Arch Jap Chir 47 (5), 613~623 , Sept., 1978

Adrenal Insufficiency in Surgical Fields

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Received for Publication July 10, 1978

Introduction

Recently adrenalectomy has been increasingly done not only for adrenal hyperfunction but also for palliation of some hormone-dependent cancers (e.g. breast cancer). The adrenalectomy is followed inevitably by permanent or transient adrenal insufficiency[8].

Anti-inflammatory steroids are being used widely for treatment of miscellaneous diseases, resulting not only to very favorable effects but also to many adverse effects. Among the adverse effects, adrenal insufficiency is the most dangerous and deceiving one to surgeons.

The adrenal galnd is composed of outer cortex and inner medulla, both of which play very important roles in maintenance of life, although they are of quite different origins and secrete their own specific hormones. While deficient secretions of catecholamines from the medulla can be almost completely compensated by secretions from the sympathetic nervous systems, deficient secretions of glucocorticoids (cortisol) and mineralocorticoids (aldosterone) from the cortex cause invariably overt or occult insufficiency symptoms. Therefore, by "adrenal insufficiency" is meant "adrenocortical insufficiency".

Although an apparently healthy people can abruptly fall into acute adrenal insufficiency, this is extremely rare. Most patients with occult chronic adrenal insufficiency develop adrenal crisis and die quite unexpectedly during stress such as surgical insults, infection and trauma. Every surgeon should be alert to possible insufficiency of the adrenal cortex before proceeding to any surgeries.

I. Etiology and Pathophysiology of Adrenal Insufficiency

Adrenal insufficiency can occur as a result of a primary adrenal lesion (primary adrenal insufficiency, Addison's disease), or as a result of lack of stimulations to adrenal cortex (secondary adrenal insufficiency) (Table 1)[9].

1) Bilateral adrenal hemorrhage (Adrenal apoplexy) and adrenal thrombosis.

Bilateral adrenal hemorrhage occurs after difficult delivery in newborns and during severe sepsis in children (Waterhouse-Friderichsen syndrome), and invariably causes sudden death.

Trauma on chest or abdomen can cause adrenal bleeding. Among 1,157 deaths due

Key words : Adrenalectomy, adrenal crisis, cortisol
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Table 1[2]
Classification of causes of adrenal insufficiency

I Primary adrenal insufficiency
A Anatomic destruction of gland (chronic and acute)
1 Infection
2 Invasion: metastatic, fungal, etc.
3 Hemorrhage
4 "Idiopathic" atrophy, autoimmune
5 Surgical removal
B Metabolic failure in hormone production
1 Virilizing hyperplasia, congenital (certain types)
2 Enzyme inhibitors (metyrapone)
3 Cytotoxic agents (o,p'-DDD)
II Secondary adrenal insufficiency
A Hypopituitarism due to pituitary disease
B Suppression of hypothalamic-pituitary axis
1 Exogenous steroid
2 Endogenous steroid from tumors

to trauma collected by Becker[2], 84 deaths were due to liver ruptures, 65 were splenic ruptures, 42 were kidney ruptures and 31 (2.7%) were adrenal bleedings.

Anticoagulant therapy for myocardial infarction, arterial embolism, thrombosis and so on can cause bilateral adrenal bleeding after 7 to 10 days of administration of coumarin or heparin[7].

Nowadays, severely burned patients can be salvaged by modern intensive cares, but some of them may succumb to adrenal bleeding a few days after an apparently smooth convalescence[1].

Recently, retrograde adrenal venography is increasingly done for diagnosis of adrenal lesions and is sometimes complicated by adrenal bleeding or thrombosis[3].

2) Surgery on the adrenal gland (Adrenalectomy).

Acute adrenal insufficiency can occur not only after bilateral total adrenalectomy but also after subtotal adrenalectomy and even after excision of a cortical adenoma.

In Cushing's syndrome due to unilateral adrenocortical adenoma, the contralateral cortex is so severely atrophied because of suppression of ACTH secretion via feed back mechanism that adrenal insufficiency can occur after the unilateral adrenalectomy or extirpation of the adenoma. Supplementary glucocorticoids should be given for a few months until the retained cortex resumes its normal function.

In patients with an aldosterone producing adenoma, on the contrary, the contralateral adrenal cortex is not atrophied and no postoperative supplement is needed in an ordinary convalescence.

Patients who underwent either subtotal or unilateral adrenactomy are, in general, expected to resume normal adrenocortical function through compensatory hyperplasia of the retained adrenal cortex in a few months. They should be, however, given enough care to

avoid occurrence of acute adrenal insufficiency (Addisonian crisis) during stress.

It is not infrequently quite difficult to know whether corticoid supplement is enough or not for each patient in various conditions. Surgeons should be acquainted to symptoms which predict adrenal insufficiency (Table 2). Slight fever, abdominal discomforts and small pulse pressure are most frequent prodromal symptoms.

Table 2

Prodromal symptoms of adrenal insufficiency

a)	general	fever, malaise, easy fatiguability
b)	digestive	loss of appetite, nausea, vomiting, diarrhea, abdominal pain
c)	skeletal	myalgia, arthralgia
d)	psychoneurotic	headache, restlessness, convulsion, coma
e)	circulatory	hypotension, small pulse pressure, tachycardia

3) Long and large administration of steroids or ACTH.

Large amounts of synthetic steroids and ACTH are given for long periods to the patients of bronchial asthma, nephrosis, rheumatism, ulcerative colitis, blood dyscrasia and so on. These drugs suppress ACTH secretion and induce adrenocortical atrophy. When administration of steroids or ACTH is discarded abruptly or decreased too hastily and also when dose of steroids are not increased during stress, the patients may fall into adrenal crisis.

Among severe adverse effects of prolonged steroid therapy collected by Nishikawa from 177 hospitals, adrenal insufficiency was observed in 60 cases (Table 3). And 21 patients died of shock due to adrenal crisis.

Table 3

Several adverse effects of steroid therapy

Adverse effects	No. of cases
Infection	338
Gastrointestinal complications	276
Psychosis	151
Diabetes mellitus	125
Acute adrenal insufficiency	60
Bone fracture	32
Cataract	16
Myopathy	15
Glaucoma	9

Severe weakness, nausea, vomiting, fever and hypoglycemia are frequently seen in

corticoid withdrawal syndrome, but severe dehydration and hypotension are characteristicaly absent owing to almost normal secretion of aldosterone.

Every surgeon should make sure that his patients received neither steroids nor ACTH in the past before attempting any surgeries. Moreover, every physician who gives his patients steroids or ACTH for long periods should inform the patients and their family about the probable occurrence of adrenal insufficiency.

4) Addison's disease.

In the past, the most frequent cause of Addison's disease was tuberculosis of the adrenal glands. Recently idiopathic atrophy of the adrenals has become the most common cause of the disease. It is postulated that idiopathic atrophy is due to autoimmune destruction of the adrenal cortex.

According to MIYAZAKI's review[5], adrenal crises were observed in 36 patients among 239 cases of Addison's disease. Masan et al. in England observed that among 56 deaths from Addison's disease, 32 patients died of adrenal crisis, and only 22 cases were correctly diagnosed before their deaths.

Every surgeon should be alert to symptoms suggesting Addison's disease (Table 4)[5].

Table 4[5]

Symptoms of Addison's disease (206 cases)

Symptoms	Ne. of cases
Pigmentation	206
General malaise weakness	178
Loss of body weight	86
Gastrointestinal	82
Nausea, vomiting	41
Diarrhea	23
Loss of appetite	73
Dizziness	24
Sexual disturbance	24
Headache	18
Psychosis	17
Alopecia	13
Arthralgia	6

5) Metastasis of malignant tumors to the adrenal gland.

Malignant tumors may cause adrenal insufficiency by their metastases to the bilateral adrenal glands. As shown in Table 5[5] among 58 patients who died of adrenal insufficiency, 15 deaths were due to adrenal metastases of cancer; primary sites of the cancer being the lung in 8, stomach in 3, urinary bladder in 1, multiple lymphoma in 2 and maxilla in 1. These facts should be kept in mind at surgery for malignancies.

6) Secondary or hypophyseal adrenal insufficiency.

Table 5[5]

Adrenal lesions found in 58 autopsied adrenal deaths

Adrenal lesions		No. of cases
Tuberculosis		34
Hypoplasia		2
Atrophy	idiopathic	1
	non-idiopathic	2
	hypophyseal?	2
Metastasis of cancer		15
Undertermined		2

Patients hypophysectomized for diabetic retinopathy, advanced breast cancer and so on and patients having hypofunction of the anterior pituitary due either to thalamohypophyseal tumors or to delivery of child may fall into adrenal crisis during stress. In this situation, secretion of aldosterone is maintained at almost normal level because the glomerular zone is controlled not by ACTH but by renin-angiotensin system. Moreover, secondary hypothyroidism due to panhypopituitarism suppresses the metabolism of glucocorticoids. Therefore, symptoms of hypophyseal crises are less severe than those of adrenal crises. And hypophyseal crises are of more hypoglycemic pattern in comparison to more electrolyte pattern of primary adrenal insufficiency.

Hyperpigmentation of the skin and mucosa due to augmented secretion of ATCH and β-melanocyte stimulating hormone (β-MSH) is seen in primary adrenal insufficiency but not in secondary.

Ⅱ Symptoms and Differential Diagnosis

Major symptoms of adrenal insufficiency are attributable either to deficiencies of cortisol (Table 6) or to deficiencies of aldosterone (Table 7)[4].

Table 6 Manifestations of cortisol deficiency[4]

1. Gastrointestinal: anorexia, nausea, vomiting, hypochlorhydria, abdominal pain, weight loss
2. Mental: diminished vigor, lethargy, apathy, confusion, psychosis
3. Energy metabolism: impaired gluconeogenesis, impaired fat mobilization and utilization, liver glycogen depletion, fasting hypoglycemia
4. Cardiovascular-renal: impaired ability to excrete "free water", impaired pressor responses to catecholamines, hypotension
5. Pituitary: unrestrained secretion of ACTH and MSH, resulting in muco-cutaneous hyperpigmentation
6. Impaired tolerance to stress: any of the above manifestation might become more pronounced during trauma, infection, or fasting

Addison's disease should be suspected whenever one sees a patient with the tetralogy of hypotension, weight loss, anorexia, and weakness[4].

Table 7 Manifestations of aldosterone deficiency[4)]

A.	Inability to conserve sodium
	Decreased extracellular fluid volume
	Weight loss
	Hypovolemia
	Hypotension
	Decreased cardiac size
	Decreased cardiac output
	Decreased renal blood flow
	Prerenal azotemia
	Increased renin production
	Decreased pressure response to cathecholamines
	Weakness
	Postural syncope
	Shock
B.	Impaired renal secretion of potassium and hydrogen ions
	Hyperkalemia
	Cardiac asytole
	Mild acidosis

Symptoms of acute adrenal insufficiency (Addisonian crisis) are quite similar to those of severe oligemic shock; loss of appetite, nausea, vomiting, headache, diarrhea, abdominal pain, dehydration, hypotension, severe muscular weakness, lethargy or coma and fever being most commonly seen.

If acute adrenal insufficiency is suspected, emergency treatment is commenced promptly and at the same time 10ml of blood is withdrawn for laboratory examinations, which will reveal in a few minutes low blood glucose, low sodium (110-120 mEq/l), high potassium (6-7 mEq/l), low Na/K ratio (less than 30), slight acidosis and high residual nitrogen.

Presumptive diagnosis will be obtained by: 1) recognition of causes and provocating factors, 2) correct observation of symptoms, 3) exclusion of other possible diseases, and 4) evaluation of responses to specific treatment. The final diagnosis is established by cortisol level in the blood obtained just before the initiation of the treatment.

Diffential diagnosis should be made from oligemic shock, coronary thrombosis, pulmonary infarction, sodium loss, severe infections such as peritonitis and so on.

Ⅲ. Emergency Treatment and Supplement Therapy

Principles of treatment consist of: 1) administration of cortisol, 2) correction of water and electrolyte imbalance, 3) correction or prophylaxis of hypoglycemia and 4) prophylaxis of infection.

A subcutaneous vein is secured promptly and 10 ml of blood is withdrawn for determination of electrolytes, glucose, blood type and cortisol level. Drip infusion of physiologic saline is started and 100-200 mg of cortisol or 20-40mg of prednisolone is injected rapidly. To the patients on the verge of death, hypertonic glucose solution (for example 50 ml of 20-50%

glucose solution added with 100-200 mg of cortisol) is rapidly injected intravenously. The initial one liter of physiologic saline containing 100 mg of cortisol and 50 mg of glucose is infused in 30 minutes. Pulse and blood pressure are measured at least every 15 minutes. Drip infusion is further continued, the infusion rate being regulated by patient's response. The aim of the infusion is to recover normal body water in 4 to 5 hours. Even in the most severe adrenal crisis, dehydration does scarcely exceed 10% of total body water, and infusion of water amounting to about 6% of patient's normal body weight is usually sufficient for correction of the dehydration. If hyperpotassemia is corrected by the above infusion, 20-40 mEq of potassium is added to one liter of physiologic saline in order to prevent potassium deficiency in the whole body. Acidosis is not so severe that admimstration of alkali is not needed. However, if blood bicarbonate is below 10 mEq/1, Meylon® is given intravenously. When blood pressure does not respond appreciably to the infusions, necessity of blood transfusions should be considered, after search for any bleeding lesions.

Sympathotonic drugs may be used to help raise blood pressure during the initial course of treatment. Araminon®, less vasoconstricting and more cardiotonic than noradrenalin, is prefered. Proternol® may also be given if pulse rate is less than 120. Susceptivity of catecholamine receptors is elevated by cortisol administration (a permissive action of cortisol), and the elevated susceptivity enhances the effects of catecholamines secreted by the body itself and help improve cardiac output and vascular tone. Therefore, administration of sympathotonic drugs is needed only for a short period, if necessary.

By the above mentioned regimen of infusions is given the total amount of 500 mg of cortisol, of which mineral effects render the administration of mineralocorticoids unnecessary. However, when synthetic glucocorticoids without appreciable mineral effects (e. g. methlyprednisolone, dexamethasone) were forced to be used, some mineralocorticoids should be given.

Any probable infection is searched for. Oropharyngeal secretions, sputa, urine and blood are collected. In the presence of neck rigidity, lumbar puncture should be done to diagnose meningitis. Adequate antibiotics should be given following the results of bacterial culture.

Steroids are given parenterally during the inititial 36-48 hours of treatment, then are given by mouth from the third day if possible. The dose of cortisol is decreased gradually reducing by 20 mg of cortisol on each succeeding day until reaching the final dose of 20 mg per day. In the presence of any inflammation or trauma, however, withdrawal of cortisol should be slowed down.

When cortisol more than 20 mg per day is given for a long period, excess cortisol may lead to edema, hypopotassemia and so on because of its mineral effects. In such a case, excess cortisol may be replaced by equivalent dose of some synthetic steroids (Table 8)[4].

Since the patients with adrenal insufficiency are very susceptive to morphine, barbiturates and sedatives (bromides), their administration should be avodied and used, if necessary, only after sufficient steroid therapy.

Table 8 Relative potencies of steroids[4]

	Gluco-corticoid activity	Mineralo-coricoid activity
Cortisol	1	1
Cortisone	0.7	0.7
Corticosterone	0.2	2
11-Deoxycorticosterone	nil	20
Aldosterone	0.1	400
Fludrocortisone	10	400
Prednisone	4	0.7
Prednisolone	4	0.7
Dexamethasone	30	2
Triamcinolone	3	nil
6α-Methylprednisolone	5	0.5

As for the kinds of glucocorticoids used for supplement therapy, the ones resembling the natural hormones are preferable to synthetic ones. Cortisol (20 mg per day, two thirds of which in the morning, and the remainder in the evening) or prednisolone is commonly used. Since these steroids have some mineral effects, it is unnecessary to add any mineralocorticoids to the supplement therapy, especially in Japanese who are taking large amounts of salt in their daily foods. In Europe and America, small amounts of DOCA or 9α-fluorocortisol (Fludrocortisone, Florief® 0.1 mg per day) are usually given.

It should be remembered that the patients with chronic adrenal insufficiency and those who were subjected to bilateral total adrenalectomy are prone to fall into addisonian crisis during stress due to trauma, infection and surgeries even if they are under enough supplement therapy. We have lost a patient who had been cured of Cushing's syndrome by bilateral total adrenalectomy. She died of addisonian crisis which was initiated by food intoxication during a trip, of which vomiting prohibited her oral intake of steroids. Patients receiving supplement therapy should be fully informed of significances of the therapy and also be instructed in early symptoms of adrenal insufficiency.

The patients are encouraged to take large amounts of carbohydrates and salt (10-15gm more than usual daily intake) when they are in stress. Preferably every patients carry an identification card which describes his adrenal condition. Some recommend the patients to carry always a syringe filled with 4 mg of dexamethasone.

About 15 years ago, we have clarifed that the adrenal glands contain larger amounts of essential fatty acids than the other organs (Fig. 1)[6]. The essential fatty acids participate in biosynthesis of steroids from cholesterol and their deficiency reduces the reserve capacity of the adrenal cortex. These facts indicate that essential fatty acids should be given sufficiently to the patients in stress.

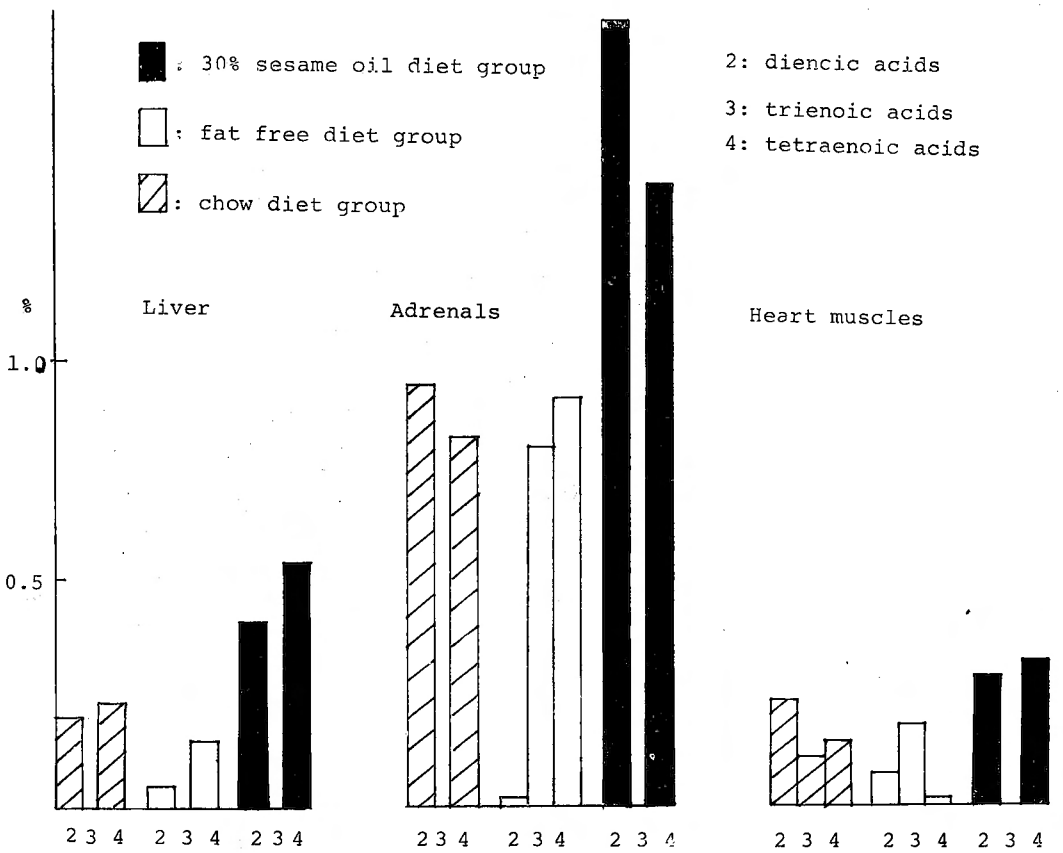

Fig. 1 Essential fatty acid concentration in various organs.[6]

Ⅳ. Surgery and adrenal insufficiency.

Although acute adrenal insufficiency can be cured by prompt and adequate treatments, its still high mortality renders its prophylaxis mandatory. Prophylactic measures are most frequently needed for the patients who have been given large amounts of steroids for a long period and are destined to undergo some surgeries. Adequate doses of steroids should be given to them before, during and after surgery in order to prevent addisonian crisis.

After a complete withdrawal of steroids which have been given in large amounts for a long period, it takes about 8 to 12 months to the thalamo-hypophyseo-adrenal axis resume its normal function. If there is an enough time, steroids are given intermittently. The intermittent administration of steroids are more effective to stimulate hypophyseo-adrenal system than traditional continuously reducing administration.

Adrenocortical reserve can be assessed by measuring plasma or urinary steroids before and during the ACTH administration.

If average daily dose of steroids which is calculated from the total amount and duration of steroid administration is less than 15 mg of predinsolone per day, adrenocortical reserve

is likely in normal range.

Conclusion

Recently prognosis of acute adrenal crisis has been greatly improved by prompt and adequate treatment using steroids, its mortality is, however, still so high that following remarks should be made.

1) Think the possibility of acute adrenal insufficiency in every patient in shock.
2) Differentiate cortisol deficiency and aldosterone deficiency.
3) First of all, infuse intravenously physiologic saline with cortisol and glucose. Then look for the cause of acute adrenal insufficiency.
4) Be alert to occult chronic adrenal insufficiency, and give enough steroids to the suspected patients before attempting any surgery.

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和文抄録

外科領域における副腎皮質不全について

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副腎の機能亢進症（クツシング症候群，アルドステロン症，褐色細胞腫）に対してのみならず，乳腺や前立腺のホルモン依存性腫瘍に対しても副腎剔除術が行なわれるが，この手術ののちには一過性または永続的な副腎皮質不全がおこり得る．

一方，現在多種多様の疾患に対して副腎皮質ステロイド製剤が広く使用されているが，その長期大量投与は副腎皮質の萎縮をきたし，慢性副腎皮質不全をおこすおそれがある．

急性副腎不全（adrenal crisis）の予後は，副腎皮質ステロイド製剤の使用によって，近時著しく改善されたとはいえ，なお相当な危険をまぬがれないから，その予防が最も重要である．

不顕性の慢性副腎皮質不全を有する患者に不用意に手術を行なうと，副腎クリーゼによる不測のショック死をきたす恐れがある．それ故，手術を企図する際には常に慢性副腎皮質不全の可能性を除外し，またショックの患者をみたならば，常に副腎クリーゼの可能性をも考慮することが必要である．

われわれの副腎手術（総計74例）の経験に基づいて，この急性，慢性の副腎皮質不全の原因，症状，治療などについてのべた．なお，副腎に他臓器とは比較にならない程大量に含まれている不可欠脂酸は，副腎におけるコレステロールからのステロイド生合成に関与しており，不可欠脂酸の欠乏は副腎皮質の予備力を低下させるものであることをのべた．