Adrenal Insufficiency (Addison’s Disease, Hypocortisolism) in Children—Symptoms and Treatment

Adrenal insufficiency is defined as the inadequate production of adrenocortical hormones (glucocorticoids, mineralocorticoids, and adrenal androgens). Adrenal insufficiency can be primary or secondary. Primary adrenal insufficiency (Addison’s disease) is caused by diseases in the gland itself, and the most common cause is autoimmune adrenalitis. Secondary adrenal insufficiency occurs due to decreased production of ACTH either from prolonged glucocorticoid therapy or disease in pituitary/hypothalamic glands. Glucocorticoids therapy is required for both forms of adrenal insufficiency. Adrenal crisis is a well-recognized life-threatening complication that requires high doses of hydrocortisone and intravenous fluids.

Introduction

The adrenal glands secrete glucocorticoids, mineralocorticoids, and androgen hormones. The hormonal output of the adrenal glands is essential for survival. Addison’s disease epitomizes a state of deficient adrenal hormones. Also known as adrenal
insufficiency (AI), it is a relatively infrequent clinical disorder. Addison’s disease is defined as the bilateral destruction of the adrenal cortex and is characterized by a deficiency in glucocorticoids, mineralocorticoids, and androgens. Addison’s disease is most often an autoimmune condition.

**History of AI in Children**

Addison’s disease is named after Thomas Addison, a renowned British physician of the 18th century who discovered this disease and elaborated on it extensively in ‘On the Constitutional and Local Effects of Disease of the Suprarenal Capsules (1855)’.

**Epidemiology of AI in Children**

The estimated annual incidence of primary AI is six new cases per one million people. In a recent audit at the Royal Children’s Hospital in Melbourne, Australia, the following was revealed about the epidemiology of primary AI in children:

- AI is more common in boys, with a male-to-female ratio of 4:1.
- During a 10-year period, only 16 new cases of primary AI were seen, further emphasizing the rarity of the condition.
- The median age at presentation in children was 7.7 years.
- A family history of AI was apparent in 2 out of the 16 cases.

While this information provides little about the exact epidemiology of the condition in the general population, it has taught us a few important lessons about primary AI in children.

The prevalence of Addison’s disease is estimated to be approximately 93–144 cases per 1 million people.

**Classification of AI in Children**

AI is classified as primary and secondary based on the pathologic level of dysfunction.

A multitude of conditions can lead to primary AI, as follows:

- Autoimmune AI
- Underdevelopment (transcription factor deficiencies)—rare
- Impaired function (enzyme production problems)—rare
- Smith-Lemli-Opitz syndrome
- Destruction of the adrenal gland (common)

Primary AI is mostly the culmination of autoimmune processes, wherein the immune system attacks the adrenal glands. About 80% of Addison’s disease patients are potentially the victims of such autoimmune destructive forces. Autoimmune primary AI often occurs as a subset of a diverse congregation of autoimmune illnesses. The presence of one of these illnesses should prompt a meticulous search for the other.

The associated autoimmune conditions can be summarized as follows:

- Type 1 diabetes
- Myasthenia gravis
- Pernicious anemia
- Hypopituitarism
- Hypoparathyroidism
Adrenal destruction causing adrenal insufficiency is the result of a multitude of diverse etiologies, as shown in the following table:

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>The most common cause of acquired AI in children, usually autoimmune destruction, may be part of polyglandular autoimmune syndrome (PAS).</td>
</tr>
<tr>
<td>Infection</td>
<td>Meningococcal sepsis (Waterhouse-Friedrichsen), tuberculosis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Adrenoleukodystrophy (ALD) X-linked, males</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Hemochromatosis, sarcoid, histiocytosis</td>
</tr>
<tr>
<td>Drugs</td>
<td>Etomidate, ketoconazole</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Birth trauma, sepsis, coagulopathy</td>
</tr>
</tbody>
</table>

Secondary AI has an identifiable inciting factor that brings about the devastation of the adrenal cortex. **The most significant relevant secondary causes of Addison’s disease can be summarized as follows:**

- Tumors
- **Fungal infections**
- **Tuberculosis**
- Anticoagulants and blood thinners
- Human immunodeficiency virus (HIV)
- Underdeveloped hypothalamic-pituitary-adrenal axis
- External glucocorticoid supplementation
- Hypothalamic/pituitary destruction secondary to tumor or infarct circumstances

The etiologies of primary AI in children differ from adults. The most common cause of primary AI in children is **congenital adrenal hyperplasia** (71.8%). **Autoimmune destruction** of the adrenal glands is reported in approximately 12.7% of the cases of pediatric Addison’s disease. On the other hand, autoimmune Addison’s disease had a frequency of 81.5% in adults with primary AI. **Tuberculosis and other infectious** causes of adrenal gland destruction are rarely seen in children.

**Etiopathogenesis of AI in Children**

Addison’s disease is primarily an AI, which is a flaw in the adrenal production of cortisol. Because the adrenal glands are affected broadly, mineralocorticoids are usually affected as well.

The spatially separate affection of the hypothalamic-pituitary-adrenal (HPA)-axis determines whether it is **primary or secondary AI**.
1. In **primary AI**, the adrenals are damaged, regardless of the etiology. Consequently, there is a decline in the production of cortisol and mineralocorticoids. The adrenal hormones are essential for survival. The clinical manifestations emerge only when more than 90% of the adrenal cortex is destroyed.

2. In **secondary AI**, it is a pituitary or hypothalamic problem resulting in decreased stimulation of cortisol. However, mineralocorticoid production is stimulated by ACTH from another part of the pituitary, so it is still produced by the functioning adrenal gland.


Clinical Presentation of AI in Children

Addison’s disease is incompatible with survival. The most frequent presentation is of an insidious-onset, progressive crippling of the whole body. Early signs and symptoms are rather non-specific and therefore often go unnoticed.

It is said that a tan without tan lines is suggestive of high ACTH levels.

A brief summary of the clinical features is as follows:

<table>
<thead>
<tr>
<th>Sign</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Weakness</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Generalized bronze discoloration of the skin</td>
<td>Salt craving</td>
</tr>
<tr>
<td>Skin-fold hyperpigmentation</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Nausea</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Symptomatic hypoglycemia</td>
<td>Poor weight gain</td>
</tr>
</tbody>
</table>

The most prevalent features in the pediatric age group are lethargy and hyperpigmentation, along with vomiting and peculiar salt cravings. Some children remain undiagnosed due to the rather non-specific nature of the illness. They then have an unfortunate emergency presentation as they develop the **Addisonian crisis** secondary to a rather minor, seemingly innocuous, illness.

A few causes of Addison’s disease have unique presenting characteristics, such as shown in the following table:

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waterhouse–Friderichsen-Syndrome</td>
<td>Mortality is very high. It is more common in children than in adults.</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>It is very rare in girls and is characterized by an inability to break down long-chain fatty acids. The build-up of fat damages myelin with resultant progressive weakness and ataxia. The adrenals are destroyed as well. The treatment is a bone marrow transplant. Damage already done is done and therefore the goal is to transplant early.</td>
</tr>
</tbody>
</table>

One needs to be aware of the phenomenon of the Addisonian crisis when dealing with pediatric patients experiencing adrenal insufficiency.

Addisonian crisis

Also called adrenal crisis or acute AI, Addisonian crisis is a potentially life-threatening complication of Addison’s disease. The sudden drop in the level of glucocorticoids, or relative acute deficiency of steroids in a patient with AI secondary to either exposure to acute stress or interruption in intake of steroids, leads to this crisis. Patients with congenital adrenal hyperplasia are also susceptible to this condition in times of stress.

One needs to be wary of the following clinical features of Addisonian crisis. The presence of a constellation of the following symptoms calls for immediate attention and urgent treatment. They are as follows:

- Acute deep pain in the back, legs, or abdomen
- Acute neurologic deterioration in the form of confusion, convulsions, psychosis, or slurred speech
- Fever
- Hypotension
- Severe vomiting and diarrhea with consequent dehydration
- Severe metabolic disturbances such as hypercalcemia, hyperkalemia, hypoglycemia, hyponatremia, and hypothyroidism
- Syncope and severe lethargy

**Diagnosis of AI in Children**

Addison’s disease is fundamentally diagnosed on the basis of **simple blood tests such as Chem-7**. The more complex tests are used to establish the etiology and document complications, if any.

The various investigations involved and their changed behavior in light of Addison’s disease are summarized in the following table for easy memorization and recall.

<table>
<thead>
<tr>
<th>Test</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem-7</td>
<td>All elements of Chem-7 are abnormal. The drift is as follows:</td>
</tr>
<tr>
<td></td>
<td>• Sodium: Levels decrease.</td>
</tr>
<tr>
<td></td>
<td>• Chloride: Levels decrease.</td>
</tr>
<tr>
<td></td>
<td>• CO₂: Levels decrease.</td>
</tr>
<tr>
<td></td>
<td>• Glucose: Levels decrease.</td>
</tr>
<tr>
<td></td>
<td>• Creatinine: Serum levels increase.</td>
</tr>
<tr>
<td></td>
<td>• Potassium: Serum levels increase.</td>
</tr>
<tr>
<td>Serum ACTH</td>
<td>High levels are documented in primary AI. Secondary AI is characterized by low ACTH levels.</td>
</tr>
<tr>
<td>Serum cortisol</td>
<td>AI shows a low cortisol level regardless of the etiology of AI.</td>
</tr>
<tr>
<td>Other blood tests</td>
<td>Blood serum level analysis of renin and aldosterone play an ancillary role in establishing the diagnosis.</td>
</tr>
<tr>
<td>Imaging studies</td>
<td>There is no frank role of imaging investigations to confirm the diagnosis of Addison’s disease. However, they do play a significant role in documenting the complications, if any. Useful tests are as follows: Adrenal magnetic resonance imaging (MRI) is used to detect any hemorrhage or tumor. MRI of the brain may be used in cases of secondary AI.</td>
</tr>
</tbody>
</table>

**Management of AI in Children**

Addison’s disease is a medical diagnosis with a medical line of management. Treatment is lifelong administration of steroids. It specifically involves the replacement of steroids either in the form of hydrocortisone or prednisolone in a customized dosage form that suits the individual patient. A subset of patients also requires mineralocorticoid replacement in the form of fludrocortisone.

In pediatric patients, clinicians must be wary of stressful circumstances that call for the use of escalated doses of steroids to avoid Addisonian crisis, a potentially life-threatening complication of Addison’s disease. Anything from dental treatment to major surgery can induce stress in these patients. Infections are commonly the nidus for the onset of an adrenal crisis.

Therefore, prompt medical attention and treatment of seemingly innocuous illnesses such as vomiting, diarrhea, and infections form an essential component of the management of Addison’s disease patients.

**Treatment of Addisonian crisis**

Specific treatment of the Addisonian crisis demands emergent management because it is life-threatening in nature. **The key management steps are as follows:**
Hydrate with enormous stocks of intravenous saline solution with dextrose.

Use simultaneous intravenous steroids replacement, a hydrocortisone if oral replacement is appropriate.

Occasional intramuscular saline injection is used if intravenous access is not available due to a myriad number of reasons.

Oral fludrocortisone is used to replace mineralocorticoids if needed.

Slowly treat hyponatremia over 1–2 days.

Rapidly fix hypoglycemia and hyperkalemia.

Special Issues of AI in Children

Growth and puberty

Most of the pediatric patients are below average standard height percentiles when diagnosed. On receiving adequate optimum treatment, eventually, the linear growth is normal. Pubertal evolution is grossly uneventful in the majority of patients.

Summary

Addison’s disease, also known as AI, is incompatible with life. It is rare in the pediatric age group and is characterized by deficient levels of glucocorticoids circulating in the body. Mineralocorticoid production is occasionally hampered.

Primary AI is most commonly secondary to autoimmune processes. The adrenal cortex is damaged.

Secondary AI involves the infliction of the hypothalamus or pituitary due to disorders such as tumors, infections, or infarcts which, in turn, disrupts the HPA axis.

The HPA axis is vital to ensuring proper steroid output to cope with different physiologic and pathologic challenges. Erratic control of the adrenals by the HPA axis in secondary AI leads to AI.

Clinical manifestations surface only when about 90% of the adrenal cortex is damaged. The first few signs and symptoms are rather non-specific, thus making early diagnosis difficult.

Addisonian crisis is acute AI triggered by a multitude of potential stressors to the body. It is characterized by sudden acute neurologic deterioration with a generalized systemic breakdown. It is potentially life threatening and requires emergency management with rapid administration of steroids and correction of the metabolic disturbances that follow.

The diagnosis of Addison’s disease rather follows a simple algorithm. Blood tests such as Chem-7 are useful for diagnosis. The determination of etiology and complications calls for more complex tests such as MRI of the adrenals and the brain. The abnormalities in Chem-7 are as follows:

- Sodium, chloride, CO₂, and glucose: Levels decrease.
- Creatinine and potassium: Serum levels increase.

Management involves steroid administration for life, along with regular monitoring for metabolic disturbances. One should always be wary of Addisonian crisis.

Final linear growth and puberty are relatively normal in optimally treated pediatric
patients with Addison’s disease.

References


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