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Original Research Paper

Medicine

PATTERN OF ADDISONS DISEASE AND ADDISONION CRISIS IN PATIENTS PRESENTING TO TERTIARY HEALTH CARE HOSPITAL IN INDIA

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ABSTRACT

BACKGROUND: Thomas Addison described a group of patients with diseased adrenal glands at autopsy, with similar signs and symptoms before death; a condition now known as primary adrenal insufficiency i.e. Addison's disease. Secondary adrenal insufficiency also causes similar symptoms and signs that are due to reduced ACTH secretion from the pituitary gland. Sometimes these symptoms and signs can be subtle and nonspecific. Patients may experience fatigue, weakness, weight loss, and gastrointestinal upset, hyperpigmentation of the skin and mucous membranes. These symptoms are gradual in progression and worsen over years, making early diagnosis difficult. The clinical presentation of adrenal insufficiency in India may be underdiagnosed and not paid sufficient attention to. We, therefore, studied the clinical profile of adrenal insufficiency.

METHODS: We used a prospective study as a study design. We studied 26 patients with adrenal insufficiency for their etiology, clinical features, and various laboratory profile including autoantibodies and cortisol levels.

RESULTS: Drug-induced adrenal insufficiency (steroid abuse) etiology was present in 46.15% of the patients. Tuberculosis was the cause in 26.92% of the patients. Septicemic shock with multiorgan dysfunction syndrome was the etiology in 23.07% of patients. Postural hypotension and salt craving and hyponatremia were noted in about 30.76% of patients with s/o mineralocorticoid deficiency.

CONCLUSION: Steroid abuse was the most common cause of adrenal insufficiency followed by septicemic shock and tuberculosis. Thus, a high index of clinical suspicion is required for a diagnosis of adrenal insufficiency in the early stages for diagnosis and prompt treatment.

KEYWORDS :

INTRODUCTION:

According to available literature, Addison's disease is very rare and about 10 cases are found in 1 million population. However, the estimated prevalence of Addison disease is one in 20,000 persons in the United States and Western Europe. high clinical suspicion is needed to avoid misdiagnosing a life-threatening adrenal crisis.

Primary hypoadrenalism refers to glucocorticoid deficiency occurring in the setting of adrenal disease, whereas secondary hypoadrenalism arises because of deficiency of ACTH. A major distinction between these two is that mineralocorticoid deficiency invariably accompanies primary hypoadrenalism, but this does not occur in secondary hypoadrenalism: only ACTH is deficient, and the renin-angiotensin-aldosterone (RAA) axis is intact. A further important cause of adrenal insufficiency in which there may be the dissociation of glucocorticoid and mineralocorticoid secretion is CAH.[1]

The prevalence of well-documented, permanent adrenal insufficiency is 5 in 10,000 in the general population. The hypothalamic-pituitary origin of the disease is most frequent, with a prevalence of 3 in 10,000, whereas primary adrenal insufficiency has a prevalence of 2 in 10,000. Approximately one-half of the latter cases are acquired, mostly caused by autoimmune destruction of the adrenal glands; the other half is genetic, most commonly caused by distinct enzymatic blocks in adrenal steroidogenesis affecting glucocorticoid synthesis (i.e., CAH.) Adrenal insufficiency arising from suppression of the HPA axis as a consequence of exogenous glucocorticoid treatment is much more common, occurring in 0.5–2% of the population in developed countries.[2]

Thomas Addison described the condition now known as primary hypoadrenalism in his classic monograph published in 1855.[3]

METHODOLOGY:

Patients who are having symptoms of Addison's disease and low serum cortisol levels were included in the study. We retrospectively analyzed all these patients and studied the different clinical presentations of such patients in the Indian population. We are presenting a case series of four cases admitted to our hospital with a diagnosis of Addison's disease /Addisonian crisis.

CASE 1

38 years old female presented to our hospital with chief complaints of generalized weakness, fatiguability, anorexia, headache, blackish discoloration of the skin over the face, lips, oral mucosa.

Clinically she was afebrile, 78/min, BP 120/80 mmHg, RR 18/min. There was no pallor, icterus, clubbing, cyanosis, lymphadenopathy. There was hyperpigmentation on the face, upper extremities and oral mucosa. Systemic examination was within normal limits.

Basic lab investigations were within normal limits except electrolytes disturbances and urine examination. There was persistent hyponatremia and potassium was towards higher side. Blood urea was 43 mg/dL; serum creatinine was 1.2 mg/dL. [R(BSL)=109 mg/dl; Bilirubin total= 0.8 mg/dL direct =0.2 mg/dL; Haemoglobin = 12.2 gm%; TLC= 7820 /cu.mm; Platelet= 288000 / cu.mm ; Urine analysis = protein +++; Serum Homocysteine = 13.67 micromole/L; Sr TSH = 31.66 mU/mL; Sr T3 = 0.8 nmol/L; Sr T4 = 1.11 pmol/L; Anti TPO antibody level =>1000 35 IU/ mL; Chest X-ray = NAD; 2D Echo = NAD; Sr. Magnesium = 2 mg/dL; Sr Iron = 50 mcg/dL; TIBC = 265 mcg/dL; HIV Not reactive; HbSAg Negative; 24 hour ECG Holter report s/o Multiple single ventricular ectopics (bigeminy and trigeminy).

Table 1: Sequential electrolytes of Case 1 patient

mmol/L	Day 1	Day 3	Day 5
Na	128	127	125
K	5.5	5.16	6
Cl	97	97	90

Due to clinical features and persistent hyponatremia and hyperkalemia, we suspected adrenal insufficiency and sent serum cortisol level (8 am) which was found to be 4 mcg/dl.

CASE 2

30 years old female - the housewife, came to OPD with chief complaints of bilateral lower limb swelling, giddiness, and tremors for 1 week associated with easy fatiguability and headache. She had a history of increased pigmentation over the face and knuckles for the past few months. She also had palpitations and sweating intermittently.

H/o similar complaints many times in the past wherein the local doctor treated her on the lines of a psychiatric disorder, mainly depressive disorder. Then she had admitted to our hospital multiple times and had received multiple blood transfusions for anemia. On the last admission workup, she was positive for the anti-parietal cell antibody. LMP 45 days back having menstrual cycles every 50-60 days.

Investigations revealed, TLC = 7800/cu.mm; Hb = 12.2gm%; PLT = 288000/cu.mm; MCV = 76 fl; R (BSL)=108mg/dl; F(BSL)=102 mg/dl; PP(BSL)=126 mg/dl; Sr Urea =69 mg/dl; Sr Creatinine = 1.10 mg/dl; Sr Na =125mmol/l; K =6.0mmol/l; Cl = 98mmol/l; Sr Bilirubin (Total) = 0.8 mg/dl (Direct) = 0.2 mg/dl; SGOT = 31 IU/L; SGPT = 23 IU/L; ALP = 89 IU/L

Given generalized hyperpigmentation, hypotension, and lab findings of hyponatremia a differential diagnosis of Addison's disease was made and an early morning 8 am blood sample sent for serum cortisol level which was found to be 9.0 ug / dL. The thyroid-stimulating hormone level was raised 31.62 mIU/L (0.4-4.2). Blood sugars were within normal limits. Montoux's test was negative.

CASE 3

55 years old female was admitted to dermatology ward for increased darkening of the skin, itching over the scalp, swelling over the face especially over the periorbital region, and difficulty while swallowing with working diagnosis of Dermatomyositis. There were deranged CPK levels. She was referred to the medical department given hypoproteinaemia; detailed examination revealed increased darkening of the skin of the face and extremities during the last few months and proximal muscle weakness. All investigations were suggestive of anemia, elevated CPK, raised LDH. Serum cortisol levels and serum electrolytes were advised which were suggestive of serum cortisol and serum sodium level on the lower side. ESR 10mm/hr; Sr LDH 1123 U/L; Sr CPK total 396 U/L; Sr TSH 3.85 mIU/L; Skin biopsy was suggestive of interface dermatitis. Serum Cortisol was found to have 11ug/ml; Sr Iron = 41 mcg/dl; TIBC = 209 mcg/dl.

CASE 4

45 years old male presented with chief complaints of generalized weakness, loss of appetite, nausea, recurrent vomiting in the last 1 month. He was a chronic alcoholic for 10 years. Initially, he was suspected as a case of alcoholic liver disease but the investigations (LFTs / Ultrasonography of the abdomen) were within normal limits. Hence alcoholic liver disease was ruled out. Then after taking a detailed history, he revealed that he was taking one tablet of Prednisolone 10mg daily which was prescribed by some local doctor 5 years ago for loss of appetite for some days. But he continued taking the tablets for over 5 years because whenever he tried to stop the tablets, he would get nausea, loss of appetite, and feeling of unwellness. So, he continued the tablets for 5 years. When he visited some private doctor two months back, he was advised to stop the tablets immediately. And after some days the symptoms began. After this history, we suspected adrenal insufficiency due to long-term exogenous steroid abuse and sudden stopping of the drug. Hence serum cortisol level sent which was found to be on the lower side. Diagnosis of drug-induced Addison's disease was made.

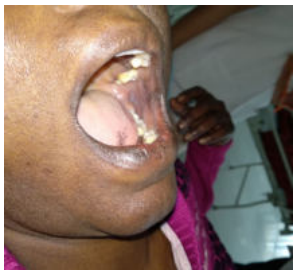

Figure 1: Mucosal Hyperpigmentation

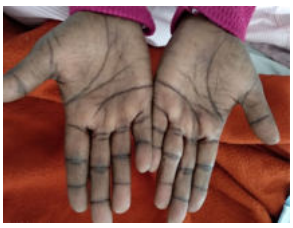

Figure 2: Hyperpigmented palmar creases

Figure 3: Darkening of sun-exposed areas (feet)

DISCUSSION

ETIOLOGY: Worldwide, infectious diseases are the most common cause of primary adrenal insufficiency.[1]

Primary adrenal insufficiency is most commonly caused by autoimmune adrenalitis in the western world. Isolated autoimmune adrenalitis accounts for 30–40%, whereas 60–70% develop adrenal insufficiency as part of autoimmune polyglandular syndromes (APS).[2] Inborn causes of primary adrenal insufficiency other than CAH are rare, causing <1% of cases.[2]

Except for tuberculosis and autoimmune adrenal failure, other causes of Addison's disease are rare.[1]

Rarer causes of adrenal insufficiency involve the destruction of the adrenal glands as a consequence of infection, hemorrhage, or infiltration; tuberculous adrenalitis is still a frequent cause of disease in developing countries.[2]

This article focuses on the diagnosis and treatment of Addison's disease and Addison's crisis in patients presenting to tertiary health care hospitals in India where tuberculosis is the most common cause of Addison's disease.

Nevertheless, it is associated with significant morbidity and mortality, but once the diagnosis is made it can be easily treated.[4]

CLINICAL DIAGNOSIS:

Because the estimated prevalence of Addison disease is one in 20,000 persons in the United States and Western Europe, a high clinical suspicion is needed to avoid misdiagnosing a life-threatening adrenal crisis. Signs and symptoms can be subtle and nonspecific. Patients may experience fatigue, weakness, weight loss, and gastrointestinal upset. Symptoms are gradual and worsen over years, making early diagnosis difficult. The symptoms relate to the degree of cortisol, mineralocorticoid, and adrenal androgen deficiency at the time of presentation.

Loss of more than 90% of both adrenal cortices results in the clinical manifestation of adrenocortical insufficiency. It can be gradual destruction as in cases of autoimmune destruction, infections – which leads to signs and symptoms of chronic adrenocortical insufficiency, and acute adrenal crisis may develop in stressful situations. Destruction of the adrenal cortex can be a rapid one as in cases of bilateral adrenal hemorrhage, and such patients usually present with acute adrenal crises.

Addison disease is usually diagnosed after significant stress or illness unmasks cortisol and mineralocorticoid deficiency, presenting as a shock, hypotension, and volume depletion (adrenal or Addisonian crisis). Cortisol and aldosterone deficiencies contribute to hypotension, orthostasis, and shock; however, the adrenal crisis is more likely to occur in primary adrenal insufficiency compared with secondary adrenal insufficiency.[5]

Symptoms and signs of chronic primary adrenocortical insufficiency include muscular weakness, fatigue, anorexia, weight loss, nausea, vomiting, orthostatic hypotension, mild hyponatremia, hypoglycemia, and hyperpigmentation - all due to cortisol deficiency. Generalized hyperpigmentation of skin and mucous membranes (buccal mucosa & gums) is one of the earliest manifestations of Addison's disease. Hyperpigmentation is usually generalized over the entire body but more in sun-exposed areas and pressure areas such as the knuckles, toes, elbows, and knees. It can be found in palmar creases, buccal mucosa, vermilion border of the lips, and around scars and nipples.[2]

Hyperpigmentation is the physical finding most characteristic of Addison disease, arising from continual stimulation of the corticotropes in the anterior pituitary. Specifically, it results from cross-reactivity between the ACTH produced by the corticotropes and the melanocortin 1 receptor on keratinocytes. It is not a feature of secondary adrenal insufficiency because of the lack of increased ACTH in these patients.

If associated mineralocorticoid deficiency is present as in advanced cases, it can lead to dehydration, hypotension, salt craving, hyponatremia, hyperkalemia, and acidosis. An acute adrenal crisis occurs during periods of stress like infection, trauma, or surgery, featuring sudden onset shock, fever, nausea, vomiting, severe dehydration, hypoglycemia, and depressed mentation.

DIAGNOSIS:

Metabolic Tests

The goal of laboratory testing is to document a low cortisol level and determine whether the adrenal insufficiency is primary or secondary. Low serum cortisol levels at 8 a.m. (less than 3 mcg per dL [83 nmol per L]) suggest adrenal insufficiency, as do low serum sodium and high serum potassium levels. Hyponatremia can be attributed to cortisol and mineralocorticoid deficiencies, whereas hyperkalemia is attributed solely to a lack of mineralocorticoids. Because the adrenal hormones are gradually lost over years to decades, the levels vary. One of the first indications that there is adrenal cortex dysfunction is an elevated plasma renin level. A rise in ACTH levels is concomitant with the loss of adrenal hormones. Yearly monitoring of ACTH levels in at-risk individuals shows that measurements greater than 50 pg per mL (11 pmol per L), which exceed the upper limit of normal, are indicative of cortisol deficiency.[5]

The diagnosis of adrenal insufficiency is established by the short cosyntropin test[2]. The serum cortisol, plasma ACTH, plasma aldosterone, and plasma renin levels should be measured before administering 250 mcg of ACTH. At 30 and 60 minutes after intravenous ACTH administration, the serum cortisol level should be measured again. The cut-off for failure is usually defined at cortisol levels of <450–500 nmol/L (16–18 μg/dL) sampled 30–60 min after ACTH stimulation[2]

Immunologic tests and Imaging

The 21-hydroxylase enzyme is necessary for cortisol synthesis in the adrenal cortex; antibodies directed against this enzyme are specific for autoimmune adrenalitis and are detectable before symptom onset.[5] Computed tomography (CT) demonstrates small adrenal glands in patients with autoimmune adrenal destruction. In other causes of Addison disease, CT may show hemorrhage, calcification associated with tuberculosis infection, or masses in the adrenal gland. However, CT is not necessary to diagnose adrenal insufficiency.[5]

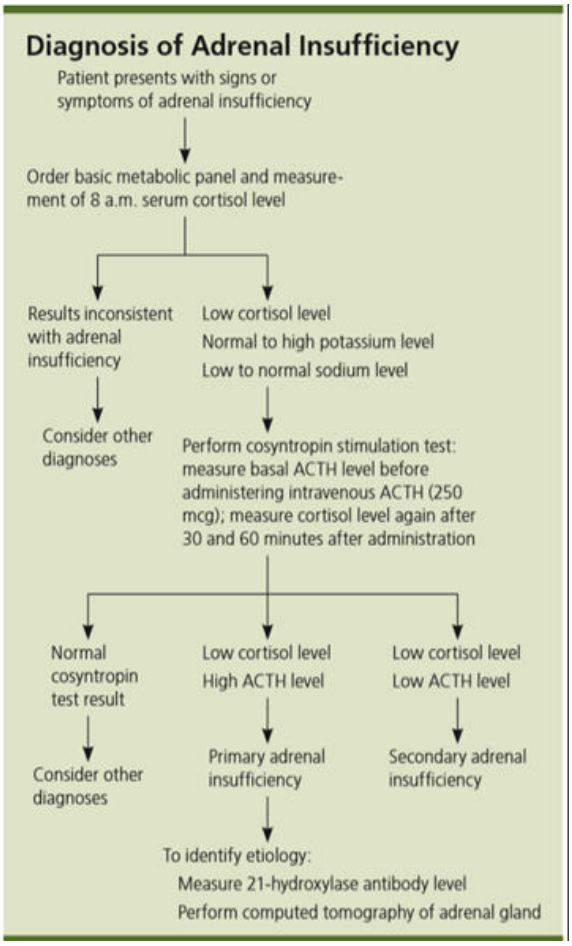

Fig 1.1 Algorithm for the diagnosis of adrenal insufficiency[5]

TREATMENT

Acute adrenal insufficiency is a life-threatening emergency, and treatment should not be delayed while waiting for definitive proof of diagnosis. However, in addition to the measurement of plasma electrolytes and blood glucose, appropriate samples for ACTH and cortisol should be taken before corticosteroid therapy is given.[6] If the patient is not critically ill, an acute ACTH stimulation test can be performed. In adults, intravenous hydrocortisone should be given in a dose of 100 mg every 6 to 8 hours. (Hydrocortisone dose 10 mg for infants, 25 mg for toddlers, 50 mg for older children and 100 mg for adolescents at 6 hourly intervals for the first 24 hours)[5] In the patient with shock, 1 L of normal saline should be given intravenously over the first hour. Because of possible hypoglycemia, it is normal to give 5% dextrose in saline. Subsequent saline and dextrose therapy will depend on biochemical monitoring and the patient's condition. Clinical

improvement, especially in the blood pressure, should be seen within 4 to 6 hours if the diagnosis is correct. It is important to recognize and treat any associated condition (e.g., infection) that may have precipitated the acute adrenal crisis.[6]

Long-term therapy aims to give replacement doses of hydrocortisone to mimic the normal cortisol secretion rate of 8 to 15 mg/day. Most patients can cope with less than 30 mg/day (usually 15 to 25 mg/day in divided doses). Doses are usually given on awakening, with a smaller dose at 6 PM.[6] In primary adrenal failure, mineralocorticoid replacement is usually also required in the form of fludrocortisone 0.05 to 0.2 mg/day.[6]

Response to therapy: Assessment of adequacy of glucocorticoid replacement is clinical, and not by biochemical measures. Adequate treatment results in the disappearance of weakness, return of appetite and sense of well-being, and the weight returns to normal. The hyperpigmentation invariably improves but may not entirely disappear. Chronic overdose with glucocorticoids leads to obesity, short stature, and osteoporosis. Adequacy of mineralocorticoid replacement may be determined by the assessment of blood pressure, electrolytes, and upright plasma renin levels. Hypertension and hypokalaemia result if the fludrocortisone dose is excessive.

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