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, 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 Adrenal Insufficiency in Children

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

Epidemiology of Adrenal Insufficiency in Children

The estimated annual incidence of primary adrenal insufficiency is 6 new cases per million population. In a recent audit at the Royal Children’s Hospital in Melbourne, Australia, the following was revealed about the epidemiology of primary adrenal insufficiency in children:

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

The prevalence of Addison’s disease is estimated to be around 93—144 cases per million population.

Classification of Adrenal Insufficiency in Children

Adrenal insufficiency is classified as primary and secondary based on the pathological level of dysfunction.

A multitude of conditions can lead to primary adrenal insufficiency. The same can be summarized as follows:

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

Primary adrenal insufficiency 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 adrenal insufficiency 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 I Diabetes**
- **Myasthenia gravis**
- **Pernicious anemia**
- **Hypopituitarism**
- **Hypoparathyroidism**
- **Vitiligo**
- **Chronic thyroiditis**

Adrenal destruction causing adrenal insufficiency is the result of a multitude of diverse etiologies such as mentioned below:

<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 PAS (polyglandular autoimmune syndrome).</td>
</tr>
<tr>
<td>Infection</td>
<td>Meningococcal sepsis (Waterhouse-Friderichsen), <strong>tuberculosis</strong></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 adrenal insufficiency has an identifiable inciting factor which 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
- **HIV**
- Underdeveloped Hypothalamic-pituitary-adrenal axis
- External glucocorticoid supplementation
- Hypothalamic/pituitary destruction secondary to tumor or infarct circumstances

The etiologies of primary adrenal insufficiency in children differ from adults. The most common cause of primary adrenal insufficiency in children is **congenital adrenal hyperplasia** (71.8 %). **Autoimmune destruction** of the adrenal glands is reported in about 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 adrenal insufficiency. **Tuberculosis and other infectious** causes of adrenal gland destruction are **rarely** seen in children.

**Etiopathogenesis of Adrenal Insufficiency in Children**

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

The spatially separate affection of the HPA-axis determines whether it is **primary or secondary adrenal insufficiency**.
1. In **primary adrenal insufficiency**, the adrenals are damaged irrespective 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 disease**, it is pituitary or hypothalamic problem resulting in decreased stimulation of cortisol, but mineralocorticoids production is stimulated by ACTH from another part of the pituitary, so it is still produced by the functioning adrenal gland.
Clinical Presentation of Adrenal Insufficiency 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 hence often go unnoticed.

It is said that 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 craving. Some children remain undiagnosed due to the rather non-specific nature of the illness. They then have an unfortunate emergency presentation as they develop Addisonian crisis secondary to rather minor seemingly innocuous illness.

Few causes of Addison’s disease have unique presenting characteristics. The same can be tabulated as follows:

<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. Adrenals are destroyed as well. Treatment is a bone marrow transplant. Damage already done is done and hence the aim is to transplant early.</td>
</tr>
</tbody>
</table>

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

Addisonian crisis

Also termed as the adrenal crisis or acute adrenal insufficiency, the 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 adrenal insufficiency 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 ill fate in times of intercurrent stressful circumstances.

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 listed below:

- Acute deep pain in back, legs or abdomen.
- Acute neurological 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 Adrenal Insufficiency 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 can be summarized as below 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 mentioned:</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 adrenal insufficiency. Secondary adrenal insufficiency is characterized by low ACTH levels.</td>
</tr>
<tr>
<td>Serum cortisol</td>
<td>Adrenal insufficiency witnesses low cortisol level irrespective of the etiology of adrenal insufficiency.</td>
</tr>
<tr>
<td>Other blood tests</td>
<td>Blood serum level analysis of rennin 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. Tests thus useful are as follows: Adrenal MRI is used to detect any hemorrhage or tumor. MRI of the brain comes in the picture in case of secondary adrenal insufficiency.</td>
</tr>
</tbody>
</table>

**Management of Adrenal Insufficiency in Children**

Addison’s disease is a medical diagnosis with a medical line of management. Treatment is steroids all lifelong. 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 mineralocorticoids replacement in the form of Fludrocortisone.

Pediatric patients have to be **wary of stressful circumstances which call for the use of escalated doses of steroids to evade the occurrence of 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 a significant relay for induction of crisis.

Hence, 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 Addisonian crisis demands emergent management as it is life-threatening in nature. The key management steps are listed as follows:

- Hydration with enormous stocks of the intravenous saline solution with dextrose.
- Simultaneous intravenous steroids replacement, hydrocortisone used if oral replacement is appropriate.
- Occasional intramuscular saline injection if used if intravenous access is not available due to a myriad number of reasons.
- Oral fludrocortisone is used to replace mineralocorticoids if need be.
- Slowly treat hyponatremia over 1—2 days.
- Rapidly fix hypoglycemia and hyperkalemia.

**Special Issues of Adrenal Insufficiency 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 adrenal insufficiency 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 adrenal insufficiency is most commonly secondary to autoimmune processes. The adrenal cortex is damaged.

Secondary adrenal insufficiency involves the inflection of the hypothalamus or pituitary due to disorders such as tumors, infections or infarcts which, in turn, disrupt the hypothalamic-pituitary-adrenal axis.

The HPA axis is indispensable to ensure proper steroid output to cope with different physiological and pathological challenges. Erratic control of the adrenals by the HPA axis in secondary adrenal insufficiency leads to adrenal insufficiency.

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 a difficult task.

Addisonian crisis is acute adrenal insufficiency triggered by a multitude of potential stressors to the body. It is characterized by sudden acute neurological 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.

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

- 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 be always wary of Addisonian crisis.

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

Review Questions

The correct answers can be found below the references.

1. Which of the following statements is false?
   A. Addison’s disease is common in children.
   B. Pubertal evolution is grossly uneventful in the majority of patients.
   C. A subset of patients with Addison’s disease also requires mineralocorticoid replacement in the form of Fludrocortisone.
   D. Adrenal insufficiency witnesses low cortisol level irrespective of the etiology of adrenal insufficiency.

2. Which of the following statements is true?
   A. Patients with congenital adrenal hyperplasia are resistant to the Addisonian crisis in times of intercurrent stressful circumstances.
   B. Hyponatremia needs to be fixed rapidly to avoid the risk of pontine demyelinates.
   C. Addisonian crisis can be triggered by minor infections and dental treatment visits if the proper prophylactic steroid dose is not administered before such events.
   D. Surgical management is the first line of treatment for Addison’s disease.

3. Which of the following statements is correct regarding Adrenoleukodystrophy?
   A. Treatment involves a bone marrow transplant.
   B. Treatment is transsphenoidal surgery.
   C. Treatment is the administration of antibodies against Gamma receptors.
   D. It is more common in boys and spares the adrenals.

References


**Correct answers:** 1A; 2C; 3A

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