, lipid profile, glucose profile, quality of life and depression, and also in signs of hyperandrogenism in women, such as acne and hirsutism. The main adverse effects were nausea and headache, and a rise in hepatic enzymes.

The LOGICS study focuses on the efficacy of levoketoconazole in 84 patients, and includes a randomisation withdrawal phase. Preliminary findings show that the drug is associated with UFC normalisation in 50% of patients compared with 4.5% in the placebo group at the end of the randomisation phase.

Phase II studies

Relacorilant is a novel selective glucocorticoid receptor antagonist. Compared with metyrapone, it has a higher affinity for the glucocorticoid receptor and, most importantly, no affinity for the progesterone receptor. In a phase II study, 35 patients with Cushing's syndrome (mainly adrenocorticotrophin-dependent) were divided into two groups according to their main co-morbidity: hypertension or glucose intolerance. The drug improved both hypertension and glucose intolerance at two different doses in up to 63 and 50% of patients respectively. Other clinical improvements were also seen.

The phase II CAPACITY study demonstrated possible use of a combination treatment.[7] In this phase II, multicentre, open label study, 68 patients with Cushing's disease received pasireotide (600–900µg/day). If they were uncontrolled, cabergoline could be added (0.5–1mg/day). In terms of UFC, 25% were controlled on pasireotide alone; a further 25% were normalised by the addition of cabergoline.

Other drugs in early stages of evaluation include retinoic acid (anti-proliferative), roscovitine (cyclin-dependent kinase inhibitor), vorinostat (histone deacetylase inhibitor), abiraterone (selective 17α-hydroxylare inhibitor) and nevanimibe (acetyl-CoA acetyltransferase 1 inhibitor), amongst others.

It is clear that the medical treatments for Cushing's syndrome, now and in the future, include a wide spectrum of drugs suitable for different patients' needs and clinical conditions.

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Corticotroph tumour progression after bilateral adrenalectomy

Katrin Ritzel *Munich, Germany*

Corticotroph tumour progression (CTP), formerly called Nelson's syndrome, is a challenging and sometimes difficult-to-treat complication of bilateral adrenalectomy (BADX). The management of these patients had not been standardised and there were a lot of unanswered questions regarding diagnosis, surveillance and treatment. Our group initiated an expert consensus meeting and, in March 2021, a first consensus statement was published.[1]

Background

After 1950, with the therapeutic availability of cortisone, the use of BADX as a treatment for Cushing's disease increased. However, it was not until 1958 that Don Nelson described the first case of hyperpigmentation, a sharp rise in adrenocorticotrophin (ACTH) and sellar enlargement. In the 1960s, hyperpigmentation, cranial nerve palsies or an enlarged sella on X-ray were primarily used to make the diagnosis.

A milestone was passed in 2007 when Assié *et al.* returned the focus to tumour progression as the central feature of CTP.[2] In the consensus recommendations, the primary diagnostic criterion is tumour progression or new detection of a pituitary tumour after BADX. Hyperpigmentation or a progressive rise in plasma ACTH after BADX is a non-mandatory, secondary criterion.

Regarding terminology, in the consensus meeting we were of the opinion that 'corticotroph tumour progression after bilateral adrenalectomy' (CTP-BADX) should replace the name Nelson's syndrome.

Occurrence of CTP after BADX

When we strictly apply the magnetic resonance imaging (MRI) criteria for diagnosis of CTP-BADX, the mean cumulative incidence is over 40%. Most patients have manifestations in the first 3 years after surgery. The consensus recommendations for surveillance after BADX are that imaging (preferably MRI) should be performed after 3 months and then every 12 months for the first 3 years. Larger intervals can be used subsequently, depending on clinical signs. The primary treatments are pituitary surgery and radiation therapy.

Pituitary surgery

Transsphenoidal surgery is the preferred approach (rarely transcranial). There have been 12 relevant studies since 1976 (187 patients), but they are heterogeneous, especially in the definition of remission, the length of follow-up and the use of previous therapies such as radiotherapy and neurosurgery. The outcome primarily depended on tumour size and the degree of extrasellar extension. If we only look at intrasellar tumours, there was a stable remission rate of about 80% after pituitary surgery.

A study in 2020 summarised the outcome for 68 patients with CTP-BADX in 13 UK pituitary centres, with 13 years of follow-up. The 10-year progression-free survival was about 62%.[3] Surgery alone, or with radiosurgery, had around 80% tumour progression-free survival, which was higher than other treatment forms.

In the consensus, it is recommended that pituitary surgery is the first-line treatment for CTP-BADX. It should be performed before extrasellar expansion of the tumour, to obtain long term remission.

Radiation therapy

Conventional radiotherapy for CTP-BADX was mainly used in earlier years, with variable outcomes in terms of remission and hypopituitarism. Use of sterotactic radiosurgery has included seven studies of gamma knife radiosurgery in 164 patients, two studies of linear accelerator systems in 15 patients and two studies of proton-based treatment in 14 patients. In the gamma knife studies, remission rates of 80–90% and post-radiation tumour volume shrinkage of about 30% were observed. The isolated effects of radiosurgery might be overestimated, as many patients were previously treated with surgery or conventional radiotherapy.

In a recent study of the outcome of gamma knife radiosurgery for CTP,[4] the 10-year progression-free survival was 91%; two of the 28 patients had a recurrence, and side effects were rare. It should be noted that this study included a large proportion of patients with microadenoma at diagnosis.

The consensus statement recommends radiotherapy for CTP patients when the tumour is not safely accessible by surgery or when complete tumour resection is not possible.

Medical therapy

Since medical therapy has only been applied in individual cases and small series, there are not enough data to generally recommend medical treatment for CTP. Pasireotide may lead to tumour shrinkage. Another possibility, temozolomide, is an alkylating chemotherapeutic agent that has been successfully applied in aggressive pituitary adenomas, such as prolactinomas, and in pituitary carcinomas. Of seven patients who were treated with temozolomide, five showed tumour reduction, one showed stable disease and one had no response.

So, the consensus states that there is no established medical therapy for CTP-BADX. Temozolomide could be discussed on an individual basis in aggressive corticotroph tumours that are resistant to other treatments.

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Key facts about corticotroph tumour progression (CTP) after bilateral adrenalectomy (BADX).

>40% of patients undergoing **bilateral adrenalectomy** develop **corticotroph tumour progression** on subsequent MRI

Close surveillance and case discussion in an interdisciplinary board are mandatory

Treatment should be performed **before extrasellar extension occurs**

Transsphenoidal resection of the adenoma is first-line treatment

Radiation/stereotactic radiosurgery is second-line treatment

Anticoagulation in Cushing's: when and how?

Carla Scaroni *Padova, Italy*

Clinical case

This clinical case forced me to change my perioperative management of Cushing's disease patients. A 30-year-old woman had florid hypercortisolism and Cushing's disease, but no family history of thrombosis or vascular disease. She had a shortened partial thromboplastin time (PTT), which is a useful simple marker of the thrombophilia present in any patient with Cushing's syndrome, and also high levels of the procoagulant factors VIII and von Willebrand Factor (vWF). The patient obtained remission of hypercortisolism after transsphenoidal surgery (TSS), and received anticoagulant thromboprophylaxis from the day after surgery for 14 days. But, 18 days after surgery, the patient presented with pulmonary embolism due to a venous thromboembolism (VTE) in the left leg.

Increased cardiovascular risk

Patients with Cushing's syndrome present with increased cardiovascular risk due to the frequent presence of hypertension, impaired glucose and lipid metabolism, central obesity and also hypercoagulability. They have a two to four times higher mortality rate than the general population, partly due to an increased risk of pulmonary embolism, stroke and cardiac failure.

In a retrospective study of 473 Cushing's patients (mostly female, mean age 42 years),[1] the incidence of thromboembolic events was 14.6 per 1000 person-years (compared with 1–2 for the general population). The incidence rate before surgery was the same in adrenocorticotrophin (ACTH)-dependent and -independent cases. After surgery, it was raised only in those with the ACTH-dependent form (Cushing's disease). In four cases, the event occurred in the first few days after TSS, even during thromboprophylactic therapy. Consideration of further studies also indicates that the risk of spontaneous VTE in Cushing's syndrome is greater than in the general population. The risk of post-operative VTE in Cushing's disease may be comparable with that following major orthopaedic surgery.

Causes of thrombotic events

The onset of a thrombotic event is multi-factorial. Some acquired factors such as infections, obesity, surgery, reduced mobility and invasive diagnostic procedures are not uncommon in the life of a Cushing's patient, as are the genetic prothrombotic factors. However, the cortisol excess is the prevalent determinant of thrombophilia. It increases procoagulant factors, such as factor VIII and vWF, and high molecular weight vWF multimers. It enhances thrombin generation, causes endothelial dysfunction and reduces PTT. Increases in anticoagulants (protein C, protein S and anti-thrombin) may not be sufficient to counteract thrombophilia.

The VTE risk is reported to be more frequent after TSS than after adrenal surgery.[1] There may be a role for ACTH levels. Pretreatment with cortisol-lowering agents might limit the risk of VTE, avoiding the post-surgery withdrawal syndrome that may be a cause of a proinflammatory and procoagulant state. There is a higher risk in the 60 days post-surgery and also for patients undergoing bilateral adrenalectomy. Many patients have more than one event.[2]

In a study of 343 Cushing's patients in Denmark,[3] the risk of VTE was high 3 years before diagnosis, so it is independent of surgery and is present before Cushing's disease is recognised. The risk is highest in the first year after diagnosis, suggesting an additional role of surgery. The risk remains elevated for 30 years after diagnosis.[3]

Recognising patients at risk of VTE

To develop a risk assessment model to identify patients at higher risk of VTE, we collected clinical, hormonal and coagulation parameters from 176 patients with active non-malignant Cushing's syndrome.[4] Statistical analysis identified six independent risk factors for VTE. These were: age >69 years (2 points), reduced mobility (2 points), previous cardiovascular events (1 point), acute severe infections (1 point), shortened PTT (1 point) and late night serum cortisol >3.15 times the upper limit of normal (1 point). Patients with a score ≥3 points were found to have a high VTE risk; 17 out of 20 VTE cases could have been prevented by treating these high risk patients.

Anticoagulant prophylaxis

Two groups of patients were compared: the first (75 patients, 1972–1981) did not receive anticoagulant prophylaxis after surgery, while the second (232 patients. 1982–2000) received prophylaxis for 14 days.[5] In the first group, 20% of patients had thromboembolic events, half of whom died. The second group had a reduced percentage of thromboembolic events (6%), with one fatality.

More recently, we have changed our perioperative thromboprophylaxis in Cushing's disease.[6] In a retrospective study of patients who underwent TSS for Cushing's disease between 2001 and 2012, 34 individuals (before 2006) received glucocorticoid cover after TSS and low molecular weight heparin (LMWH) for 14 days after surgery. A further 44 patients (after 2006) were treated with glucocorticoids only if we confirmed adrenal insufficiency 48 hours after surgery. They received LMWH for 30 days starting the day after surgery, we also applied early mobilisation and elastic stockings from the day before surgery. There were three events, including a fatal pulmonary embolism, in the first group within 30 days of surgery. In the second group there were no VTEs after surgery.

Due to the rarity of Cushing's disease, a multicentre study of a larger number of cases is warranted.

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Managing the risk of VTE in Cushing's: what to do and what to avoid.

What to do	What NOT to do
Apply the Cushing's VTE score[4]*	Smoke
In the peri-operative period: • reduce cortisol levels before surgery? • use compression stockings • mobilise as soon as possible • use prophylactic LMWH for 30 days (60 days in some cases?)	Use oestrogens
	Ignore acquired/genetic thrombotic risk factors
	Ignore a shortened PTT
	Ignore an earlier thromboembolism
	Believe that LMWH removes risk of thromboembolism
Increase awareness of thrombophilia in Cushing's	Use excessive peri-operative glucocorticoids
	Use a peripherally inserted central catheter (if possible)

*Not yet validated.

What really is remission in Cushing's?

Richard Feelders *Rotterdam, The Netherlands*

Cushing's disease causes multisystem morbidity, with changes in body composition and in other endocrine systems, as well as neuropsychiatric disturbances, metabolic syndrome and hypercoagulability. It is therefore not surprising that many studies have shown an increased mortality in these patients compared with other individuals, for instance, patients with a non-functioning pituitary adenoma or acromegaly.[1] Mortality remains about fourfold higher in patients with persistent hypercortisolaemia after treatment, and so it is important to aim for complete normalisation of cortisol production in patients with Cushing's disease.

What is the ideal scenario in terms of treatment outcome? First of all, one would hope for biochemical remission, followed by a reversal of clinical morbidity, and accompanied by preservation of pituitary function.

Biochemical remission

In patients who are treated surgically for Cushing's disease (first-line treatment), a low post-operative morning cortisol level is highly predictive of clinical remission. We also want to normalise urinary free cortisol (UFC) and late night salivary cortisol.

The problem of persistent morbidity

Despite long term biochemical remission, 40–60% of patients have persistent co-morbidities. For some co-morbidities, the percentage may even be higher. So there is a discrepancy between biochemical and clinical remission, which we see in practice. A spectrum of clinical outcomes follows treatment of Cushing's disease. On one hand, we have patients with active Cushing's disease, while on the other, patients have complete reversal of clinical co-morbidity. In between, there is a large group with persistent morbidity to a variable degree. Overweight and obesity persist, despite biochemical remission, in up to 40% of patients. Impaired glucose tolerance and diabetes also persist in up to 60% of patients, and hypertension persists in up to 75% of patients. Nephrolithiasis, psychopathology and major depression can also persist and only partial reversibility has been shown for cognitive deficits and osteoporosis. Not surprisingly, this results in impaired quality of life in patients with treated Cushing's disease, despite normal cortisol levels.[2]

Why can co-morbidity persist despite biochemical cure?

First, it may be related to hydrocortisone substitution. Secondly, some patients can have cyclical Cushing's syndrome, and intermittent periods of hypercortisolism can maintain associated morbidity.

Thirdly, there may be irreversible changes at tissue level. Examples can be found in the brain, including brain atrophy, smaller grey matter volumes (see Figure below), decreased cortical thickness and decreased brain metabolite concentrations.[3] In muscle tissue, irreversible changes include impaired grip strength and increased intramuscular fat infiltration.[4] These changes might be related to the duration of hypercortisolism before the diagnosis was made, and might also be modulated by differences in glucocorticoid sensitivity or resistance at tissue level. One determinant of this is polymorphisms in the gene encoding the glucocorticoid receptor.[5]

A fourth explanation for persistence of morbidity despite biochemical cure is that biochemical tests may only partly reflect the function of the hypothalamic-pituitary-adrenal (HPA) axis and the tissue glucocorticoid exposure.

In one trial, patients were treated for 1 year with either 10mg or 30mg long-acting pasireotide per month.[6] Many patients had normalised UFC at, or just below, the upper limit of normal. But, of course, we don't know the individual HPA axis set-point of each individual patient. It might be that a UFC level just below the upper limit of normal is too high for a patient with a set-point in the mid-normal range. Perhaps we should aim for UFC levels lower in the normal range than is currently the case. Interestingly, a discrepancy was observed in a subset of patients between UFC results and late night salivary cortisol concentrations.[7]

The cortisol diurnal rhythm was found to be restored in only a subset of patients.[8] This is an important observation, and the question is whether patients with normalised UFC concentration but without recovery of cortisol diurnal rhythm are really in remission. Presumably the answer is no. Absence of cortisol rhythmicity is associated with higher tissue cortisol exposure. This might have a sustained modulatory effect on target gene expression, including clock genes which have an important role in the regulation of several metabolic processes.

In conclusion

The question of whether patients are really in remission after reaching biochemical remission is difficult to answer. The persistence of co-morbidities indicates that biochemical remission is only partly predictive of clinical remission. The definition of biochemical remission is hampered by discrepancies between different parameters that reflect the activity of the HPA axis. Various mechanisms may explain why co-morbidities persist despite 'cure'.

We need further studies to explore the mechanism of irreversible changes induced by cortisol excess and whether recovery of co-morbidities is associated with recovery of the cortisol diurnal rhythm. There is an unmet need for new parameters or biomarkers or bioassays that can assess eucortisolaemic states and tissue cortisol exposure; these may improve the treatment outcome for patients with Cushing's disease.

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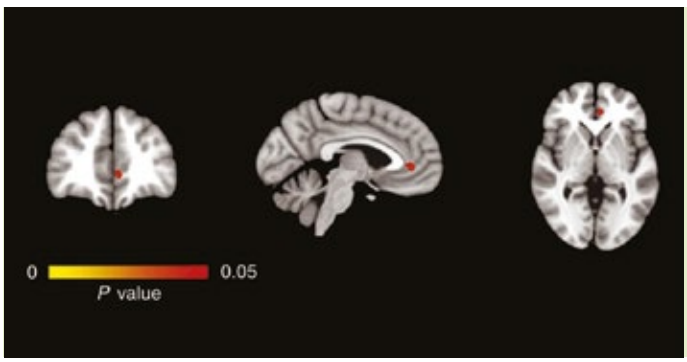

Patients with predominantly long term remission of Cushing's disease showed smaller grey matter volumes in the left perigenual region of the anterior cingulate cortex, compared with controls. Reproduced by permission from *European Journal of Endocrinology* **169** 811–819.[3]

Case presentations

Case 1. Cyclical Cushing's detected by weekly potassium levels

Ingrid Reppo *Tartu, Estonia*

A previously healthy 65-year-old man was admitted to hospital with acute psychosis and severe hypokalaemia (1.5mmol/l). Lab analysis revealed adrenocorticotrophin (ACTH)-dependent hypercortisolaemia, with ACTH >20pmol/l and cortisol almost 1500nmol/l. Magnetic resonance imaging (MRI) showed a normal pituitary, and a whole body computed tomography scan showed a compression fracture in the lumbar spine, which indicated the hypercortisolaemia was probably of long duration. He remained in hospital for 3 weeks. The hypercortisolaemia and hypokalaemia resolved and he was discharged.

About 5 months later, he returned to hospital, complaining of severe weakness and palpitations. Severe hypokalaemia and ACTH-dependent hypercortisolaemia were detected again. His appearance was not overtly Cushingoid. His hormone levels showed, surprisingly, that hypercortisolaemia was not present and there was also a normal diurnal rhythm. We also measured 24-hour urinary free cortisol (UFC) four times, and all measurements were well within the reference range. So a diagnosis of cyclical ACTH-dependent Cushing's syndrome was made, but further hormone testing and bilateral inferior petrosal sinus sampling (BIPSS) were postponed, due to the silent phase of the disease. Additional imaging was performed but nothing abnormal was detected. Since previous exacerbated disease presented with severe hypokalaemia, we decided to test for hypokalaemia weekly. The potassium level stayed relatively stable, well above 4mmol/l, for many weeks. Then there was a sudden drop to 3.8mmol/l. The patient was admitted to our hospital and blood tests revealed exacerbated disease, with morning ACTH of almost 50pmol/l, cortisol >2600nmol/l, and late night values also stayed also extremely high. We measured 24-hour UFC levels twice and daily cortisol excretion exceeded 28 000nmol/day.

BIPSS and corticotrophin-releasing hormone stimulation confirmed a central: peripheral ACTH gradient >8. MRI showed a possible 4.6-mm pituitary adenoma, and transsphenoidal surgery was performed. This did not result in a cure, and the pathology report came back as normal as well. A ^{68}Ga-DOTANOC positron emission tomography scan also gave negative results. We decided to do a bilateral adrenalectomy.

Unfortunately the source of the ACTH remains unknown, but the patient is feeling well at the moment, and is happy that the diagnostic process is over.

Case 2. Cushing's syndrome: diagnostic caveats

Tanja Miličević *Split, Croatia*

Our 56-year-old female patient had an interesting medical history. This included treatment for a polynodular thyroid goitre, recurrent deep vein thrombosis, chronic kidney disease with treatment by haemodialysis, osteoporosis, thromobocytopenia, depression with repeated suicide attempts, epilepsy and unregulated hypertension that presented with hypertensive crises.

Some characteristics could be attributable to hypercortisolism, such as round face, proximal myopathy, central obesity and signs of facial hirsutism. These components made us think of autonomous hypercortisolism. The cortisol level after a 1-mg dexamethasone suppression test (DST) was elevated, and so was the serum cortisol at midnight, but morning adrenocorticotrophin (ACTH) was suppressed. We proceeded to a computed tomography scan of the adrenals. This revealed a right adrenal gland adenoma of 2.6 x2.4cm. Washout values indicated a benign lesion, but we questioned whether this adenoma was really functional and, if so, whether it should be surgically removed.

Of the patient's many medications, only oxcarbazepine, and her chronic kidney disease, could interfere with the cortisol concentration and its interpretation. Antiepileptics increase dexamethasone clearance and can cause false positive results on DST. On the other hand, the elevated value of midnight serum cortisol could be explained by the chronic kidney disease as part of pseudo-Cushing's, as chronic kidney disease disrupts the normal circadian ACTH and cortisol rhythm.

Measurement of salivary cortisol was not available in our institution. Since our patient had chronic kidney disease and was treated by haemodialysis, there was inadequate urine volume, so urinary free cortisol measurement was not appropriate or available. Considering our patient's baseline cortisol levels after the DST and cortisol level at midnight, we thought that this could be part of pseudo-Cushing's syndrome. Either chronic kidney disease or depression can cause a phenotype that is similar to neoplastic hypercortisolism but which is not neoplastic. However, the suppressed level of ACTH ruled out pseudo-Cushing's syndrome.

We concluded that we have a patient with ACTH-independent endogenous hyper-cortisolism. However, it is very problematic to define the level of hypercortisolism, since she takes oxcarbazepine and has chronic kidney disease.

The second question was whether to remove this adenoma. The surgical decision must be individualised but, in fact, the patient refused any other diagnostic or therapeutic procedures in the context of hypercortisolism. She is being followed-up regularly.

Case 3. Work-up and treatment of unexplained hypercortisolism

Sadiq Al Lawati *Vancouver, Canada*

A 77-year-old woman had a 6-month history of failure to thrive, poor oral intake, 9-kg weight loss and significant mood changes. Medical history revealed hypertension, dyslipidaemia and type 2 diabetes; she was on a statin, metformin and ramipril. She had a history of depression and was on venlafaxine.

Her body mass index was only 18. She had multiple bruises, thin skin but no other Cushingoid features. She had hyponatremia (122mmol/l); serum osmolality was low, and her urine specific gravity was high. Her hyponatremia was attributed to volume depletion.

She was admitted to the internal medicine service. Her plasma thyrotrophin was normal, but morning cortisol was very high at 1600nmol/l with an adrenocorticotrophin (ACTH) of 16pmol/l (normal <14pmol/l), indicating ACTH-dependent Cushing's. Her 24-hour urine cortisol was 10 times the upper range of normal. After an overnight 1-mg dexamethasone suppression test (DST) and an overnight 8-mg DST, she failed to suppress cortisol. Other pituitary hormones were normal. It is worth mentioning that, during her admission, she required a course of 10 sessions of electroconvulsive therapy, after which she was much better from a psychiatric standpoint.

Magnetic resonance imaging (MRI) of the pituitary sella showed a very small (3-mm) T2 hyperintense lesion: either a cystic microadenoma or another type of cyst. She was not co-operative, so gadolinium-enhanced images were not obtained. Computed tomography (CT) scans of the neck and chest were negative. CT of the abdomen and pelvis showed some irregularity in the stomach, Oesophagogastroduodenoscopy was performed, and pathology was negative for malignancy. Both adrenals were bulky on CT, but no discrete lesions or masses were seen. An ^{111}In-octreotide scan was negative.

On inferior petrosal sinus (IPS) sampling, the right IPS was cannulated successfully, but the left was hypoplastic. The test findings were in keeping with Cushing's disease. A left-sided cystic pituitary lesion was visualised on transsphenoidal surgery. Small hypophysectomy removed 20% of the pituitary gland. The pathology showed squamous metaplasia in a Rathke's cleft cyst and normal fragments of anterior and posterior lobes. There was no evidence of pituitary adenoma.

She was sent home in a stable condition and followed up as an outpatient. Despite clinically doing much better, her morning cortisol is now 761nmol/l, her 24-hour urine cortisol is twice the upper limit of normal, and her ACTH is 13.6pmol/l. MRI only showed post-operative changes.

Is this a true case of Cushing's disease or does she have non-neoplastic hypercortisolism secondary to depression? The severe urine cortisol elevation and elevated late-night salivary cortisol suggest true Cushing's syndrome, while her severe depression and the lack of Cushingoid features argue for pseudo-Cushing's.

Hypercortisolism can occur in many conditions other than true Cushing's syndrome. Pseudo-Cushing's should be excluded when evaluating patients with hypercortisolism. If the diagnosis is unclear, and the patient has mild hypercortisolaemia, re-evaluate the patient in 6–12 months.

Case 4. A patient with Cushing's syndrome and disease

Mirsala Solak *Zagreb, Croatia*

A 52-year-old woman had incidental masses in both adrenal glands. Physical examination showed signs of Cushing's: facial plethora, easy bruising and truncal obesity. Her medical history included arterial hypertension and nephrolithiasis. She was taking antihypertensive medications. Her lab results were all within normal limits except for mild leucocytosis and slightly elevated neutrophils.

A computed tomography scan revealed two adenomas in the right and left adrenal glands which were both rich in lipids. Her initial hormone work-up showed unsuppressed cortisol in the 1-mg dexamethasone suppression test (DST), her adrenocorticotrophin (ACTH) was low, and her urinary free cortisol (UFC) and late night plasma cortisol were high. We diagnosed ACTH-independent Cushing's syndrome and referred her for laparoscopic surgery of her larger right adrenal gland. Histopathology reported two adenomas, consisting of uniform clear cells with no cell atypia or mitotic activity and no vascular or capsule invasion.

Surprisingly, her morning plasma cortisol was normal 1 week after surgery. A 1-mg overnight DST showed her cortisol was partially suppressed. Her ACTH was normal. Was she in biochemical remission? We were not sure.

She came to clinic for follow-up 3 months after adrenal surgery. Her symptoms and physical examination did not show any improvement; indeed, she had gained 4kg. She still had facial plethora, easy bruising and truncal obesity. Her 1-mg overnight DST again showed high cortisol, her midnight plasma cortisol was high and so was her UFC. Her ACTH was normal.

We wondered if she had Cushing's disease. Pituitary magnetic resonance imaging (MRI) revealed a cystic adenoma 9mm in diameter. A corticotrophin-releasing hormone (CRH) test showed an increase in ACTH and cortisol consistent with Cushing's disease. We referred her for transsphenoidal surgery; the pathological review identified a pituitary adenoma. Immunohistochemical staining was positive for ACTH. The pathologist's diagnosis was corticotrophinoma.

At 3 months after pituitary surgery, her cortisol is suppressed after a 1-mg DST, her UFC is normal and her ACTH is 2.4pmol/l, so she is in biochemical remission. Did we make a mistake by removing the adrenal gland, and would the clinical course have been different if we had removed the pituitary tumour first?

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