Approach to the Cushing's Disease Patient With Persistent/Recurrent Hypercortisolism After Pituitary Surgery

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Although it is the ideal treatment, pituitary surgery is not always successful, and success is not always lasting. Close surveillance, clinical and biological, will detect immediate failure or late recurrence. The reason must be thoroughly explored with the somewhat dogmatic rule that the patient should be offered the best surgery in expert hands, and a repeat surgical attempt must be systematically discussed. When repeat pituitary surgery is not indicated or has failed, then comes the difficult task to choose between a number of options directed toward different targets: directly suppress tumor ACTH by pituitary radiotherapy (conventional or stereotaxic) or with medications (somatostatin analog such as pasireotide, or dopaminergic drug such as cabergoline), directly suppress adrenocortical activity with medications (inhibitors of adrenal steroidogenesis such as ketoconazole or metyrapone, or the adrenolytic Lysodren), or by surgery (bilateral adrenalectomy), and finally oppose peripheral cortisol action with the antiglucocorticoid mifepristone. No single option is ideal, able to provide at the same time a high success rate and a rapid onset of action, to restore a normal pituitary adrenal axis, and to have good tolerability. Close follow-up and thorough evaluation of the cortisolic status will eventually dictate a switch in treatment options and/or combination strategies over time. The tumor status and its possible oncogenic threat, the severity of the hypercortisolism, and the patient perspectives (wish of fertility) are among the major parameters that can help a multidisciplinary approach toward the best option. (*J Clin Endocrinol Metab* 98: 1307–1318, 2013)

Clinical Case

A 30-year-old female was referred to a specialized center for persistent hypercortisolism after pituitary surgery. One year ago she was diagnosed with Cushing's disease after she had developed weight gain, high blood pressure, mood change, fatigability, hirsutism, and amenorrhea. Urinary cortisol (UC) was unequivocally high (360 μg/d; normal, 20–90), with the absence of normal circadian variations of the plasma cortisol levels, and plasma ACTH levels were at the upper limit of normal (normal, 10–50 pg/ml) with a strong response to the CRH test (from 50 to

Abbreviations: BIPSS, bilateral inferior petrosal sinus sampling; DOC, deoxycorticosterone; MRI, magnetic resonance imaging; QoL, quality of life; UC, urinary cortisol.

200 pg/ml). The pituitary magnetic resonance imaging (MRI) was inconclusive with a possible microadenoma near the left cavernous sinus.

Transsphenoidal exploration was difficult due to profuse local bleeding. The left part of the pituitary was preferentially removed, and pathological examination showed only normal intermingled pituitary cells that stained for all pituitary hormones.

One week and 2 months after surgery, UC was essentially the same and was 2 to 3 times the upper limit of normal. The patient's clinical condition was unchanged.

She was referred to a specialized referral center for persistent Cushing's disease.

Pituitary Surgery as the First-Line Approach to Cushing's Disease

The perfect treatment

Treating Cushing's disease remains a challenge (1–4).

The 4 goals of treatment are to control adrenocortical oversecretion, to ablate or destroy the primary tumoral lesion, to respect anterior pituitary functions and if possible restore normal pituitary-adrenal axis, and to reverse the peripheral manifestations of chronic steroid excess.

Pituitary surgery is the only therapeutic approach that can attain these objectives. In many cases it does—for example, if a small, noninvasive corticotroph adenoma can be entirely resected by partial hypophysectomy, and if the clinical manifestations of hypercortisolism are still reversible in young patients whose plastic tissues have not been exposed to glucocorticoid excess for many years or decades.

However, pituitary surgery is not always successful, and success is not always lasting.

Analyzing the outcome of pituitary surgery

Pituitary surgery can fail immediately (persistent hypercortisolism) or after a transient period of eucortisolism or even hypocortisolism (recurrent hypercortisolism). The immediate post-pituitary surgery status should be thoroughly analyzed by the neurosurgeon, the pathologist, the radiologist, and the endocrinologist to distinguish between different situations, their likely explanations, and their possible prognostic implications (Figure 1).

Persistent hypercortisolism ("immediate failure")

The patient remains hypercortisolic. There are several explanations that must be systematically considered.

If there was no evidence of corticotroph adenoma at pathology
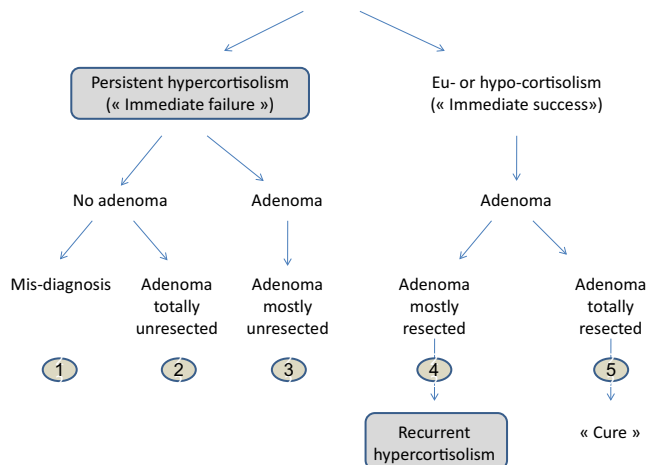
Figure 1. Assessing the outcome of pituitary surgery. The 5 tracks.

- There was no corticotroph adenoma in the pituitary, and Cushing's disease had been misdiagnosed for a patient with ectopic ACTH syndrome, or pseudo-Cushing, or other disease. Such cases are observed in referral centers for patients previously managed elsewhere. They require a thorough retrospective investigation of the evidence (clinical, biological, and imaging) that led to the "diagnosis" of Cushing's disease and to pituitary surgery, and also detailed analysis of the surgical procedure, what the surgeon actually saw, and the pathology report. If necessary, diagnostic investigations should be repeated in the referral center, including more sophisticated or invasive tests such as bilateral inferior petrosal sinus sampling (BIPSS).

- Alternatively there was, indeed, a corticotroph adenoma in the pituitary, but it was totally unresected. There are situations which provide an obvious explanation for unsuccessful pituitary exploration, including: profuse local bleeding, often due to dural venous sinus, may prevent clear exposure of the gland; a pituitary adenoma may be located above the sella or even be ectopic, in the sphenoid sinus; a lack of sphenoidal pneumatization may have prevented sellar exploration by the neurosurgeon. Probably the most common situation is that the adenoma is small, cannot be found visually, and is not properly resected. All of these difficulties are maximized if the neurosurgeon has little experience with Cushing's disease patients and/or rarely performs transsphenoidal surgery (5–7).

If there is evidence of corticotroph adenoma at pathology. There was indeed a corticotroph adenoma in the pituitary, but it was mostly unresected for reasons similar to those listed above.

Reccurrent hypercortisolism (after "immediate success")—the second situation

- There was a pituitary corticotroph adenoma, which was mostly resected. Diagnosis is certain when there is both positive evidence of the pathology and control of hypercortisolism immediately after partial hypophysectomy. Subsequent recurrence of hypercortisolism in such cases is the consequence of the progression of remnants of the adenoma.
- Clonal analysis of recurrent tumor samples from sporadic cases have suggested that it is possible to have 2 different pituitary corticotroph adenomas in the same gland (8). This might theoretically also occur in patients with a genetic predisposition to pituitary adenomas, with germline mutations of the *menin* or *AIP* (aryl-hydrocarbon receptor interacting protein) genes.

It is extremely important to distinguish between all these different situations to determine the likely "post-pituitary surgery trajectories" for Cushing's disease patients (Figure 1).

Anticipating residual corticotroph tumor and the risk of persistent/recurrent hypercortisolism

In the immediate postsurgery period

Persistent hypercortisolism immediately after pituitary surgery, with clear confirmation of corticotroph adenoma-like tissue at pathology (Figure 1, tracks 2 and 3), is obviously diagnostic of residual corticotroph tumor. Caution is needed, however, to ensure that hormone evaluations are conducted a sufficiently long time after surgery (several days or a few weeks) because in rare patients cortisol secretion normalizes only gradually.

Residual corticotroph tumor may be suspected if the surgeon had technical difficulties, was not able to identify the adenoma, or found an adenoma with nonanticipated evidence for dural invasion.

During follow-up of patients after "immediate success" (Figure 1, track 4)

- Rigorous evaluation of the ACTH-adrenal axis may reveal subtle suggestive features when the patient is still "eucortisolic" (normal UC): lack of circadian variation of "normal" cortisol plasma values, and ACTH and cortisol responses to the desmopressin test (9). The major value of the desmopressin test in patients with ACTH-dependent Cushing's syndrome is to establish the responsiveness status of the corticotroph adenoma (the test does not adequately distinguish Cushing's dis-

ease from ectopic ACTH tumors, about 30% of the latter also respond).
- Pituitary MRI is key. Analyzing the postsurgical content of the sella turcica is a difficult task, and false-positive images are frequent. The best evidence for residual tumors, rather than a nonspecific "postsurgical scar," is the growth of the feature with time. Careful analysis of imaging results is essential when possible subsequent pituitary surgery is considered. Therefore, systematic post-pituitary surgery MRI at 3 months is essential for all Cushing's disease patients, including those who are apparent cases of "immediate success" at this time.
- In many cases there may be no clues in the case history or in the biological or imaging findings that recurrent Cushing's disease should be particularly feared, but nevertheless recurrent hypercortisolism may occur. It is our policy that every single patient scored as an "immediate success" after pituitary surgery for Cushing's disease should be followed for life. This is not easy to explain to a patient who is told that he/she has been "cured."

Demonstrating persistent/recurrent hypercortisolism

Persistent hypercortisolism ("immediate failure")

Persistent hypercortisolism is easy to demonstrate if pituitary surgery is a total failure, and there is simply no improvement in the biological criteria that led to the diagnosis (Figure 1, track 2). In other patients (Figure 1, track 3), there may be some improvement, but the criteria for hypercortisolism (see *Recurrent hypercortisolism*) are still present.

Recurrent hypercortisolism (after "immediate success")

The clinical diagnosis of recurrent hypercortisolism can be difficult. It is indeed a challenge to correlate common and nonspecific clinical features (such as obesity, diabetes, high blood pressure, and mood disorders) with mild and mildly progressive cortisol oversecretion. Difficult decisions have to be taken in cases of weak or partial clinical/biological evidence of recurrence.

The biological diagnosis of recurrent hypercortisolism is based on the same principle that is used to diagnose Cushing's disease. Increased UC is generally accepted as the "gold standard." Elevated midnight serum and/or salivary cortisol titers are widely used as alternatives, and a recent study suggests that these markers may be more sensitive for the early detection of recurrence (10). Dexamethasone suppression tests can be informative, although they have probably been less widely used in recent times.

Repeat pituitary surgery

Pituitary surgery in Cushing's disease has 2 formidable advantages: obviously, it can be successful; but also in cases of failure, all other therapeutic options remain possible, including repeat pituitary surgery.

Repeat pituitary surgery should be systematically envisaged, given the unique quality of cure such surgery can provide (see *The perfect treatment*). However, repeat pituitary surgery generally has a lower rate of success (in the 50–60% range), and this must be weighed against the increased risk of pituitary failure and, in young female patients in particular, the risk of compromising future fertility, with the possible need of inducing ovulation (11, 12).

Immediate failure

In cases of immediate failure of pituitary surgery, some advocate rapid reoperation within weeks (13, 14). In this situation:

- The diagnosis of Cushing's disease should be systematically discussed again in view of the initial diagnosis criteria and the results of the first surgery, when there was no clear pathological evidence of corticotroph adenoma tissue being removed. If necessary, further investigations should be undertaken.
- The conditions of the first surgery should be used to determine the utility of a rapid second attempt and the likelihood that the adenoma will be found and entirely removed. In other words, why should the second operation work when the first failed?

Cases of a late recurrence

- There is no reason to reconsider the initial diagnosis of Cushing's disease.

Imaging evidence of the residual pituitary tissue indicates that there is a better chance of cure (11, 12). This again illustrates the need for reference postoperative imaging after the first pituitary surgery in "immediate success" patients.

Back to the Patient

Dialogue 1

The patient: Are we sure that I have Cushing's disease?

The endocrinologist: The likelihood is high according to your clinical history and the initial hormonal workup. However, the failure of surgery and the lack of adenoma tissue at pathology do not allow absolute certainty.

The patient: How can we be certain?

The endocrinologist: We will repeat some tests and conduct further investigations. In particular, we will perform BIPSS (I will explain it to you) that will provide us with an almost certain result.

The patient: If BIPSS is positive, then what?

The endocrinologist: We will consider repeat pituitary surgery: removing the pituitary adenoma is the best thing that can be offered to a Cushing's disease patient, and everything should be done to be sure that you have been offered the best possible treatment.

The patient: Why should a second pituitary surgery do better than the first?

The endocrinologist: We suggest that you have the second operation for the following reasons:

- *BIPSS provides almost absolute certainty that your pituitary does (or does not) harbor a corticotroph adenoma.*
- *We think that local operative difficulties prevented optimal exploration during the first surgical intervention, such that it is worth trying again with a highly skilled surgical team; in general, we have a better than 50% chance of immediate success on second surgery.*
- *In any case, we will take no risks with your overall anterior pituitary function, and particularly we will protect the gonadotropic axis and your chances of remaining fertile.*
- *The patient: If the operation is successful, will there be a risk of recurrence?*
- *The endocrinologist: The risk can never be completely eliminated, and we always recommend lifelong monitoring. If there is recurrence after a second, partial hypophysectomy, all other therapeutic options will remain open.*
- *The patient: OK, let's go with your propositions.*

Immediate success after the second pituitary surgery

The BIPSS showed a clear central/peripheral gradient (baseline and after CRH stimulation), and a desmopressin test induced a brisk ACTH surge (not for diagnostic reasons but as a pharmacological marker of the corticotroph tumor for follow-up). Repeat MRI at 3 months, just before surgery, did not identify a clear image of adenoma.

Cautious surgery avoided bleeding such that adenomatous tissue was successfully visualized in the left part of the gland, allowing an apparently "complete removal." Pathology confirmed the corticotroph adenoma consisting of monomorphic tumor cells staining exclusively with ACTH antibody.

Two weeks after surgery, both serum cortisol (less than 10 ng/ml) and ACTH (less than 5 pg/ml) were undetectable, with no response to desmopressin.

The patient had apparently jumped from track 2 . . . to track 5 (Figure 1)!
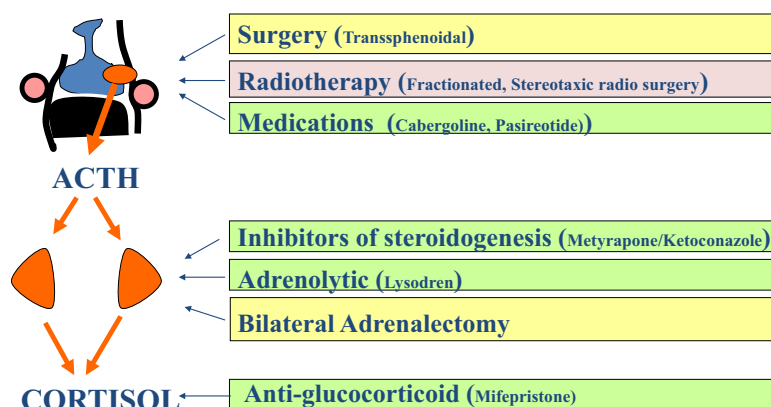
Figure 2. The therapeutic targets in Cushing's disease and the corresponding therapeutic approaches.

Follow-up after the second pituitary surgery

The patient's clinical features rapidly improved: she lost weight, she remained normotensive off medications, and she resumed spontaneous menses 1 month after surgery.

Pituitary MRI 3 months after the second surgery showed a definitive reduction in the left part of the pituitary.

The patient was followed regularly, and her condition was stable for 2 years.

After 2 years, although she was clinically and biologically eucortisolic (normal UC), the desmopressin test showed unequivocally positive ACTH and cortisol responses.

After 3 years she presented with evidence of clinical recurrence (amenorrhea, weight gain), and unequivocal biological hypercortisolism. The comparison of her pituitary MRI with that 3 months after the last surgery revealed evidence of new tissue growth in the left part of the sella, highly suggestive of an invasive adenomatous tissue remnant.

The patient was now 33 years old and just married, although not wanting a baby, yet!

The "Nonpituitary Surgery" Therapeutic Approaches to Cortisol Excess

After pituitary surgery has definitely failed, there are still 3 targets that can be exploited to control cortisol excess in Cushing's disease patients (Figure 2). We can:

- Oppose ACTH production by radiotherapy, and/or anticorticotroph drugs.
- Oppose cortisol production by antiadrenocortical drugs or adrenal surgery (antagonists to the ACTH receptor are not yet available for human use).
- Oppose the effects of cortisol with the antiglucocorticoid, mifepristone (RU 486, Korlym).

Targeting the pituitary corticotroph adenoma

Pituitary radiotherapy

Pituitary radiotherapy can in some cases control ACTH oversecretion and recurrent hypercortisolism, as well as tumor growth. Depending on local availability it can been performed in different ways, either classically by conventional fractionated radiotherapy, or by stereotaxic radio surgery (gamma knife or proton beam therapy).

In all cases, radiotherapy acts gradually on the tumors, and success rates for controlling hypercortisolism are very different between series, depending in part on the doses administered and the time of observation. In general, it is not better than 50% at 2 years, although success increases further with time (15–17). There is no clear evidence that stereotaxic radio surgery accelerates the time to disease control. Thus, it is not a treatment option for a rapid cure, at least when used alone. In most studies, this approach has been combined with medical therapy, usually inhibitors of steroid synthesis.

Also, radiotherapy does not "spare" the normal pituitary tissue, and failure of some pituitary functions is expected in up to 50% of the patients. There is no clear evidence that targeted stereotaxic radio surgery minimizes this adverse effect. There is also a potential risk of cerebrovascular complications, although these are probably minimized with modern radiotherapy techniques (18, 19).

Radiotherapy is indicated if the oncogenic characteristics of the pituitary adenoma are apparent and, for women, if there is no fertility issue. Good targets for stereotaxic radio surgery are well-visualized small adenoma remnants showing evidence of growth at repeat MRI, with suspicious invasive characteristics close to the cavernous sinus.

Medical treatments

Two classes of drugs can act directly on the corticotroph adenoma to reduce ACTH secretion. Dopaminergic and somatostatinergic drugs can reduce ACTH secretion from the corticotroph adenomas that express their respective receptors. However, they clearly have limited efficacy, and sometimes serious adverse effects, which is why they are not considered as first-line options. Because they can be very effective in some individual patients (20) (Figures 3 and 4), they should be considered after the failure of pituitary surgery or for cases of late recurrence.
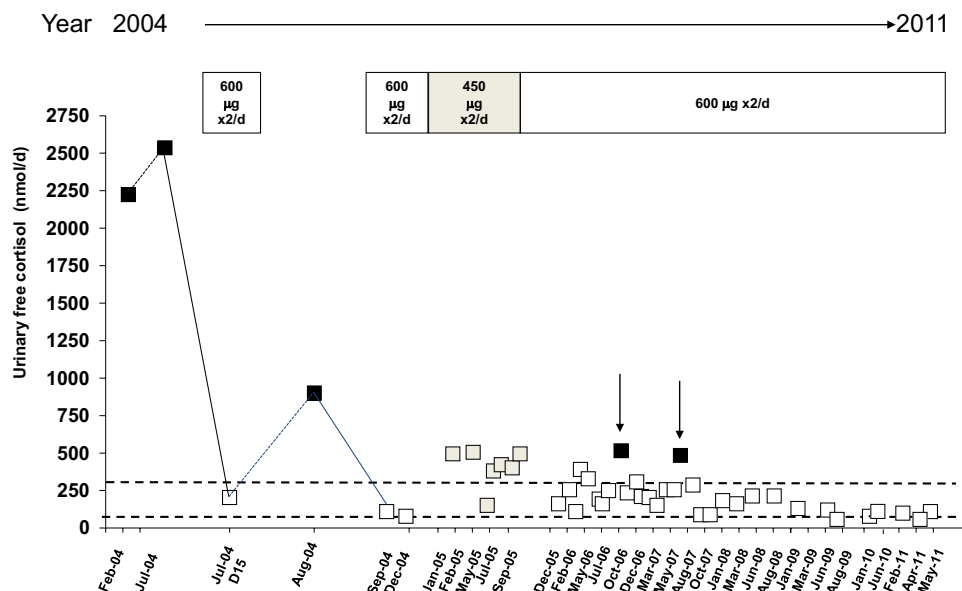
Figure 3. Pasireotide after failure of pituitary surgery. Seven years continuous control. UC is shown under treatment (□) or off treatment (■); UC is constantly normal under 600 μg twice daily, whereas it was slightly elevated under 450 μg twice daily, and on two occasions when treatment was shortly interrupted (vertical black arrows). [Adapted from R. Libé et al: Pasireotide in Cushing's disease. *N Engl J Med*. 2012;366:2134 (20), with permission. © Massachusetts Medical Society.]

Cabergoline. Several studies have reported that this dopamine D2 receptor agonist can normalize UC in about 30% of Cushing's disease patients (21–23). For unknown reasons, some patients seem to escape from treatment efficacy after a few months of treatment. Other than the adverse effects common to all dopaminergic drugs, cabergoline is generally well tolerated.

Pasireotide. Pasireotide is a new somatostatin analog (SOM 230) that, in comparison with octreotide, has higher affinity toward the type 5 somatostatin receptor, explaining its beneficial action on corticotroph adenomas (24, 25). A large multicentric phase III trial (actually comparing 2 different doses of the same drug) reported that doses up to 900 μg twice a day given as sc injections were effective in some Cushing's disease patients: 50% of the patients showed a definitive decrease in UC from baseline, although UC was eventually normalized in only 26% of the patients (26). The classic, mainly gastrointestinal adverse events of somatostatinergic drugs were observed.
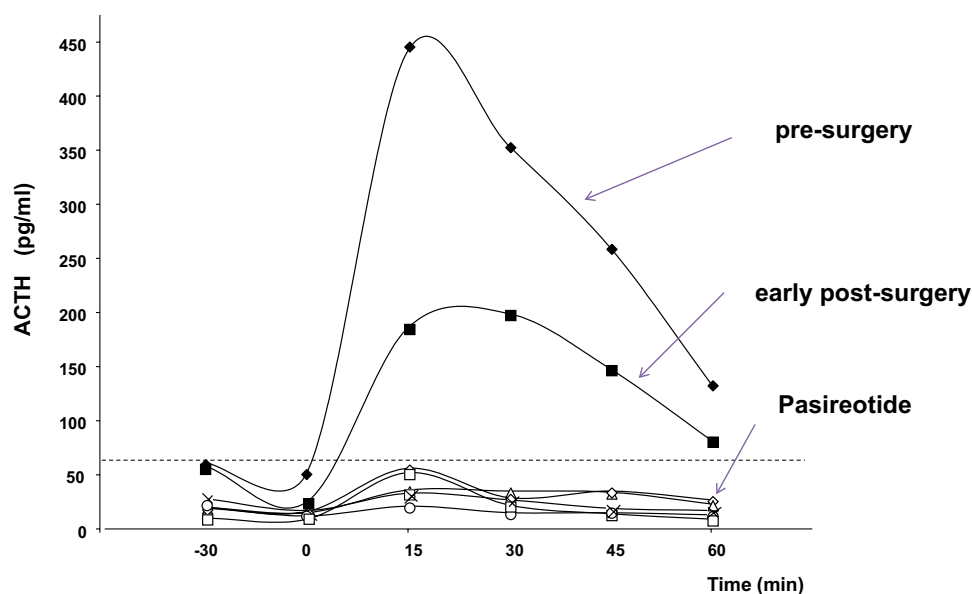
Figure 4. Pasireotide after failure of pituitary surgery. Decreased ACTH response to desmopressin. ACTH responsiveness to desmopressin is still present after failed pituitary surgery and disappears and remained negative under long-term pasireotide treatment. [Adapted from R. Libé et al: Pasireotide in Cushing's disease. *N Engl J Med*. 2012;366:2134 (20), with permission. © Massachusetts Medical Society.]

However, a major drawback of this treatment is a frequent adverse effect causing hyperglycemia events in as many as 75% of the patients, undoubtedly because the drug also inhibits insulin secretion.

Targeting the adrenal cortex

This approach can be performed medically or surgically.

Inhibition of adrenal steroidogenesis
Ketoconazole and metyrapone

- Cortisol synthesis can be rapidly suppressed with 2 oral agents that are available worldwide, ketoconazole and metyrapone (the latter under special request in the United States) (27–30). The most recent studies and the largest series in Cushing's disease are with ketoconazole, which shows a success rate of approximately 50% (31).
- Lowering cortisol in Cushing's disease patients will inevitably trigger an ACTH response by the pituitary adenoma with the risk of escape from treatment efficacy (32).
- There are various adverse effects: liver injury, androgen defects with ketoconazole, excess mineralocorticoid and adrenal androgens due to CYP11B1 blockade with metyrapone creating hypertension, edema, hypokalemia, and hirsutism in women.
- These medications are rarely used as long-term monotherapy in Cushing's disease; rather, they can be used as nonpermanent adjuncts, in preparation to pituitary surgery, waiting for the full effects of radiotherapy, or in special situations where severe hypercortisolism contraindicates immediate surgery and the rapid onset of action of these drugs is useful, particularly in combined treatment (see *Combined Targeting: The "Cushin-game"*). Particular attention should be given to hypertensive patients.

Two other inhibitors. Etomidate, given iv, is used in rare cases and particularly in emergency situations (33). LCI 699 is a new inhibitor of CYP11B2 and CYP11 B1 with promising efficacy in the first and recent trial in 12 patients with Cushing's disease (34).

A dedicated adrenolytic: Lysodren

- Of the antiadrenocortical drugs, Op'DDD (Lysodren) has a unique adrenolytic action: it specifically destroys the adrenocortical cortex, resulting in a "chemical adrenalectomy."
- Op'DDD treatment leads to reduced cortisol production in about 80% of patients with Cushing's syn-

drome. Direct indicators of plasma free cortisol, such as salivary or UC titers, are the best markers to monitor its efficiency. Cortisol production declines slowly and is only manifest after 1 or 2 months of treatment.
- Although Op'DDD is a highly effective adrenolytic drug with unique properties, its use as the sole therapy for Cushing's syndrome has several limitations. Because of its numerous, albeit not very serious, side effects (gastrointestinal effects, altered central nervous system functions, and hypercholesterolemia), its particular kinetics, and its highly variable bioavailability, it necessitates a close and repeated monitoring. Although its efficacy may last for years in a given patient, the benefits are most often only transient.
- The largest series of Cushing's disease patients on long-term O,p'DDD treatment as the sole therapy was recently reported, and UC was normalized or suppressed in 71% of the patients (35). Lysodren plasma levels above 8 mg/L were associated with the control of hypercortisolism.

Bilateral adrenalectomy

- The obvious and major advantage of this surgical option is its unequaled efficacy for controlling the hypercortisolic state. The success rate is 100%, immediately!
- This efficacy, furthermore, is permanent, in almost all patients. Unexpectedly, some patients resume endogenous cortisol secretion that may even lead to recurrence of their hypercortisolism years after a total bilateral adrenalectomy. This is not exceptional, being reported in as many as 10% of cases.
- Currently, the laparoscopic approach is standard, and several teams have reported a mortality rate of zero but some definitive morbidity. It remains a difficult surgical procedure that should be performed in referral centers, and if necessary after medical preparation. Several recent series have also assessed the quality of life (QoL) of these operated patients and showed it to be clearly improved and similar to or better than the QoL after a—somewhat—less major surgical procedure (transsphenoidal surgery) (36–38).
- Adrenalectomized patients will require lifelong steroid coverage with gluco- and mineralocorticoids, with the unavoidable constraints, need for adaptation, education, and the risk of acute adrenal insufficiency.
- The pituitary tumor, by definition, remains. However, the risk that Nelson's syndrome could occur has clearly been reduced in the modern era because of the availability of tools such as ACTH measurement and pituitary MRI, which were obviously lacking in the 1950s when Don Nelson established "his" syndrome (39). Currently, the possibility of "corticotroph tumor pro-

gression" after bilateral adrenalectomy should be considered, and recent studies (40, 41) have shown that: 1) any such progression is variable; 2) it can be detected early by repeat plasma ACTH assays and pituitary MRI follow-up; 3) when it occurs, the early stages are manageable; and 4) it is not accelerated by pregnancy. Routine pituitary radiotherapy after adrenalectomy has been debated, but it does not seem to be a validated, or necessary, procedure.

Targeting the glucocorticoid receptor

Mifepristone

Mifepristone (RU 486), originally developed as an antiprogesterone drug (and currently used in many countries as a contragestive), was also found to be an antiglucocorticoid drug potentially active in man.

Several studies and a review of them provided evidence that it could be of benefit in some cases of Cushing's syndrome, including patients with Cushing's disease (42, 43).

The SEISMIC study in the United States was the first that systematically enrolled a series of adult patients with various causes of Cushing's syndrome and type 2 diabetes mellitus or hypertension, including 42 patients with Cushing's disease after failed pituitary surgery (44). This 24-week, open-label, multicenter study administered mifepristone as a single daily oral dose (between 300 and 1200 mg/d). There were clear beneficial effects on some peripheral features of cortisol action: the mean weight dropped 5.7%; and there were significant improvements in glucose metabolism, insulin resistance, cognition, and QoL. Common adverse events were observed, and 88% of the patients experienced study-related adverse events: fatigue, arthralgia, nausea, vomiting, headache, low potassium, edema, and endometrial thickening in women often leading to abnormal vaginal bleeding.

This study shows that this original approach, that of opposing glucocorticoid action, can be effective, but it also causes problems as anticipated, given the mode of action of the drug and the pathophysiology of ACTH oversecretion in Cushing's disease (45). There are numerous questions raised by this approach:

- How to assess treatment efficacy when cortisol measurement becomes meaningless (UC actually increases 7-fold on average)?
- How to adapt the treatment (clinical judgments are based only on the peripheral—and not very specific—actions of cortisol)?
- How to diagnose adrenal insufficiency and to treat it, if necessary, when circulating cortisol levels are high?
- How to cope with side effects associated with the inescapable ACTH increase and the mineralocorticoid ac-

tions of both further increased cortisol and deoxycorticosterone (DOC) that can act at the mineralocorticoid receptor without any opposition?
- How to cope with the antiprogestin action of the drug in women, its associated adverse effects on uterine endometrium, and its incompatibility with pregnancy?

Combined Targeting: the "Cushingame"

There is a further more complex question: why not combine several treatments, acting at different levels of the pituitary adrenal axis (Figure 2), so as to improve effectiveness and reduce adverse effects. This type of approach has long been proposed, typically, for example, for patients undergoing pituitary radiotherapy and treated concomitantly with some sort of steroid synthesis inhibitor (16), or O,p'DDD (46), while waiting for the full effect of radiation therapy, and also for patients who were successively given cabergoline and ketoconazole (47).

Two "combination" approaches have been documented in rather convincing studies, in 2 contrasting situations:

- In patients with Cushing's disease severe enough for any type of surgery to be clearly contraindicated (cardiac failure, recent pulmonary embolism, etc.), a "tritherapy" approach was used. Two steroid inhibitors, ketoconazole and metyrapone, acting at different steps of steroidogenesis, and small doses of O,p'DDD, acting as a slow adrenolytic were administered (48). This cocktail was highly effective, resulting in normalization of extremely high initial UC within a few days. After a few weeks, the steroid inhibitors could be withdrawn in many cases, at a time when the adrenolytic action of O,p'DDD had been fully efficient, eliminating the risk of escape phenomena.
- In a different setting, patients with classic Cushing's disease (not severe) were "sequentially" treated with up to 3 different medications, starting with pasireotide alone first, then adding cabergoline, and finally ketoconazole, as needed (49). Under this sequential approach, most patients (15 of 17) were eventually controlled (UC normalized).

Of course, with as many of the options now available to treat Cushing's disease, any well-informed endocrinologist can exercise his or her own imagination in a sort of "Cushingame" where the best possible combination has to be identified and selected (Figure 5).

How to Choose? How to Evaluate? The Impossible Algorithm!

There are a large number of therapeutic alternatives, often with variable side effects, contraindications, rapidity of
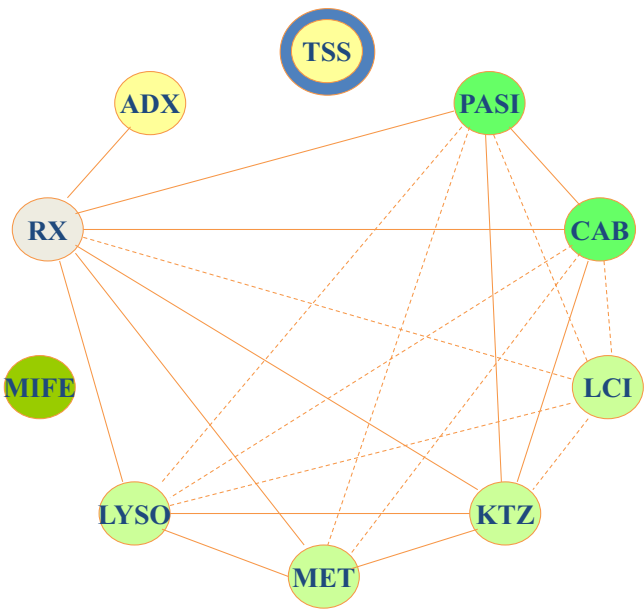
Figure 5. Combined strategies: the "Cushingame." TSS, transsphenoidal surgery; PASI, pasireotide; CAB, cabergoline; LCI, LCI699; KTZ, ketoconazole; MET, metyrapone; LYSO, Lysodren; MIFE, mifepristone; RX, radiotherapy; ADX, adrenalectomy.

action, probability of success, and other specificities making selection difficult (Table 1).

Rather than draw 1 more algorithm, essentially based on some personal intuitive feeling, we will try to present some general considerations that could help.

These comments are largely logical deductions to be applied to the current and thoroughly evaluated status of any particular patient, including his/her wishes or fears. They address the advantages and drawbacks of each individual therapeutic option.

- There are situations when immediate control of severe hypercortisolism is essential, with no time for hesitation or trial and error. The recently developed "tritherapy" approach (metyrapone, ketoconazole, and O,p'DDD) or bilateral adrenalectomy should be considered in such cases.
- When the pituitary tumor itself is a threat, radiotherapeutic approaches should be favored. Treating the hypercortisolism may be necessary with adrenal and/or pituitary directed- medications until radiotherapy is possible and effective.
- When choosing an adrenal steroid inhibitor, ketoconazole is undoubtedly more appropriate for women to avoid the consequences of elevated androgens caused by metyrapone.
- All medications, whether directed at the pituitary or adrenal, as well as mifepristone, are either contraindicated or not recommended for pregnant women. The "default" choice is often between pituitary radiotherapy and adrenalectomy. If Cushing's disease recurs during a pregnancy, in addition to symptomatic treatment for diabetes and/or hypertension, metyrapone is the drug that has been used the most often.
- In children, Cushing's disease is a difficult situation, with few studies (50). In comparison, with adults one should cautiously monitor pituitary function after radiotherapy, and fear that corticotroph tumor progression after adrenalectomy may be more aggressive than in adults. Medications may have serious adverse events that limit their long-term use.
- Complications are always possible and should be prevented by routine and standard therapeutic actions; in particular, the risk of venous thrombotic events (51) is high in Cushing's disease patients and may occur after failed pituitary surgery.

Table 1. Comparing the Various Therapeutic Approaches

Option	Action	Success Rate, %	Adverse Events	Problems
Repeat pituitary surgery	Immediate	~50	Pituitary insufficiency	
Pituitary radiotherapy	Years	~40–70	Pituitary insufficiency	Fertility
			Cerebral complications	
Cabergoline	Weeks	~40	Tolerability	Pregnancy?
				Lifelong?
Pasireotide	Weeks	~26	Diabetes	Not in pregnancy
				Lifelong?
Adrenal inhibitors	Immediate	~5	Escape	Lifelong?
Ketoconazole			Liver, androgen defect	Not in pregnancy
Metyrapone			Tolerability, excess androgens/mineralocorticoids	Pregnancy?
Lysodren	Delayed	~70	Central nervous system, gastrointestinal, liver enzymes, drug interactions...	Not in pregnancy
Adrenalectomy	Immediate	100	Lifelong adrenal insufficiency	Corticotroph tumor progression
Mifepristone	Immediate?	~60	Nausea, fatigue, hypokalemia, high blood pressure, endometrial thickening, adrenal insufficiency	Women fertility, steroid coverage, monitoring, lifelong?

- Choosing the right treatment is difficult, and evaluating its effect can be just as problematic. Any Cushing's disease patients with recurrence will be diagnosed during their regular follow-up, hopefully at a stage when the hypercortisolism is still mild. In many patients, activities of the original tumor (the pituitary adenoma) fluctuate or even cycle, so it may simply be impossible to distinguish between treatment efficacy and spontaneous fluctuations of the Cushing's disease, even when assessing ACTH.
- Most, if not all, studies examining the various therapeutic approaches in Cushing's disease have serious limitations: they are retrospective, uncontrolled, and on a limited number of patients. The Pasireotide study (26) is presented as a phase III prospective, multicenter, randomized trial, which compared 2 different dosages of the same drug.

How to Change an Endocrine Nightmare Into an Endocrinologist's Dream

There are few situations that provide an endocrinologist with as much reward as "curing" a Cushing's disease patient, but how can the nightmare of failure be avoided?

Improving the effectiveness of the pituitary surgery, and the development of new videoscopic techniques would be beneficial. Also, a better understanding of the detailed biology of corticotroph adenomas may reveal new signaling pathways to manipulate and help with the design of new drugs that are more effective than those we just happen to have (52–55). The identification of specific markers of the peripheral action of cortisol to assess its role would be valuable and better than the nonspecific clinical features that are currently used.

Back to the Patient

Dialogue 2

The patient: What is your appreciation of my present situation? Would a third attempt at pituitary surgery be a good idea?

The endocrinologist: Your recurrent hypercortisolism is due to the progressive regrowth of your pituitary adenoma. It could probably not be "totally" resected even by the best neurosurgeon because part of it is invading the cavernous sinus. In rare cases, a third pituitary surgery may have induced a success. In your case, I cannot see any good reasons for a third trial.

The patient: Is there a medical treatment for this "remnant" pituitary adenoma?

The endocrinologist: There are two.

The patient: Why not use them? Which one? And for how long do I have to take them?

The endocrinologist: One is with pills, the other with subcutaneous injections. The probability that they work (normalize your daily cortisol production) is about 20 to 30%. The present understanding is that, if they work, they should be continued indefinitely, but there have not been enough long-term observations to be certain.

The patient: Does that mean "lifelong"? And what if I want to get pregnant?

The endocrinologist: Yes. Both treatments are either not recommended or contraindicated during pregnancy.

The patient: Are there other medical treatments?

The endocrinologist: We can oppose the action of cortisol with a new drug that was just recently authorized in the United States (mifepristone, Korlym); its use is restricted to Cushing's disease patients with type 2 diabetes, which is not your case. Other types of medication work directly on the adrenals to inhibit cortisol synthesis; they can be effective, but they all have some specific adverse events. Also, like the 2 treatments we just discussed, they are either contraindicated during pregnancy or to be used ". . . if the risk to the fetus is outweighed by the risk of nontreatment."

The patient: If I understand you, as long as I do not want to get pregnant, I could try any of these medications (except mifepristone), hoping that one of them works well enough to normalize my cortisol production, without too many adverse events. If my pituitary adenoma does grow to the point that it needs a specific treatment, only radiotherapy would be of any use. If I want to get pregnant, I should stop all of these medications, and there would be a high risk of hypercortisolism recurring. Then there would be 2 options: bilateral adrenalectomy, which will definitely eliminate the hypercortisolism, immediately with 100% chance success; I will still have the pituitary tumor, that might grow, but be securely followed, and treated, if and when necessary by radiotherapy. I understand that pregnancy will not increase this risk. Alternatively, I may choose to have immediate pituitary radiotherapy, possibly stereotaxic, with a good probability of curing the pituitary adenoma and the Cushing's disease. However, this usually takes some time and may require additional, transient, medical treatment. It will also compromise pituitary function and my spontaneous fertility, such that other treatments would be needed to induce ovulation.

The endocrinologist: I see you understand perfectly.

The patient: Well, at least there will still be work for you doctors!

Acknowledgments

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