TREATMENT OF CUSHING'S SYNDROME : WHAT PLACE FOR MEDICAL TREATMENT?

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Abstract

Surgery plays a major role as a first-line treatment of the different etiologies of Cushing's syndrome (CS) and bilateral adrenalectomy (BA) is extremely effective as a second line, so that there seems to be little room for medical treatment (MT). However, during the past years several drugs acting either on ACTH secretion or cortisol synthesis have been developed, so that MT of CS might be reassessed.

After briefly analyzing the efficiency and tolerance of surgical and medical treatments of CS we try to distinguish consensual and controversial indications for MT. We believe the former include "pre-operative treatment" in rare patients in whom the severity of CS is likely to increase the risks of surgery; "inoperability" for rare patients who cannot be operated even when CS is controlled and "surgical failure or recurrence", mainly in patients Cushing's disease (CD) not in remission after TSS. Controversial indications include "unavailability of an expert surgeon", which we believe does not make sense when the cost of MT is taken into consideration. Finally in patients with the "surgical failure or recurrence" indication the balance between efficacy and side effects of MT should be balanced with the efficacy and side effects of BA.

Key words: Cushing's, pituitary surgery.

INTRODUCTION

Endogenous Cushing's syndrome (CS) represents the clinical consequences of cortisol hypersecretion. Cushing's syndrome can be related to ACTH hypersecretion by a pituitary corticotroph adenoma (Cushing's disease (CD)), or more rarely a non pituitary tumor (ectopic ACTH Cushing (EAC)), or to cortisol secretion by a tumoral or hyperplastic adrenal: adrenocortical adenoma (CPA), adrenocortical carcinoma (ACC), primary bilateral macronodular hyperplasia (PBMAH) or primary pigmented nodular adrenal disease (PPNAD) (Fig. 1). Endogenous CS is rare, the most frequent etiology

being CD, which represent 70% of the cases with an estimated incidence at 1.2 to 2.4 new cases / million inhabitants/year.

CS is associated with very significant morbidity (obesity, diabetes, hypertension, osteoporosis, amyotrophy, infections, thrombo-embolic events, cognitive dysfunction and psychiatric disorders) and some cardiovascular or infectious disease related mortality so that effective treatment of CS is of the highest importance to patients.

As all etiologies of CS are of tumoral origin (except for "pseudo Cushing" also called non neoplastic Cushing's syndrome (1)), surgical removal of the ACTH or cortisol secreting tumor (or hyperplasia) is a logical and very effective treatment, which makes "specific" surgery the first line treatment in most patients. Furthermore in all etiologies of CS, except recurring ACC, failure of specific surgery will lead to persistent or recurring CS due to hypersecretion of cortisol by normal or hyperplastic adrenals that can be removed by surgery: bilateral adrenalectomy (BA) will provide remission of CS to almost all patients with CS who have not been cured by "specific surgery", which makes it a very effective second line treatment.

This appears to make little room for medical treatment of CS but during the past years some new agents have been introduced, such as pasireotide, mifepristone and some "older" drugs, such as cabergoline, ketoconazole, metyrapone and mitotane have been better evaluated, so that it might be useful to reassess the place of medical treatment (MT) of CS. We will first review the efficacy and side effects of the different surgical and medical treatments of CS so that we can better discuss the place of MT. This review will be brief and for more details on treatment of CS we direct the reader to the reference reviews (2-5).

This paper is dedicated to the memory of Carmen Vulpoi, Professor of Endocrinology and President of the Romanian Society of Endocrinology, friend and co-worker in many francophone projects.

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Figure 1. Causes of Cushing's syndrome CD: Cushing's disease; EAC: Ectopic ACTH Cushing; PBMAH: Primary Bilateral Macronodular hyperplasia; CPA: Cortisol producing adenoma; ACC: Adrenocortical Cancer.

Figure 2. Medical treatments of Cushing syndrome. CD: Cushing's disease. CS: Cushing's syndrome.

Efficacy of surgical and medical treatment of CS

Efficacy of "Etiologic" surgery of CS

Surgery is almost always the first line treatment for CS and this is due to the high remission and cure rates offered by the different types of surgeries specific for the different etiologies.

Transsphenoidal surgery of pituitary corticotroph adenoma in CD

In CD transsphenoidal surgery (TSS), which now uses an endoscopic approach, offers a remission rate of 80 to 90% when performed by an expert

neurosurgeon, with a 10 year recurrence rate around 20% (4). Importantly, expert neurosurgeons have a remission rate almost as high (74%) in patients with CD corticotroph adenoma which are not visualized at MRI despite a pituitary ACTH gradient at bilateral petrosal sinus sampling (6).

The limitation of TSS is essentially adenoma invasion of the cavernous sinus, a problem more common in corticotrophic macroadenomas, whose remission rate is lower (50%), but which remain a minority.

Surgical resection of extra pituitary ACTH secreting tumor

In EAC surgical removal of the tumor offers a high remission rate in the most frequent well differentiated carcinoid ACTH secreting tumor (2, 7). Bronchial carcinoid tumors do not necessarily require lobectomy and can be managed by more limited resection procedures but lymph node dissection may be necessary. Pancreatic endocrine tumors require partial pancreatectomy appropriate to the location of the tumor. For ACTH-secreting pheochromocytomas adrenalectomy requires prior control of hypertension by combining alfa-blockers, secondarily associated with beta-blockers.

The limitations of surgery of EAC are linked to the aggressivity and dissemination of the tumor responsible for ACTH secretion. Surgery is not appropriate for poorly differentiated and highly proliferative endocrine tumors that require chemotherapy, while less aggressive metastatic tumors may benefit from anti tyrosine kinase

therapies, somatostatin analogs or internal vectorized radiotherapy. Some distant metastases can benefit from locoregional treatment: radiofrequency, cryotherapy, chemoembolization.

Unilateral adrenalectomy for cortisol secreting adrenal tumors

In cortisol producing adrenal adenoma (CPA) unilateral adrenalectomy cures 100% of CPA and uses a laparoscopic approach, while in ACC adrenalectomy, which should be done by an expert surgeon, will generally require a laparotomic approach and may need to be completed by en bloc resection of surrounding organs and lymphadenectomy (8). Such ACC surgery will induce at least short term remission of CS in most patients with cortisol secreting ACC. Limitations of surgery for the control of CS related to ACC are secreting metastasis, one of the rare causes of CS that cannot be cured by BA.

Unilateral adrenalectomy for primary bilateral macronodular hyperplasia (PBMAH)

In PBMAH unilateral adrenalectomy (UA) offers a 85 to 100% remission rate (9, 10) with a 20% recurrence rate. Patients who are not cured by UA or who recur may need BA, and a recent study suggests that long term outcome of PBMAH treated by UA may include some mortality, related to persistent or recurrent autonomous cortisol secretion (10).

In all the etiologies listed above surgery will on the long term preserve adrenal function, after a period of post operative secondary adrenal insufficiency (AI), so that on the long term the patient will not be exposed to the morbidity and mortality of definitive AI.

Efficacy of Bilateral adrenalectomy

Bilateral adrenalectomy (BA), which can generally be performed by laparoscopic surgery, offers remission of CS in virtually 100% of the patients with any cause of CS that has not been cured by etiologic surgery, except for recurring or metastatic cortisol secreting ACC.

Although BA generally provides a definitive cure for CS, at the price of total and definitive AI (see below), it does not solve the potential complications related to the origin of CS such as tumoral progression of the corticotroph adenoma (Nelson's syndrome) in CD or progression of the ectopic ACTH secreting tumor in EAC.

Efficacy of Pharmacological treatments

All medical treatments of CS aim to normalize at least quantitatively the secretion of cortisol, as assessed by the normalization of urinary free cortisol (UFC), except for mifepristone, which acts as a

glucocorticoid receptor antagonist (11, 12).

Inhibitors of cortisol synthesis

At the adrenal level different steroidogenic enzymes inhibitors are available, including the CYP 17 and CYP11B1 inhibitor ketoconazole (efficacy 50 %) (13), the CYP 11B1/ CYP11B2 inhibitor metyrapone (efficacy 43%) (14). Recently another CYP11B1/ CYP11B2 inhibitor, osilodrostat, has been developed and showed up to 79% efficacy in a short term pilot study (15). Mitotane is also a steroidogenic enzyme inhibitor, but it has in addition a cytotoxic effect. It has been credited of 72% efficacy but in a study where only 7/67 patients were reported to take the drug for more than 12 months (16).

Inhibitors of corticotroph adenoma ACTH secretion

These are drugs which act on pituitary corticotroph adenoma receptors to inhibit ACTH secretion. The dopamine receptor agonist cabergoline was credited for a 40% efficacy at 1 year and 23% on long term (17) while the somatostatin receptor agonist pasireotide, in the only large prospective study of medical treatment in CS, showed an efficacy of 26% (18).

Antagonist of the Glucocorticoid receptor (GR)

Mifepristone acts as an antagonist of GR and thus does not reduce cortisol production and cannot be evaluated by UFC. It can only be evaluated by the corrections of the clinical consequences of CS such as hypertension and diabetes and has been credited with reducing diastolic blood pressure in 38% of the patients and improves glycemic control in 60% (12).

Inhibitors of abnormally expressed receptors in PBMAH

Finally some drugs are specific for the treatment of CS related to PBMAH as they target abnormal expression in PBMAH of receptors such as GIP, adrenergic or LH/hCG receptors (19) however there are few examples of long term control of CS by somatostatine, beta-blockers or GnRH agonist with many patients finally treated by UA, so that the overall efficacy of this therapeutic strategy is likely limited.

Limitations of efficacy common to all pharmacological treatments

Regarding efficacy of pharmacological treatment of CS an important point is that "quantitative" control of cortisol secretion, as assessed by UFC (except for mifepristone), does not restore a normal circadian rhythm of cortisol secretion. This is likely a significant difference when comparing medical and surgical treatment of CS as there is some evidence that

even with a normalized UFC the lack of suppression of cortisol secretion during late evening and first part of the night might be responsible for some mortality (20).

Efficacy of radiotherapy

Radiotherapy may be used to control some tumors responsible for EAC and may also be used as an adjuvant therapy in ACC but the main use of radiotherapy in the treatment of CS is pituitary radiotherapy for the treatment of CD, essentially for surgical remnant or recurrences of pituitary corticotroph adenoma. Modern pituitary radiotherapy uses gamma-knife or fractionated stereotaxic surgery. Overall radiotherapy can control approximately 2/3 of patients on long term (21) so that the use of radiotherapy generally requires the use of either pharmacological treatment while waiting for radiotherapy to be effective, or the use of BA.

Side effects of surgery and medical treatment of CS

Side effects of Transsphenoidal surgery

Serious complications of TSS remain rare: carotid hemorrhage, CSF leakage, meningitis. Less severe complications are more common, mainly sinusitis. In the immediately post-operative period complete resection of a corticotrophic adenoma is usually accompanied by profound corticotrophic insufficiency, due to the fact that the remaining normal corticotrophic pituitary cells have been suppressed by hypercortisolism and will need some months to restore their ACTH secretion, but this should be viewed as an expected consequence of surgical remission, that will recede in some months, rather than a complication. Surgical lesions of the normal pituitary may occur, including diabetes insipidus which may be followed by transient SIADH within 5 to 8 days after surgery. These hormonal complications require immediate postoperative follow-up in close coordination with an endocrinological team. Finally, there is some risk of postoperative thromboembolic complications (4).

Side effects of surgical resection of extra pituitary ACTH secreting tumor

These side effects include the morbidity of the specific surgery required for resection of the EAC tumor, such as partial pulmonary lobectomy, partial pancreatectomy, thymectomy, which can be significant.

Side effects of unilateral adrenalectomy

Unilateral laparoscopic adrenalectomy has a morbidity of 5-14% and mortality below 1% (22). In CPA UA leads to transient secondary AI in all patients and in PBMAH in 40% of the patients (9, 10).

Side effects of Bilateral Adrenalectomy

Bilateral Adrenalectomy, generally performed

by laparoscopic adrenalectomy, has a surgical morbidity and mortality that were 6% and 4% in a study including patients operated from 1990 to 2013 comparable to unilateral adrenalectomy (23). Its main side effects are obviously to result in a total (glucocorticoid and mineralocorticoid) and definitive adrenal insufficiency, which does expose the patient to the risk of adrenal crisis and is responsible for some mortality, even in educated patients (24) and even in 2018 (25).

Side effects of Pharmacological treatments

Ketoconazole

The main concern of side effect for ketoconazole is hepatotoxicity. Fatal hepatitis has rarely been described in the very large number of patients treated with ketoconazole for fungi infection (26). This serious adverse event has never been reported so far in the much smaller number of patients treated for control of CS but less severe hepatitis has been reported and the risk for potentially severe hepatotoxicity is real and justifies a close monitoring of liver enzymes at the initiation of treatment and after every increase in dosage (27). Due to its inhibition of CYP17 ketoconazole can induce suppression of adrenal and testicular androgen production.

Metyrapone

As a direct consequence of its mechanism of action metyrapone can increase production by the adrenal of both androgen and desoycorticosterone, which have some mineralocorticoid effects, and may be responsible for hirsutism, acnea, high blood pressure and hypokalemia. These side effects may be corrected by the addition of spironolactone. Metyrapone can also be responsible for non severe digestive side effects and less common side effects include hair loss (28).

Osilodrostat

The side effects of this new CYP11B1-CYP11B2 agent are still under study but it is reasonable to think that it will meet the same increase in adrenal androgen and mineralocorticoid precursor as described above for metyrapone.

Mitotane

Mitotane is often responsible for digestive side effects and can also induce neurological toxicity. Neurological toxicity is however generally observed when mitotane is used for the treatment of ACC at concentrations higher than 20 mg/mL, which are higher than the concentration required for inhibition of cortisol synthesis (29).

Cabergoline

Cabergoline can be responsible for nausea, vertigo, hypotension, which are common side effects

of dopamine receptor agonists. These side effects are frequent at initiation but will disappear in most patients, still leaving 20% of patients unable to continue this treatment on long term. Cardiac valvular sclerosis is probably not a significant risk at the doses used in CD which are similar to those used in acromegaly (30) and prolactinoma.

Pasireotide

Pasireotide is frequently responsible for digestive effects (diarrhea, abdominal pain, cholelithiasis) common to all somatostatin analogs. In addition the specific anti SST5 agonist effect of pasireotide is responsible for inhibition of insulin secretion, so that treatment for diabetes had to be introduced to 41% of the initially non diabetic patients and reinforced in 64% of previously diabetic patients (18).

Mifepristone

Mifepristone is not only an antagonist of the GR but also of the progesterone receptor, which explains a risk for endometrium hyperplasia (11).

Side effects of radiotherapy

Radiotherapy is responsible for a long term risk of hypopituitarism. In addition it has been related to an increased risk for optic nerve damage, cerebrovascular disease and for a second brain tumor, such as meningioma (21).

DISCUSSION

What place for medical treatment of CS?

From the brief analysis of efficacy and side effects reported above we propose to distinguish between “consensual” and “controversial” indications

of MT in CS (Fig. 3).

“Consensual” indications for either surgical or medical treatment of CS

Surgery without previous medical treatment

To our belief these indications include patients who are operable, with a CS not severe enough to induce increased surgical morbidity, with the following etiologies (and corresponding surgery): CD and a clear MRI image of adenoma (TSS), CPA (laparoscopic UA), non metastatic ACC (laparotomic adrenalectomy). Based on our own results we advocate that CD with a pituitary origin of ACTH secretion at BIPSS and no clear image of adenoma at MRI also belong to this category (6), but this remains controversial, as discussed below.

Medical treatment before considering surgery

These indications would include patients with very severe CS linked to EAC or CD requiring pharmacological multitherapy to avoid rescue bilateral adrenalectomy (31); patients with CS severe enough to justify medical treatment as a preparation for surgery (32); patients with EAC and occult disease, all patients who are judged to be inoperable, regardless of the severity of CS, and finally patients who refuse surgery.

Medical treatment after failure of surgery

After failure of pituitary surgery for CD, and except in the few cases where a second pituitary TSS makes sense, it seems logical to try MT first rather than perform BA right away, as some patients may experience both a good efficacy and few side effects of MT and may thus benefit from long term MT. Of note some of these patients will also be treated by pituitary radiotherapy, and in these patients there is the hope that medical treatment might be stopped when radiotherapy finally becomes effective.

Bilateral adrenalectomy after failure of medical treatment in patients with failure of surgery

The patients described just above are not so frequent, so that failure of MT in these patients should lead to BA.

Controversial indications for Medical treatment

We believe there might be 3 indications of medical treatment that are controversial: in pre-operative medical treatment the true benefits of MT are not well known in patients who do not have a very severe CS so that MT might induce a delay for remission in patients who may have been treated surgically right away. A second controversial issue, still in CD patients is the “non availability of an expert pituitary surgeon” which has been proposed as a reason for MT by some authors

Figure 3. The places of medical treatment in the management of the different etiologies of Cushing syndrome. MT: medical treatment. MPT medical pre treatment CD: Cushing's disease; EAC: Ectopic ACTH Cushing; PBMAH: Primary Bilateral Macronodular hyperplasia; CPA: Cortisol producing adenoma; ACC Adrenocortical Cancer.

(4). We believe this indication does not make much sense, as long term medical treatment is so expensive that patients who live in a country that can afford these treatments are necessarily living in a country that also has at least one expert pituitary surgeon team available, to whom the patient could be sent at a much lower price than MT and with a much higher chance of remission. In France the cost of MT of only one patient for 30 years would cover the cost of BIPSS and TSS for 15 to 90 patients, who will experience a 80 to 90% long term remission rate.

In conclusion, we think a third controversial issue might be the indefinite continuation of MT in patients with failure of surgery who are not completely in remission with MT and who might have a better long term outcome with BA.

Conflict of interest

O.C. declares having received speaker fee and/or invitation to congress by Novartis, Ipsen and HRA Pharma. J.C. has no conflict of interest.

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