

Case Report: A Case of Addison's Disease

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Abstract

Addison's disease is chronic adrenocortical insufficiency. Adrenocortical insufficiency (AI) could be due to congenital or acquired causes. Congenital causes include inborn defects of steroidogenesis, adrenal hypoplasia congenita, adrenoleukodystrophy, and familial glucocorticoid deficiency. Acquired causes include autoimmunity (Type 1 and 2 autoimmune polyendocrinopathy), infections such as tuberculosis and meningococemia, drugs such as ketoconazole, rifampicin, phenytoin, and phenobarbitone, and hemorrhage into adrenals as a consequence of difficult labor, metastasis, amyloidosis, and surgical excision. Although autoimmunity is the major cause of AI in developed countries, infections like tuberculosis still remain an important cause in developing countries like India. Addison's disease can be easily missed due to its presentation with non-specific symptoms. Serum cortisol levels can also be misleading due to variations in circadian rhythm and increase during stressful situations. Hence, strong clinical suspicion is the key to early diagnosis and treatment. We report here a case Addison's disease secondary to tuberculosis.

Key words: Adrenocortical insufficiency, Autoimmunity, Hyperpigmentation, Tuberculosis

INTRODUCTION

Adrenocortical insufficiency (AI), popularly known as Addison's disease, is rare endocrine disease. Addison's disease has an incidence of 0.8/million and a prevalence of 40–60/million in the USA and European countries. It affects males and females in equal numbers and can potentially affect individuals of any age.^[1] In India, the prevalence of Addison's disease is estimated around 12/million.^[2] Addison's disease was first described by Thomas Addison of University of Edinburgh Medical School in 1855 as a syndrome of weakness and hyperpigmentation. Interestingly, all the 11 cases of adrenocortical insufficiency described by Thomas Addison in his initial report had tuberculosis of adrenals.^[3] Famous Addisonian includes President John F Kennedy, Jane Austen, and Osama bin-Laden.

Although Addison's disease is a rare disorder, it is seen in all the social and economic strata of the society in all the countries. Since the presentation is vague, not only the

diagnosis is delayed leading to increased morbidity and mortality but it also leaves a number of undiagnosed cases in the society. A survey of patients with Addison's disease revealed that 60% had sought medical attention from two or more physicians before the correct diagnosis was made and there are a number of undiagnosed patients.^[4] Acute adrenocortical insufficiency (Addisonian crisis), a potentially catastrophic condition, is seen in nearly 6–8% of cases of AI and if not managed promptly and aggressively, can be life threatening.^[5] Awareness about this condition and high index of suspicion is required for timely diagnosis and intervention. We present the case report of a child whose non-specific manifestations resulted in 2 years' delay in reaching proper diagnosis.

CASE REPORT

A Three and half-year-old female child presented with fever and cough of 1-month duration. This child had been suffering from recurrent upper respiratory tract symptoms along with generalized weakness, malaise, loss of appetite, and poor weight gain for previous 2 years. There was no history of pain abdomen or vomiting. On examination, her height (92 cm) and weight (13 kg) were below the 10th percentile. Her body mass index was 14.4 kg/m². Her pulse was 92 beats/min, respiratory rate 18 cycles/min, and blood pressure was 80/50 mmHg. There was no orthostatic hypotension. The child had generalized hyperpigmentation

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of the skin, buccal mucosa, hard palate, gums, and over palms and soles [Figure 1] which the parents first noticed around 2 years back and had been gradually increasing. Rest of the general examination was non-contributory. The sexual maturity rating (Tanner stage) was pre-pubertal. Respiratory system examination revealed crackles over the right inframammary and infra-axillary areas. Rest of the systemic examination was unremarkable. Possibility of chronic adrenocortical insufficiency was considered in view of hyperpigmentation and growth retardation and history of recurrent respiratory tract infections pointed to tuberculosis as the cause.

Laboratory work-up revealed hemoglobin 10.2 g/dl, total leukocyte count (TLC) 10,200/ μ l, differential leukocyte count-P42 L48 M06 E04, and ESR 32 mm in the 1st h. Biochemical parameters including serum glucose, renal and liver function tests, and serum electrolytes were normal. X-ray chest posteroanterior revealed non-homogenous opacities over right lower zone [Figure 2] and Mantoux test showed a wheal and induration of 12 mm diameter (normal

<10 mm). Gastric aspirate for acid-fast bacilli (three early morning samples) was negative. Serum cortisol level was low; 4.2 μ g/dl (normal <18 μ g/dl). Plasma adrenocorticotrophic hormone (ACTH) level was 978 pg/ml (normal <46 pg/ml). On ACTH stimulation test, there was no increase in cortisol levels at 30 min and 60 min following administration of cosyntropin 250 μ g. Non-contrast computed tomography (CT) abdomen revealed bilateral enlarged adrenal glands [Figure 3]. Taking into consideration, the clinical profile and investigation results, the diagnosis of Addison's disease secondary to pulmonary tuberculosis was made. Adrenal biopsy was not done as it is an invasive procedure and would have added little to the patient management.

Child was managed with anti-tubercular treatment (ATT-2EHRZ +4HR) along with intravenous hydrocortisone at 100 mg/m²/day initially for 1 week and subsequently discharge on replacement dose of oral hydrocortisone at 10 mg/m²/day in three divided doses.



Figure 1: Hyperpigmentation of the skin

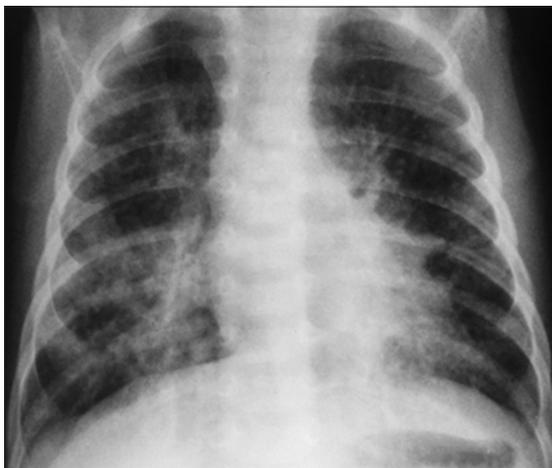


Figure 2: Non-homogenous opacities right lower lobe



Figure 3: Non-contrast computed tomography abdomen – bilateral enlarged adrenal glands



Figure 4: After 3 months – fading hyperpigmentation and weight gain

On follow-up after 3 months, the child had gained 2 kg weight and the hyperpigmentation disappeared [Figure 4]. Plasma ACTH level at 6 months was 202 pg/dl.

The parents were counseled regarding the nature of the disease and the need for lifelong replacement therapy and periodic follow-up with the pediatrician/physician.

Parents were also explained about the need to carry a disease identity card/bracelet and the need for stress dose steroids before dental/surgical procedures.

DISCUSSION

Addison's disease is a rare disorder. AI may be caused by destruction or dysfunction of adrenal gland (primary AI, Addison's disease), deficient pituitary ACTH secretion (secondary AI), or deficient hypothalamic secretion of corticotropin-releasing hormone (Tertiary AI).

The most common cause of primary AI in children is congenital adrenal hyperplasia (CAH) which accounts for 70% of pediatric patients with AI, whereas autoimmune adrenalitis accounts for 15% of cases.^[4] The most common cause of CAH is 21-hydroxylase deficiency, accounting for ~ 90% of all CAH cases, with an incidence of 1 in 14,000 live births.^[6] Autoimmune Addison's disease may be associated with other autoimmune diseases such as autoimmune polyendocrine syndromes types 1 and 2. Iatrogenic tertiary AI caused by suppression of the hypothalamic-pituitary adrenal axis secondary to glucocorticoid administration is the most common cause of central AI, with an estimated prevalence of 150–280 per 1,000,000. In developed countries, only about 10% of cases of Addison's disease have infectious etiology. In developing countries like India, the infectious etiology is more common. Tuberculosis accounts for about 20–30% of cases of Addison's disease in developing world. Adrenal tuberculosis is one of the five most common sites of extra-pulmonary tuberculosis. Lam and Lo reported 6% incidence of adrenal tuberculosis in the patients with active tuberculosis at autopsy.^[7] Other infections include HIV, opportunistic infections like cytomegalovirus, and fungi such as *Cryptococcus*, *Histoplasma*, and *Coccidioides*.^[8] It is possible that infections play a role in the development of AAD.^[9]

Presentation is usually insidious but can be acute during an adrenal crisis. The clinical features of AI are manifested only after more than 90% of the adrenal gland has been destroyed. The most common symptoms such as lethargy, weakness, anorexia, nausea, and vomiting are vague, usually delaying the diagnosis. Hyperpigmentation

is the most frequent feature seen in 90% of the cases of AI. Other clinical signs include failure to thrive, orthostatic hypotension, hyponatremia, hyperkalemia, and hypoglycemia. Hyponatremia is the most commonly found metabolic abnormality. A high index of suspicion is needed to diagnose AI.^[10] Diagnosis is based on clinical presentation, electrolyte changes (hyponatremia and hyperkalemia), low cortisol levels, abnormal ACTH stimulation test, and CT abdomen findings. CT abdomen can also help correlate the clinical duration of Addison's disease.^[11] In cases where etiology of AI remains uncertain, percutaneous biopsy is a safe, accurate procedure for the diagnosis of pathologic conditions of the adrenal glands.^[12] Percutaneous biopsy is largely indicated in cases where malignancy needs to be ruled out.

Differential diagnosis includes other causes of hyperpigmentation such as melasma, malignant melanoma, and anorexia nervosa. AI should be kept as a possibility in the patients presenting with hyponatremia. In cases presenting in Addison's crisis, sepsis, gastroenteritis, acute abdomen, and hypovolemic shock need to be ruled out.

Treatment includes intravenous hydrocortisone during the acute episode followed by chronic replacement with oral hydrocortisone and if needed, fludrocortisone. Usually, the patients require lifelong replacement therapy with steroids. Since plasma cortisol levels and ACTH stimulation test does not usually return to normal after completion of antitubercular therapy.^[13] Prognosis is good with proper control and special attention to drug interactions. One of the most important aspects of the management of AI is patient and family education. The reason for lifelong replacement therapy, the need to increase the dose of glucocorticoid during stress, and shift to injectable steroids in emergencies cannot be overemphasized.^[14] Starting doses of glucocorticoids should be 15–20 mg for hydrocortisone or equivalent, preferably weight adjusted, with one half to two-thirds of the total daily dose being given in the morning. The long-acting synthetic glucocorticoids should be avoided because their longer duration of action may produce manifestations of chronic glucocorticoid excess. Timed release hydrocortisone tablets and continuous subcutaneous hydrocortisone infusion are promising new treatment modalities.^[15]

Adrenal crisis, also termed acute AI, is the most dreaded and acute life-threatening complication. Even with proper recognition and treatment, the adrenal crisis may result in death. Other complications of Addison's disease include arrhythmias, seizures and coma etc due to electrolyte abnormalities such as hyponatremia, hyperkalemia and hypoglycemia. Hypotension may lead to hypoperfusion and organ failure as well.

CONCLUSION

Addison's disease is a rare disorder that has vague and non-specific presentation often leading to delay in diagnosis and requires high index of suspicion for timely management. Failure to identify the disorder in time may result in life-threatening emergency of adrenal crisis. Education of the patients and the parents is the key to successful management. All patients must be counseled regarding need for lifelong treatment and need to carry a medical alert identification card.

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