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Management of Acute Hypercortisolism

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An occasional patient with Cushing's syndrome may require urgent management primarily because the chronic ravages of hypercortisolism have caused the patient to be in a precarious metabolic condition. The side effects of prolonged excess corticosteroids increase the risk of operations in such patients and must be considered in overall management. Among the many effects of hypercortisolism to be considered are hypertension, diabetes, ocular hypertension, myopathies, dermatologic changes including skin infection, pancreatitis, osteoporosis, pathological fractures, peptic ulcers, renal calculi, coagulopathies, hypokalemia, poor wound healing, and increased susceptibility to infection. The most effective way to avert these complications is by earlier diagnosis and definitive treatment of Cushing's syndrome. The present report includes a review of the etiology and diagnosis of Cushing's syndrome and the management of problems associated with hypercortisolism.

Hypercortisolism producing Cushing's syndrome is not generally considered as a condition requiring emergent surgical management. However, patients with untreated or unrecognized Cushing's syndrome may present with overwhelming, uncontrolled infection, acute psychosis, pituitary apoplexy associated with acute adrenal insufficiency, or with a concomitant disease requiring emergent surgical intervention. An occasional patient with Cushing's syndrome may require urgent management primarily because the chronic ravages of hypercortisolism have caused the patient to be in a precarious metabolic condition. The side effects of prolonged excess corticosteroids increase the risk of operations in such patients and must be considered in overall management. Among the many effects of hypercortisolism to be considered are hypertension, diabetes, ocular hypertension, myopathies, dermatologic changes including skin infection, pancreatitis, osteoporosis, pathological fractures, peptic ulcers, renal calculi, coagulopathies, hypokalemia, poor wound healing, and increased susceptibility to infection [1–4].

The most effective way to avert these complications is by earlier diagnosis and definitive treatment of Cushing's syndrome. This paper will, therefore, review the etiology and diagnosis of Cushing's syndrome and then consider the management problems associated with hypercortisolism.

Cushing's Syndrome

Etiology

The most common cause of Cushing's syndrome is the excessive administration of exogenous glucocorticoids. Iatrogenic Cushing's syndrome may be associated with any or all of the complications that may be seen in patients with endogenous overproduction of cortisol [4]. The diagnosis should be readily apparent by physical examination and an adequate history.

In the 50 years since Cushing's classic description of the clinical manifestations of pituitary basophilism, much new knowledge about the syndrome has accumulated [5]. The most common primary condition causing hypercortisolism is now known to be bilateral adrenal hyperplasia due to excess ACTH and accounts for approximately 80% of all cases [3–13]. A pituitary tumor, usually a basophilic adenoma, is the source of ACTH adrenal stimulation in 65% of patients with the syndrome. Only

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15% of pituitary tumors causing Cushing's disease were detected when only conventional skull roentgenographic studies were used. Even with sophisticated imaging procedures, some microadenomas may not be identified. They may remain undetected until the pituitary gland has been explored by modern microsurgical techniques. In approximately 5% of the patients, the excess secretion of ACTH by the pituitary will not be associated with an adenoma. It is currently believed that in this group of patients, a neurohypothalmic disturbance causes the CRF/ACTH regulatory mechanism to function improperly. A non-pituitary, ectopic, or paraendocrine source of ACTH is the cause of Cushing's syndrome in about 10% of all cases [14, 15].

Cushing's syndrome results from a functioning adrenal neoplasm in 20% of all cases. One-half of these tumors are adenomas, whereas the others are corticocarcinomas that have maintained sufficient endocrine function to produce excessive amounts of steroids. Functioning adrenal tumors secrete autonomously and inhibit the normal production of ACTH, resulting in suppression and atrophy of the contralateral adrenal gland [16, 17].

Diagnosis

Usually, the physical stigmata of Cushing's syndrome are present at the time of diagnosis. These include truncal, head, and neck obesity; plethora; hirsutism; hypertension; proximal muscle weakness and wasting; atrophic skin; purple striae; bruises; and acne of the face and trunk. Additional features frequently include amenorrhea, osteoporosis, glucose intolerance, and mental disturbance. The hypertension of Cushing's syndrome is attributed to chronic hypervolemia and is usually not severe. An occasional patient, however, may develop congestive heart failure or suffer a cerebrovascular accident as a late complication of the disease. When Cushing's syndrome is of rapid onset and severe, weight loss and pronounced generalized muscle wasting may be the predominant clinical features. This is most likely to occur in patients with malignant paraendocrine tumors producing ACTH.

The therapy of Cushing's syndrome requires that a specific etiologic diagnosis be determined. First, it must be established that the patient has Cushing's syndrome (Table 1). A loss of the normal diurnal pattern of cortisol secretion by the adrenal glands occurs in all cases. A simple screening test to make this determination is the single-dose overnight dexamethosone suppression test. If there is suppression of the 8-A.M. cortisol level, Cushing's syndrome can be ruled out. Because suppression may not occur in a number of patients who do not have Cushing's syndrome, the 2-mg dose dexamethosone test is performed as a more definitive study. Once it has been established that a patient does have Cushing's syndrome, a more precise etiologic diagnosis is determined by plasma ACTH levels, high-dose dexamethosone suppression, and metyrapone tests. These tests will determine whether the hypercortisolism is pituitary ACTH dependent, due to ectopic ACTH, or caused by an autonomously secreting corticoid neoplasm (Table 2) [3, 6, 18].

Most pituitary adenomas causing Cushing's disease are too small to be detected by radiological techniques formerly used, including angiography and pneumoencephalography. Computed tomography (CT) has replaced multidirectional tomography as the imaging procedure of choice in preoperative evaluation of those patients without obvious enlargement of the pituitary fossa. CT sections 2 mm or less with coronal-sagittal reconstruction allow for precise visualization of bony structures of the pituitary fossa and sphenoid sinus. Also, the cavernous portion of the carotid artery, cavernous sinus, pituitary gland with microadenoma, and suprasellar cistern can all be seen on one examination [8, 13, 17, 19, 20].

Treatment

Thirty years ago patients with Cushing's disease were frequently treated by bilateral adrenalectomy [9]. Patients with demonstrated pituitary tumors were treated with hypophysectomy or pituitary radiation therapy. The recognition of the high incidence of pituitary microadenomas has, however, resulted in a revolutionary change in the management of Cushing's syndrome in recent years. Currently, the most popular definitive treatment of Cushing's disease in which a basophilic ACTH-secreting adenoma is assumed or proven to be present, is the transsphenoidal microsurgical technique. It is a therapeutically successful procedure with minimal morbidity and mortality when performed by a skilled neurosurgeon and considered the treatment of choice in many centers [7, 8, 10, 12, 13, 20]. Bilateral adrenalectomy with radiation therapy to the pituitary remains as an effective alternative therapy [9, 21]. External irradiation of the pituitary from conventional sources, as a definitive treatment, has largely been abandoned because it was frequently ineffective and was associated with delayed remissions of from 6 to 18 months even when a response did occur. Newer techniques including closed stereotactic radiosurgery, interstitial irradiation, and proton beam irradiation are currently being evaluated and may prove to be satisfactory alternatives to surgical therapy. One of

Table 1. Screening tests for Cushing's syndrome.

Test	Method	Normal	Cushing's syndrome	Comments
Plasma cortisol (A.M./P.M.)	Blood sample	A.M. 3–34 μg/100 ml P.M. 0–22 μg/100 ml	Loss of A.M. and P.M. variation; elevated	Many false-positive and false-negative values. Loss of variation in acutely ill and alcoholic patients
Urinary free cortisol	24-hour urine collection	≤108 μg/day	Elevations >108 μg/day	Useful screen when a reliable 24-hour urine can be obtained. Few false-positives and false-negatives
Urinary 17-hydroxy and 17-ketosteroids	24-hour urine collection	3–7 mg/day/g urine creatinine	>9 mg/day/g urine creatinine	Much overlap between normal and Cushingoid patients and those with Cushing's disease
Single-dose overnight dexamethasone suppression	Administer 1 mg dexamethasone orally at midnight. Measure A.M. plasma cortisol	<3.5–10 μg/100 ml (depending on assay method)	No suppression. Levels >3.5–10 μg/100 ml	Low incidence of false-negatives. False (±)'s in patients on dilantin or estrogens
2 mg low-dose dexamethasone suppression	Administer 0.5 mg dexamethasone orally every 6 h for 2 days. Measure 24-hour urinary 17-OH steroids	<2.5 mg/24 h/g urine creatinine	≥4 mg/day/g urine creatinine	Definitive diagnostic test for Cushing's syndrome

Table 2. Tests to determine etiology of Cushing's syndrome.

Test	Method	Adrenal adenoma	Pituitary adenoma	Ectopic ACTH	Nodular hyperplasia	Comments
High-dose dexamethasone suppression	Obtain baseline 24-hr urine 17-OH steroids. Administer 2 mg dexamethasone orally every 6 h for 2 days. Measure 24-h urine 17-OH steroids on second day of test	Nearly all patients fail to suppress to 40% baseline	Nearly all patients do suppress to 40% baseline	No suppression in 75% of patients. Tumors may exhibit cyclic hormonogenesis	No suppression in most patients	Most useful in distinguishing pituitary disease from non-pituitary causes of Cushing's syndrome
Plasma ACTH levels by RIA	Blood sample	Low or undetectable	Normal or elevated	Normal or elevated	Normal, elevated or low levels	Important to determine adrenal adenoma vs. ectopic ACTH
Metyrapone test	Administer 750 mg metyrapone orally every 4 h for 6 doses. Obtain urinary 24 h 17-OH steroids day before, day of, and day after metyrapone	Fall in urinary 17-OH steroid excretion	Increase in 17-OH steroid excretion	About ½ of patients will show an increase (small sample tested)	About ½ of patients will show an increase (sample tested is small)	Dilantin or estrogens increase hepatic metabolism

the real drawbacks to bilateral adrenalectomy, in addition to the critical need for life-long replacement therapy, is the development of Nelson's syndrome in 20–40% of long-term surviving patients [22, 23]. This complication can be decreased by pituitary irradiation, but some patients eventually develop enlarging pituitary tumors and show the stigmata of excess ACTH secretion. The most compelling reason to consider adrenalectomy is that the operation immediately cures hypercortisolism. One of the advantages of transsphenoidal pituitary microsurgery is that it can be performed in relatively poor risk patients. Another major advantage is that most patients do not require replacement therapy permanently.

Currently, bilateral adrenalectomy is reserved for those patients in whom other forms of therapy including drug, radiation, and/or transsphenoidal microsurgery have failed or when the severity of Cushing's syndrome requires urgent definitive cure.

Another alternative to either surgery or pituitary irradiation for the definitive treatment of Cushing's disease is drug therapy with mitotane (Lysodren®, or o,p'-DDD). This drug inhibits the biosynthesis of cortisol and, when administered long-term, destroys the cortical cells in the zona fasciculata. Schteingardt treated 36 patients at the University of Michigan with low doses of mitotane and achieved a remission in 29 patients that persisted after the drug was discontinued [11]. The failures of this therapy were eventually treated with either transsphenoidal microsurgery or bilateral adrenalectomy.

Each of the previously mentioned therapeutic measures will continue to play some role in the management of Cushing's disease. Those patients with the severest metabolic derangements from advanced disease, presenting to a surgeon, may require bilateral adrenalectomy because the other acceptable alternatives have already failed.

One additional indication for bilateral adrenalectomy is primary adrenal nodular hyperplasia, a rare disease of obscure etiology that usually occurs in young patients. In this disease, ACTH levels are either low or completely suppressed and even high-dose dexamethasone suppression of cortisol may not occur. Both CT scans and NP-59 scintiscans may show bilateral adrenal enlargement. Bilateral adrenalectomy is curative. Radiation therapy to the pituitary is not indicated in these rare cases.

In patients with the ectopic ACTH syndrome producing Cushing's syndrome, the onset of disease may be very rapid. The presenting features typical of Cushing's syndrome are frequently absent. These patients often have pronounced generalized muscle wasting, weakness, and weight loss. They also have symptoms or findings from the primary neoplasm secreting ACTH. Unfortunately, 60% or more of such patients will have a highly malignant pulmonary neoplasm. The prognosis in these cases is poor, and usually complete resection of the primary neoplasm cannot be accomplished. Occasionally, radiation therapy or chemotherapy may be beneficial. When the primary tumor is an apudoma, surgical resection may be possible for cure. Cushing's syndrome has been associated with carcinoid tumors, medullary carcinomas of the thyroid, thymomas, and less frequently islet-cell tumors of the pancreas. Even when these have not been cured by surgical resection, debulking procedures may be palliative and furthermore, some response may be obtained with further therapy directed to the primary tumor using both radiation and/or chemotherapy. Whereas ACTH levels have been reported to decrease in patients with metastatic disease who have undergone irradiation of their primary lesion, this should not be expected to be very effective in most cases. Bilateral adrenalectomy may be considered in patients with unresectable primary tumors in whom the prognosis is fair to good. A trial of either metyrapone or o,p'-DDD should be attempted first, however. If the response is good and the drug tolerated, bilateral adrenalectomy may be avoided. It is important to monitor closely any patient being treated by drug therapy with steroid levels and to be aware that severe metabolic derangements, especially hypokalemia, hypochloremic alkalosis, gastric ulceration, hypercalciuria with formation of renal calculi, psychosis, or overwhelming sepsis may occur if the response is not sufficient. Some patients who do not respond to medical therapy will require urgent bilateral adrenalectomy after expeditious correction of electrolyte and other metabolic abnormalities.

Adrenal Neoplasms

Although there is a confusing variety of therapeutic measures available for the treatment of Cushing's disease, there is no controversy about the treatment of hypercortisolism caused by an adrenal adenoma. Surgical excision through a unilateral posterior approach through the bed of the 12th rib is curative. Furthermore, after a period of 3 to 6 months, the contralateral, suppressed adrenal gland recovers function and steroid replacement therapy may be withdrawn. A unilateral posterior approach is associated with less morbidity than an anterior transperitoneal operation. This requires that the tumor be localized preoperatively. Lateralization can be obtained in nearly all patients by computed tomography. Important additional information, however, can be obtained from iodocholesterol or NP-59 scintiscans. Characteristically, an adenoma will

show unilateral uptake, confirming that the tumor is benign. There will be no uptake on the contralateral suppressed side. In contrast, an adrenocortical carcinoma causing Cushing's syndrome is incapable of sufficient NP-59 uptake for imaging. Therefore, the presence of bilateral nonvisualization of the adrenal glands in a patient with clinical and biochemical evidence of Cushing's syndrome is presumptive evidence of malignancy [24]. An anterior surgical approach is used in operations for patients with adrenocortical carcinoma. A curative procedure is attempted when feasible. Efforts are made to remove as much tumor as possible even when distant metastases are present. The patient is then started on mitotane, 6 g per day, and tapered to a well-tolerated 2 g per day dose within several weeks. The lower dose is usually well tolerated and maintained indefinitely. In a series of 23 patients with adrenal carcinoma treated at the University of Michigan, 6 patients who underwent resection of the primary tumor and/or local radiation therapy but received no chemotherapy survived for an average of only 10 months [17]. In contrast, 17 patients who were treated with mitotane had a mean survival of 47 months. The longest survival times occurred in a group of patients who received mitotane as adjuvant therapy before clinical evidence of metastases was noted and in those who were treated with mitotane and repeated surgery for recurrent tumor. The mean survival for this group was 74 months. Several patients treated with mitotane for pulmonary metastases experienced reduction in the size or disappearance of the lesions. With the improved survival of patients with adrenal carcinomas who have received combined surgical and mitotane therapy, aggressive efforts to excise as much tumor as possible appear fully justified. If recurrence of tumor occurs after initial response, repeated debulking operations are indicated.

Drug Management of Cushing's Syndrome

Although drugs do not cause remission of Cushing's syndrome as rapidly as either pituitary microsurgery or bilateral adrenalectomy, they have proven useful in preparing some patients for operation and more recently as definitive therapy in others [11, 25]. The use of drugs requires a thorough understanding of their mechanism of action, dose schedule, and side effects. Treated patients require careful clinical and biochemical assessment during therapy and careful supervision. The most commonly used drugs in the treatment of Cushing's syndrome and in replacement therapy will be considered in this section. Dosage schedules for these drugs are given in Table 3.

Centrally Acting Drugs

The purpose in using these drugs is an attempt to suppress secretion of ACTH by the pituitary gland. Theoretically, these drugs should be most effective in patients with a disorder of the CRF/ACTH regulatory mechanism and in patients with Cushing's disease due to microadenomas [26–32].

Cyproheptadine, a serotonin antagonist, has been used with mixed results [26–28]. Its mechanism of action is believed to be the inhibition of CRF at the hypothalmic level, as this hormone's release is mediated by serotonin. In 3 patients treated by Krieger, cortisol levels returned to normal [27]. There was prompt, objective, and subjective clinical improvement, but the follow-up period was short. In one patient, symptoms recurred as soon as the drug was withdrawn. Other authors have noted similar responses and have concluded that this drug is not a substitute for surgery but may be useful in improving patients with Cushing's disease in preparation for operation.

Bromocriptine is a dopamine agonist. It activates dopaminergic cells in the pituitary and may inhibit pituitary ACTH secretion in some patients with pituitary-dependent Cushing's disease. It has proven effective in the treatment of prolactin- and growth hormone–producing adenomas, but its usefulness in Cushing's disease remains to be proven [29, 30].

Enzymatic Inhibitor

Metyrapone is one of two commonly used drugs in Cushing's syndrome that enzymatically inhibit the formation of cortisol by the adrenal cortex [18, 33–36]. Its action is to inhibit selectively the hydroxylation of 11-deoxycortisol to form cortisol. Because the biosynthetic process stops at the 11-deoxycortisol level, a steroid that does not inhibit ACTH secretion by the pituitary, a resultant increase in both plasma ACTH and urinary 17-hydroxycorticosteroids will occur, providing the adrenal-pituitary axis is intact. This is the basis for the metyrapone test used to determine the pituitary's capacity to secrete ACTH. When ACTH rises in a patient after receiving metyrapone, it is of pituitary origin. If it is being secreted by an ectopic tumor, there is no increase in plasma levels when this drug is given.

This drug has been successfully used in the long-term medical management of Cushing's disease and for the preparation of patients undergoing either pituitary or adrenal operations for Cushing's syndrome. Metyrapone administration usually causes remission within weeks or months in nearly all patients with Cushing's syndrome. Unpleasant side

Table 3. Dosages of major drugs used in Cushing's syndrome.

Drug	Dosage	Comment
Metyrapone	0.25 g twice daily to 1.0 g 4 times a day, orally	Dose should reduce mean fluorogenic corticosteroid concentration to 11–14.5 μg/100 ml [18]
Aminoglutethimide	250 mg, 2–4 times daily, orally	A high percentage of patients have adverse reactions which cause them to stop the drug [16]
Bromocriptine	7.5–25 mg/day, orally	
Cyproheptadine	0.5 mg/kg/day	Has antihistamine, cholinergic, and sedative effects as well as anticholinergic ones; commonly prescribed as an antipruritic or antihistamine (Periactin)
o,p'-DDD (mitotane)	2–12 g/day	Requires 2–4 months to show full effect. Dose can be decreased, once suppression of cortisol has been demonstrated [19]. Steroids must be replaced as adrenal secretion is suppressed

effects when it is used chronically limit its use. Those include nausea and vomiting, skin rashes, acne, and hirsutism in women. It is currently used most frequently as an adjunct to pituitary irradiation, other drugs, or as preparation for operation [34].

Aminoglutethimide inhibits the first reaction of steroidogenesis, the conversion of cholesterol to pregnenolone [33, 37]. It, therefore, interrupts the production of both cortisol and aldosterone. It, too, has undesirable side effects, the most common being sedation. Currently, it is used most frequently in combination with metyrapone as palliative treatment for functional adrenal cortical carcinoma and in the preparation of patients with Cushing's syndrome for operation [38–41].

Adrenolytic Drugs

Mitotane or o,p'-DDD is a byproduct of insecticide research [25]. The drug was noted to cause selective destruction of the adrenal cortices in experimental dogs. Although the mechanism of action has not been determined, its relatively selective attack upon both the normal and neoplastic adrenal cortical cells is well established. It causes necrosis of the zona fasciculata initially, but when used for a prolonged period of time can also destroy the zona reticularis. It has been the only drug that since its clinical introduction in 1960 has proven effective in patients with metastatic adrenocortical carcinoma [16]. Side effects of the drug when used in high doses have severely limited its use. Low-dose mitotane therapy, however, is better tolerated and can be administered for prolonged periods [11, 16]. It has been shown to be of value in a high percentage of patients with pituitary ACTH-dependent Cushing's disease when combined with pituitary irradiation [11, 25]. Permanent remissions occurred in some patients after prolonged use [11]. Recently, adjuvant mitotane chemotherapy has been shown to bring about prolonged survival of patients with nonmetastatic adrenal carcinoma [16]. The most common side effects of this drug are anorexia and nausea which occur in nearly all patients. These symptoms are dose dependent and tolerated by most patients when low-dose therapy is administered. Other effects include diarrhea, vomiting, memory loss, skin rash, gynecomastia, arthralgia, and leukopenia [11]. The adrenolytic effects of mitotane occur over a 2–4-month period but may take as long as 16 months. Adrenal insufficiency occurs in responding patients. Consequently, replacement therapy with glucocorticoids should be administered as soon as a response has been demonstrated. When mitotane has been given for prolonged periods, mineral corticoid replacement therapy may also be necessary.

Table 4. Relative potencies of various glucocorticoids.

Compound	Equivalent dose
Hydrocortisone (cortisol)	20 mg
Cortisone	25 mg
Prednisone	5 mg
Prednisolone	5 mg
Methylprednisolone	4 mg
Dexamethasone	0.75 mg
Betamethasone	0.6 mg

Synthetic Corticosteroids

The most common cause of Cushing's syndrome, as was noted earlier, is iatrogenic and due to the excessive or prolonged administration of exogenous steroids. Either acute or chronic toxic effects may develop in these patients and withdrawal of the

Table 5. Protocol for glucocorticoid withdrawal.

Interval	Observation	Result	Glucocorticoid and dose
Variable	Underlying disease	Worsening of underlying disease	Variable; gradual decrements of dose to biological equivalent of hydrocortisone 20 mg/day
		Symptoms and signs of steroid withdrawal	Raise dosage for flareup of disease; continue if disease is quiescent; supplement for stress
4 wk	8 A.M. plasma cortisol	When < 10 μg/100 mg	Begin hydrocortisone 20 mg/day, then taper by 2.5 mg/day once/wk to 10 mg q.A.M. and continue this dosage; supplement for stress
		When > 10 μg/100 mg	Stop maintenance hydrocortisone; supplement for stress
4 wk to indefinite	8 A.M. 250 μg/m ACTH test (cosyntropin)	When plasma cortisol increment < 6 μg/100 ml or maximum < 20 μg/100 ml or both	Supplement for stress
4 wk to indefinite	8 A.M. 250 μg/m ACTH test	When plasma cortisol increment > 6 μg/100 ml and maximum > 20 μg/100 ml	Stop supplementation for stress

From Byyny R.L: Withdrawal from glucocorticoid therapy. *N. Engl. J. Med.* 295:30, 1976 [44].

drugs may become necessary. A variety of synthetic corticosteroids are widely used clinically. Individual compounds have considerable differences in potency and anti-inflammatory and glucocorticoid effects [42]. The relative potencies of commonly used steroids as compared to hydrocortisone are shown in Table 4. When administered in doses greater than the equivalent of 25–30 mg of hydrocortisone per day, any of these drugs can suppress the pituitary secretion of ACTH and eventually cause adrenocortical atrophy [43]. The degree of ACTH and adrenal suppression is related to the particular compound, dosage, frequency of dosage, plasma half-life, and route of administration. Compounds having a longer half-life have greater ability to suppress ACTH and probably have a greater potential for producing adrenal atrophy [42]. A regimen for steroid withdrawal is shown in Table 5. This schedule is predicated on the fact that the pituitary precedes the adrenal gland in recovering from withdrawal following steroid suppression, and that the adrenal recovery is associated with renewed responsiveness to challenge with ACTH [44]. Steroid-induced adrenal atrophy cannot be overcome by using ACTH, for reasons that are not entirely understood. It has been observed that when ACTH is used in patients after steroid withdrawal, its discontinuance results in return of the adrenals to an atrophic state [45]. Recovery gradually occurs over a period of months.

Addisonian crisis, or acute adrenal insufficiency, can develop in any patient inadequately treated following the withdrawal of steroids and in any patient treated for Cushing's syndrome with drugs, operation, or radiation therapy who becomes incapable of producing an adequate daily amount of cortisol. Acute pituitary insufficiency may be the cause when there is hemorrhage into a pituitary tumor causing edema or infarction. This complication can occur spontaneously but has also been reported after irradiation and o,p'-DDD therapy. Symptoms can range from mild meningeal irritation to severe headache, visual impairment, blindness, opthalmoplegia, cerebral infarction, and cardiovascular collapse. Treatment of acute adrenal insufficiency must be initiated immediately. A CT scan can then confirm the diagnosis by demonstrating areas of hemorrhage within the tumor or areas of low density corresponding to areas of infarction.

Following bilateral total adrenalectomy, patients require life-long daily replacement therapy with the equivalent of 25–35 mg of hydrocortisone in divided doses, with approximately ⅔ being administered in the morning and ⅓ late in the afternoon. Mineral corticoid replacement with 0.1–0.2 mg of fludrocortisone is usually required as well as glucocorticoid replacement therapy. An occasional patient may require as much as 1.0 mg daily of 9-alpha-flurocortisol to remain in good electolyte balance, however. In the post-adrenalectomy patient, an increase in steroid dose may be necessary for even minor stress and is critically important during major illnesses and operations. As a general guideline, 100 mg of hydrocortisone every 8 hours should be

begun 8 hours prior to an operation and continued through the first postoperative day. Approximately ½ of this dose may be given every 8 hours on the second day and the dosage then tapered as tolerated to maintenance levels thereafter. The schedule will vary depending upon the nature of the surgical procedure and the patient's postoperative course. Because the intravenous route may not always be continuously reliable, it may be safer to administer the first day's replacement as cortisone acetate intramuscularly. Hydrocortisone may be given as an intravenous drip or intramuscularly as the hemisuccinate or phosphate compound.

Résumé

Il est possible qu'un malade atteint de maladie de Cushing ait besoin d'être traité sans attente en raisons de troubles métaboliques sévères dus aux effets nocifs de l'hypercortisolisme chronique qui augmentent les risques opératoires et doivent être pris en considération avant tout traitement. Il en est ainsi de l'hypertension, du diabète, de l'hypertension intra-oculaire, des lésions dermiques comprenant l'infection cutanée, la pancréatite, l'ostéoporose, les fractures pathologiques, l'ulcère peptique, les calculs rénaux, les coagulopathies, l'hypokaliémie, la lenteur du processus de cicatrisation et l'augmentation de la suceptibilité à l'infection.

Le meilleur moyen d'éviter ces complications est de porter sans retard le diagnostic de maladie de Cushing et de la traiter radicalement dès que le diagnostic est posé.

Le présent rapport comporte une revue de l'étiologie et du diagnostic de la maladie de Cushing ainsi que du traitement des problèmes qui sont associés à l'hypercortisolisme.

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