REVIEW
Early Identification and Diagnosis of Adrenal Crisis after Retroperitoneal Laparoscopic Unilateral Adrenalectomy

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ABSTRACT
The occurrence of adrenal crisis after retroperitoneal laparoscopic unilateral adrenalectomy is usually concealed. If not timely diagnosis and treatment, it may cause shock, and even lead to death. It is very difficult to distinguish the clinical manifestations of adrenal crisis from nausea, vomiting, fatigue, gas separation from the lower diaphragm, abdominal pain, hypotension, hypertension, fever and hypothermia after operation. This makes it very difficult to identify and diagnose adrenal crisis early. This article mainly discusses the early recognition, diagnosis and treatment of adrenal crisis after unilateral adrenalectomy by retroperitoneoscope.

1. Introduction
Adrenal crisis (AC) is a serious endocrine crisis caused by adrenocortical insufficiency. AC is a clinical syndrome characterized by weakness, fatigue, anorexia, abdominal pain, weight loss and hypotension. Although the prognosis of patients with AC has been significantly improved since the advent of synthetic glucocorticoids, adrenal crisis is still one of the main causes of death after unilateral adrenalectomy due to atypical symptoms and difficulty in early identification. An investigation has shown that the mortality rate of patients with adrenal crisis can reach 0.5%~2% of patients with adrenal cortical dysfunction. So far, the description of AC in the international classification of diseases (ICD10) is only a note of “severe adrenal insufficiency”. It does not give any accurate definition of AC symptoms or signs. Therefore, we cannot achieve a unified definition of adrenal crisis. Although Allolio summarized a widely accepted definition in 2015: (1) causing serious damage to health, and having at least two symptoms or signs: hypotension (systolic blood pressure < 100mmhg), nausea or vomiting, severe fatigue, hyponatremia, hypoglycemia, hyperkalemia. (2) After intravenous administration of glucocorticoid preparations, symptoms and signs can be significantly improved. However, the definition does not

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provide a time window for the onset of intravenous gluco-
corticoid replacement therapy. Through a large number of
clinical practices, we found that glucocorticoid can take
effect within 1 hour after intravenous drip. However, if
does not work, it indicates that the clinical syndrome
of the patient may be combined with other causes, or it
is not AC. Although there is no research data to prove
the incidence of AC after unilateral adrenalectomy,[7]
it is undeniable that AC should not be ignored. Most of
the clinical manifestations of AC are nonspecific, often
manifested as abnormal temperature, abnormal pain, ab-
normal blood pressure, nausea, fatigue and other atypical
symptoms. But after the operation of general anesthesia,
nausea, vomiting, wound pain, fever, hypother-
mia and other symptoms often appear. These symptoms
superimpose on the fluctuation of normal blood pressure
after unilateral adrenalectomy, which makes the diagnosis
of AC after unilateral adrenalectomy very difficult. And in
the occurrence of AC, it can also cause the adrenal gland
to produce aldosterone, which leads to the disorder of wa-
ter, electrolyte and acid-base balance while blood pressure
fluctuates violently.[9] Therefore, in-depth understanding
and early identification, timely diagnosis and treatment of
AC has very important clinical significance.[9]

2. Clinical Manifestations of Adrenal Crisis

Different patients may have different clinical manifes-
tations of adrenal crisis, but there will be multiple system
abnormalities. The clinical manifestations of AC are lack
of specificity. In the early stage, only abnormal changes
of blood pressure (decreased or increased), halophilic,
anorexia, or pain (abdominal pain, muscle pain, joint
pain)[10,11]. Some patients may have high fever (body tem-
perature > 38 ℃, the temperature of some patients can be
as high as 40 ℃), while the other may show hypothermia
(body temperature < 34 ℃, or even lower than 24.6 ℃).
However, surgical procedures, anesthetic drugs, absorp-
tion of bad dead objects, incision infection and adrenal
crisis itself may cause changes in body temperature and
blood pressure[12]. Some patients will also appear dry skin
mucosa, poor elasticity and other dehydration performance
and fatigue. The above symptoms can worsen rapidly in
tens of minutes or several days, and even life-threatening
[13]. The main clinical manifestations of each system are as
follows.

2.1 Circulation System

Due to the deficiency of glucocorticoid, the permissive
effect of catecholamine is weakened, and the balance of
water and sodium is disordered, which changes the effec-
tive circulating blood volume. Therefore, the fluctuation
of blood pressure, the weakness of pulse, the dampness
and coldness of skin, arrhythmia and other symptoms, and
even shock[14].

2.2 Digestive System

Anorexia, abdominal distension, nausea, vomiting,
diarrhea, abdominal pain, and even total abdominal
colic[15] may occur, which is easy to be misdiagnosed as
acute abdomen or gastrointestinal perforation.

2.3 Nervous System

In the early stage, they may only be depressed, but
with the fluctuation of blood pressure, they may become
restless, drowsy, delirium, delirium, and even coma. If
accompanied by hypoglycemia, patients may soon appear
sweating, blurred vision, diplopia and even coma[16].

2.4 Other Performance

In addition, oliguria, hypercalcemia, hyponatremia
can occur, and blood potassium can be low or high. If not
timely rescue, it can be fatal. It can also be manifested as
pigmentation, which is mainly located in exposed and eas-
ily rubbed parts (buccal, dorsum of foot, palmar surface,
etc.), and can also appear in non-exposed positions, such
as fold of hands and buccal mucosa[17].

The symptoms of nausea, vomiting, fatigue, wound
pain, absorption heat, hypothermia may occur after gen-
eral anesthesia, and the blood pressure fluctuation after
unilateral adrenalectomy makes the diagnosis of adrenal
crisis after unilateral adrenalectomy extremely difficult.
Therefore, patients with atypical symptoms such as ex-
cessive fatigue, fatigue, nausea, vomiting, dizziness, skin
pigmentation, abdominal pain, blood pressure fluctua-
tion, body temperature fluctuation or electrolyte disorder
should exclude AC, especially those with autoimmune
diseases and related family history[18].

3. Early Recognition of Adrenal crisis

Studies have shown that about 8% of patients with
adrenal gland surgery may have adrenal crisis,[19], and pa-
tients with history of adrenal crisis attack are more likely
to relapse.[20]. When patients with recurrent adrenal crisis
attack, the mortality rate can be as high as 40%-50%.[19].
Therefore, early identification of adrenal crisis is very im-
portant.

75.8% of AC patients are diagnosed with Cushing syn-
drome before operation[6]. However, for patients without
cortisol, such as primary aldosteronism, because of the
ACTH promoting the secretion of cortisol and increase
the secretion of cortisol during stress, will make the diagnosis of adrenal crisis more difficult. Due to the lack of specificity in clinical manifestations of adrenal crisis, it is very important to inquire about the relevant family history, autoimmune disease history, and glucocorticoid, left thyroid hormone and rifampicin related drug history. Above all, the laboratory diagnosis of AC should be carried out with the following two parts: (1) confirm that the cortisol level is lower than the lower limit of reference value, but there is no unified reference value lower limit due to the increase of cortisol secretion during surgical stress. According to the endocrine society, the early morning plasma cortisol level ≤ 82.8 nmol/L is likely to indicate AC, and the determination every 6-12 hours is more helpful for the diagnosis. (2) To confirm whether cortisol deficiency is ACTH dependent. If ACTH > 22 pmol/L, primary AC should be considered. If the plasma ACTH and cortisol levels are lower than the lower limit of the reference value, the secondary AC should be considered. For the patients with cortisol > 82.8 nmol/L, 250 μg tictitide stimulation test is feasible. This test has high sensitivity and specificity (97% and 95%), but the patients with recent pituitary stroke or pituitary surgery are not available. Of course, the positive feedback effect of ACTH on adrenal gland is enhanced due to surgical stress, thus, the original reference value may have some errors. Our analysis needs to be in detail.

Because of the lackage of safety test in clinical trials, insulin hypoglycemia test is not recommended as the gold standard for evaluating the integrity of the hypothalamus-pituitary-adrenal axis. The corticotropin releasing hormone (CRH) and methylprednisolone stimulation test are also not recommended because of their potential risk for adrenal crisis. The thyroid function, thyroid antibody, 21-hydroxylase antigen and 17-hydroxylase antigen are detected. If necessary, MRI is performed to determine whether there is tumor, tuberculosis, fungal infection, etc.

In addition to laboratory examination, the patients after unilateral adrenalectomy have the following conditions, which need to be suspected of adrenal crisis: (1) dehydration, blood pressure fluctuations, body temperature fluctuations, shock and other manifestations that cannot be explained by the current state. (2) On the basis of unexplained changes in fatigue, nausea and mental state, abdominal pain and other symptoms similar to acute abdomen or gastrointestinal perforation occur, without obvious or matching abdominal pain, muscle tension and other peritoneal irritation signs. (3) Unexplained hypoglycemia. (4) Unexplained skin flush or new pigmentation. (5) Hyponatremia, hyperkalemia or hypokalemia. (6) Other biochemical indicators are abnormal, including azotemia, hypercalcemia and hypoproteinemia.

4. Treatment of Adrenal Crisis

Once suspected for adrenal crisis attack, it is necessary to immediately take blood for ACTH, and cortisol. In addition, 300 mg hydrocortisone will be given intravenously within 1 hour, which made the plasma cortisol concentration reach the level of normal people under severe stress. After that, intravenous drip of 100 to 200 mg of hydrocortisone is going to be continued for 6 to 8 hours. On the second and third day, it can be reduced to 100mg twice or three times per day. If the patient’s condition improves, continue to reduce the intravenous hydrocortisone to 200mg/day and the next day to 100mg/day. After the patient stopped vomiting and resumed eating, prednisone acetate 10mg daily is taken orally. Active treatment of infection, trauma, cold, psychological stress and other incentives, the use of necessary vasoactive drugs and albumin supplement to maintain blood pressure, and timely correction of hypoglycemia, maintain water and electrolyte balance is also very important.

Before the advent of glucocorticoid replacement therapy, the mortality rate of AC is more than one third. With the emergence of hormone replacement therapy, the prognosis of patients with AC identified in time is good. However, some patients do not follow the principle of long-term adherence or not adjust the dose in time, resulting in life-threatening adrenal crisis. Therefore, early and accurate identification and scientific treatment of AC after unilateral adrenalectomy are very important. It is generally believed that a daily dose of hydrocortisone in excess of 50 mg is sufficient for mineralocorticoid receptor action, so there is no need for additional corticosteroids. However, if the symptoms of AC can’t be effectively controlled after using more than 1000 mg hydrocortisone, or the AC attacks repeatedly and frequently, it is necessary to consider whether 50 to 200 μg of fludrocortisone (25 times of hydrocortisone activity) should be supplemented daily.

5. Prevention of Adrenal Crisis

For patients with AC, glucocorticoid replacement therapy can only be evaluated by clinical symptoms and signs. There is no objective evaluation index. However, patients with AC who are not treated properly in time will soon suffer from hypovolemic shock, unconsciousness and even life-threatening. Attention should be paid to the prevention of infection, cold stimulation, massive bleeding, vomiting, diarrhea, water loss and other stress situations. Hydrocortisone 200 mg can be given imme-
mediately after adrenalectomy, and then again within 6 hours after surgery [35]. According to the prospective study of Hahner et al. [16], 184 patients (184/423 cases, 43.50%) developed adrenal crisis during the 2-year follow-up period after adrenalectomy. Because of timely identification and intervention, only 4 patients died of adrenal crisis. The cause of their death is related to the sudden withdrawal of prednisone acetate during long-term regular oral administration [36].

Although the occurrence of adrenal crisis after retroperitoneal laparoscopic unilateral adrenalectomy is relatively hidden, and if not treated in time, it may cause shock and even lead to death. However, if doctors can early and accurate identification, and timely use of hydrocortisone intervention, the prognosis of patients with AC is generally good.

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