Consultation with the Specialist: Treatment of Adrenocortical Insufficiency

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Consultation with the Specialist

Treatment of Adrenocortical Insufficiency

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The adrenal cortex secretes three types of hormones: mineralocorticoids, glucocorticoids, and androgens. Acute or chronic deficiencies of aldosterone, the primary mineralocorticoid, or of cortisol (hydrocortisone), the primary glucocorticoid, can rapidly become life-threatening.

Etiology

Adrenocortical insufficiency can be primary or secondary (Table 1). The most common causes of adrenocortical insufficiency today are congenital adrenal hyperplasia in the newborn and failure to provide adequate stress doses of glucocorticoids to patients receiving long-term treatment with these agents.

Symptoms

The symptoms of adrenocortical insufficiency depend on whether cortisol or both cortisol and aldosterone are deficient (Table 2). Pure aldosterone deficiency is rare, but does occur in children who have a defect in the enzyme complex corticosterone methyl oxidase. Pseudohypoaldosteronism produces similar symptoms but presumably is due to a defect in the aldosterone receptor. Hyporeninemic hypoaldosteronism is even rarer. Patients who have acquired immunodeficiency syndrome (AIDS) can develop a mineralocorticoid deficiency without concurrent cortisol deficiency.

Hyperpigmentation, a sign of cortisol deficiency, develops over time and is seen most easily on the backs of the hands, elbows, and knees; in the

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TABLE 1. Etiology of Adrenocortical Insufficiency

Primary
- — Hereditary
  - • Congenital adrenal hyperplasia
  - • Congenital adrenal hypoplasia (X-linked and autosomal recessive often associated with anencephaly)
  - • Adrenocortical unresponsiveness to adrenocorticotropic hormone (ACTH)
  - • Adrenoleukodystrophy
  - • Adrenomyeloneuropathy
  - • Mineralocorticoid deficiency
    - — Corticosterone methyloxidase deficiency
    - — Pseudohypoaldosteronism
  - • Refsum disease
  - • Wolman disease
- — Autoimmune
  - • Isolated adrenal insufficiency
  - • Polyglandular autoimmune syndrome, type I (Addison disease, hypoparathyroidism, chronic mucocutaneous candidiasis)
  - • Polyglandular autoimmune syndrome, type II (Addison disease, autoimmune thyroid disease, insulin-dependent diabetes mellitus)
- — Infections
  - • Tuberculosis (the original etiology as described by Addison)
  - • Systemic fungal infections (histoplasmosis, blastomycosis, coccidiomycosis, cryptococcosis)
  - • Human immunodeficiency virus (HIV)-associated infections (previously noted fungal, cytomegalovirus)
- — Adrenal hemorrhage
- — Medications
  - • Decreased steroid synthesis (ketoconazole, etomidate)
  - • Increased steroid metabolism (rifampin, phenytoin, phenobarbital)

Secondary
- — Hypothalamic/Pituitary disease
  - • Tumors, surgery, radiation therapy
- — Isolated ACTH deficiency
- — Withdrawal from glucocorticoid therapy
- — Inadequate glucocorticoid replacement

Modified from Castillo and Chernow, 1993

TABLE 2. Signs and Symptoms of Adrenocortical Insufficiency

Aldosterone deficiency
- Hyponatremia and hyperkalemia
- Acidosis
- Dehydration
- Prerenal azotemia

Cortisol deficiency
- Weakness and fatigability
- Weight loss
- Hypotension
- Shock
- Gastrointestinal problems (nausea, vomiting, pain, and diarrhea)
- Hyperpigmentation
- Hypoglycemia
- Normochromic anemia
- Eosinophilia
- Mild hyponatremia (due to free water retention)

Suspect adrenocortical insufficiency in moderately to severely ill children who have unexplained hypoglycemia, hyponatremia, or hyperkalemia; antecedent weight loss; hyperpigmentation; vitiligo; vomiting; normochromic anemia; or unexplained eosinophilia.

Modified from Castillo and Chernow, 1993.

creases of the hands; and on the buccal mucosa. Hypoglycemia, particularly in the young child, can be a prominent feature and cause seizures.

Diagnosis

The diagnosis of adrenocortical insufficiency must be considered in any sick newborn who has ambiguous genitalia or in any sickly male newborn, especially apparent males who have bilateral cryptorchidism. Typically, the symptoms of cortisol and aldosterone deficiencies do not appear until 4 to 10 days of age, but their appearance can be delayed for as long as 4 weeks. Those most at risk for a missed diagnosis are males who have salt-losing congenital adrenal hyperplasia and any infant who has bilateral adrenal hemorrhage, congenital adrenal hypoplasia, or the rarer forms of nonvirilizing congenital adrenal hyperplasia.

In the older child, making the diagnosis of adrenocortical insufficiency requires a high degree of suspicion. In general, any disproportionality between the severity of an illness and the degree of collapse should lead to consideration of the diagnosis. It is particularly important to suspect the diagnosis in a child who has been taken off glucocorticoid therapy within the past 6 months or who has been receiving glucocorticoid replacement but has not had the dose increased to compensate for the stress of illness or surgery. Any child who has a pituitary deficiency and develops a thyroid deficiency should be tested for an adrenocorticotropic hormone

TABLE 3. Laboratory Evaluation

Tests needed to guide therapy
- Serum electrolytes
- Glucose
- Urea nitrogen

To confirm the diagnosis

The *critical sample* properly collected and stored to quantify:
- — Cortisol
- — ACTH
- — Renin
- — Aldosterone
- — 17-hydroxyprogesterone (in the newborn)

Interpretation of results

	Cortisol	ACTH	Aldosterone	Renin
Addison disease	Decreased	Increased	Decreased	Increased
Aldosterone deficiency	Normal*	Normal*	Decreased	Increased
Pseudohypoaldosteronism	Normal*	Normal*	Increased	Increased
Adrenal hypoplasia	Decreased	Increased	Decreased	Increased†
Unresponsiveness to ACTH	Decreased	Increased	Normal§	Increased†

** For a stress condition, cortisol >20 µg/dL.*

† A decrease in effective blood volume can increase renin activity.

§ A decrease in ACTH responsiveness can decrease aldosterone response somewhat.

TABLE 4. Emergency Treatment of Adrenocortical Insufficiency

Emergency Measures
(Do not forget to obtain the critical pretreatment sample.)

- Fluids to restore intravascular volume and renal perfusion:
  - — Infuse 0.9% NaCl at rate of 500 mL/M^2 over 1 h. Repeat if needed to ensure adequate urine output.
  - — If hypoglycemic, give intravenous 25% glucose, 2 mL/kg (10% glucose in newborns)
- Glucocorticoid replacement:
  - — Hydrocortisone sodium succinate, 75 mg/M^2 per day in four doses. The first dose is an IV bolus; subsequent doses are administered IM or IV.

    This amount of hydrocortisone has mineralocorticoid activity and, with the amount of sodium being given IV, can make up for the lack of a parenteral form of mineralocorticoid available in the US.
- Treatment of hyperkalemia (monitor ECG):
  - — Sodium polystyrene sulfonate, 1 g/kg lowers the serum potassium by about 1 mEq/L. The oral route is more effective than the rectal route. Suspend in 3 mL of water, syrup, or if constipation is a problem, in 70% sorbitol (10% glucose in neonates) per gram of resin. Can repeat dose every 4 to 6 h.

    Because serum potassium does not reflect intracellular depletion, the ECG must be monitored to prevent overtreatment with Na-K exchange resins.
  - — Dangerously high levels of potassium should be treated by giving 10% calcium gluconate IV to stabilize cardiac membrane potentials, 0.5 mL/kg over 10 min, monitoring the heart rate to avoid bradycardia.

    Follow with $NaCO_3$, 1 mEq/kg given over a few minutes, then an infusion at a rate of 1 mEq/kg/hr. Insulin (0.3 U/g glucose) + glucose (0.5 g/kg) infusion is used in extreme circumstances and with great caution. Both therapies shift potassium intracellularly.

Maintenance and repair (over the next 36 to 48 hr)

- Administer IV 0.9% NaCl with 5% to 10% glucose at twice the maintenance rate.
  - — Do not give potassium until serum concentration is normal, <5 mEq/L, and the patient is urinating.
  - — When the serum sodium is >135 mEq/L, the IV fluid can be changed to 0.45% NaCl with 5% glucose.
- Continue to provide hydrocortisone as before.
- Monitor electrolytes and BUN every 4 h, glucose every 2 h.
- If aldosterone is deficient, add oral fludrocortisone, 0.1 mg, later.

(ACTH) deficiency before being treated with levothyroxine; if ACTH is deficient as well, the child may develop acute adrenocortical insufficiency unless treated concomitantly with glucocorticoids.

Laboratory Evaluation

Two types of laboratory tests are necessary for the management of patients who are suspected of having adrenocortical insufficiency (Table 3). The critical sample can be collected without delaying urgent treatment; very little blood is required by current laboratory techniques. In some patients, a subsequent cosyntropin (synthetic ACTH) stimulation test may be needed to establish the diagnosis; 0.125 mg is given to children younger than 2 years of age and 0.25 mg to older children. Serum adrenal steroids are sampled 45 minutes after the intravenous injection.

Treatment

The acute management of patients who have combined cortisol and aldosterone deficiencies is outlined in Table 4. Patients who have isolated cortisol deficiency usually will not experience hyperkalemia or significant sodium and water loss. However, it is critical that they receive immediate treatment with hydrocortisone sodium succinate and volume expansion to counter hypotension as well as glucose if they are hypoglycemic. Aldosterone secretion is under the primary control of the renin-angiotensin system, not ACTH. When patients who have an ACTH deficiency have mild hyponatremia, it is caused by free water retention; cortisol is required for excretion of a water load.

Prevention is the most important aspect of treating adrenocortical insufficiency in patients receiving treatment with glucocorticoids. Although older studies suggested a normal cortisol secretory rate of 12.5 ± 3 mg/M^2 per day, recent studies suggest a rate of 7 ± 2 mg/M^2 per day. Because of partial absorption after oral administration and its passage through the liver, the oral dose is about twice the secretion rate. The oral physiologic maintenance dose of hydrocortisone is 15 to 20 mg/M^2 per day in three divided doses. During an illness, this dose must be tripled to provide the extra cortisol that the adrenals normally secrete during stress. If the patient vomits within 1 to 2 hours of receiving the dose, it should be repeated. If the patient vomits a second time, hydrocortisone sodium succinate must be given by injection. The family should be trained to give an intramuscular injection at home. During severe stress, the secretion of cortisol increases by four- to eightfold. Therefore, a parenteral dose of 75 mg/M^2 per day in four divided doses either by intravenous bolus or intramuscularly is reasonable. In patients receiving mineralocorticoids, no adjustment in the dose of fludrocortisone is needed, but these patients still can have

problems with sodium and potassium balance if their intake of NaCl is too low during the anorectic phase of an illness.

In patients undergoing elective surgery, parenteral doses of hydrocortisone (75 mg/M^2 per day) are given the evening before and throughout the day of surgery. Depending on the patient's condition, hydrocortisone may be reduced to normal maintenance doses the next day. The patient's usual dose of fludrocortisone should be given the day of surgery. Intravenous fluids should contain 0.45% NaCl with 5% glucose initially and adjusted depending on the patient's electrolyte levels, which should be monitored every 4 hours.

Conclusion

Adrenocortical insufficiency is uncommon; therefore, a high index of suspicion is needed for early diagnosis and successful treatment. It cannot be overemphasized that any disproportionality between the severity of the illness and the degree of collapse should lead to consideration of the diagnosis.

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