ADDISON'S DISEASE

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Abstract: Addison disease is a chronic primary hypoadrenalism that lead to deficiency of adrenocortical hormones. Patient may present chronically or acute superimposed on chronic. A number of causes leading to Addison, disease. The most common cause being autoimmune destruction. Other common causes include tuberculosis, granulomatous disease, bilateral adrenal metastasis, bilateral adrenalectomy, bileral adrenal haemorrhage or infection. Clinical presentation include nausea, vomiting, abdominal pain, diarrhea or constipation, postural hypotension. Weakness, fatigue, confusion, pigmentation over knuckles, posterior neck, buccal cavity, palmer creases and nail beds. Addison disease diagnosed by measurement of plasma cortisol, ACTH level and short ACTH stimulation test. Management include glucocorticoides and Mineralocorticoides.

Key words: Hypoadrenalism, Glucocorticoides, Mineralocorticoides ACTH, Cortisol.

DEFINITION:

Addison's disease is chronic hypoadrenalism in which primary adrenal insufficiency (there is destruction of entire adrenal cortex) lead to deficiency of adrenocortical hormones i-e glucocorticoids, mineralocorticoids and adrenal androgens. Patient may present chronically or acute superimposed on chronic.

AEITIOLOGY & PATHOPHYSIOLOGY:

There are number of causes leading to Addison's disease, the most common cause is autoimmune destruction (alone, or as part of type I or type II polyglandular autoimmune syndrome i-e type 1 diabetes mellitus, pernicious anemia, thyroiditis and premature ovarian follicles). Other common causes include tuberculosis, granulomatosis diseases, bilateral tumor metastasis, bilateral adrenalectomy, bilateral adrenal haemorrhage or infection, HIV and CMV. Less commonly Hemochromatosis, amyloidosis, congenital adrenal hypoplasia and adrenoleukodystrophy.

It is predominantly common in females. In Addison's disease reduced cortisol level results in increase production of CRH (corticotrophin releasing hormone) and ACTH (adrenocorticotrophic hormone) by negative feedback mechanism. Addison's disease differs from hypothalamic-pituitary disease in which mineralocorticoid secretion and androgens remain intact.

DIFFERENTIAL DIAGNOSIS:

Differential diagnosis of Addison's disease includes hemochromatosis, sarcoidosis,

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tuberculosis, hyperkalemia, adrenal suppression due to corticosteroid therapy, hyperthyroidism, occult malignancy and anorexia nervosa.

CLINICAL FEATURES:

Patient may present chronically or acute superimposed on chronic (adrenal crisis). Symptomology is nonspecific, chronically glucocorticoids insufficiency includes gastrointestinal manifestations (anorexia, nausea, vomiting, abdominal pain, diarrhea and constipation), central nervous system manifestations (weakness, fatigue, confusion, depression and mental irritability). ACTH excess lead to skin manifestations include cutaneous or mucosal (vitiligo or pigmentation dull, slaty, grey-brown, predominantly over knuckles, posterior neck, buccal cavity, elbow, palmar creases and nail bed).Others include postural systolic hypotension (orthostatic) due to hypovolaemeia and sodium loss (glucocorticoids deficiency lead to postural hypotension whereas mineralocorticoids deficiency lead to hypotension), myalgia. Adrenal androgen insufficiency should be considered in patients with decreased body hairs and impotence/amenorrhea.

When acute superimposed on chronic, patient presents with an acute adrenal crisis (surgery or complications of diseases are etiological factors) manifestations include circulatory shock, hypoglycemia, hyponatremia, hyperkalemia and pyrexia of unknown origin (3S shortage of salts, sugar and steroids).

Clinically the diagnostic criteria of Addison's disease includes triad of i. Weakness or emaciation (100% cases), ii. pigmentation (90%) and iii. hypotension (80%).

INVESTIGATIONS:

If Addison's disease is suspected immediately random blood sample should be taken for measurements of plasma cortisol and short ACTH stimulation test (also called short Synacthen test or tetracosactrin test). Blood sample ideally should be taken prior to administration hydrocortisone in patient of primary adrenal insufficiency.

The best screening test for Addison's disease is cortisol response 60 min after 250µg ACTH intravenously or intramuscularly. Cortisol level should exceed 18 µg/dL 30-60 min after ACTH. If the response is abnormal, then primary and secondary deficiency may be distinguished by measurement of aldosterone from the same blood samples. In secondary adrenal insufficiency the aldosterone level normally increased from base line (≥ 5 ng/dL). Moreover plasma ACTH values are increased in primary adrenal insufficiency whereas plasma ACTH values are decreased or inappropriately normal in secondary adrenal insufficiency. There is normal response to rapid ACTH stimulation test in patients with partial pituitary insufficiency. Serum cortisol <5 mg/dl (< 100nmol/L) in early morning (or randomly < 550nmol/L) with simultaneously elevation of ACTH (> 200 pg/ml) is diagnostic. In 50% patients of autoimmune Addison's disease the Anti-adrenal antibodies are present. For mineralocorticoids assessment, adequately assessed by electrolytes measurements since hyponatermia and hyperkalemia occurs. Plasma renin and aldosterone should be assessed in supine position because in mineralocorticoids deficiency plasma renin activity is high and aldosterone is in lower part of reference range. Non specific investigations includes serum urea , imaging of adrenal gland with CT or MRI, plan x

ray or ultrasound for tuberculosis causes calcification and complete blood count for neutropenia, lymphosytosis, eosinoplhillia.

MANAGEMENT:

Management plan of patient with primary adrenal insufficiency depends on cause, sign and symptoms. Presentation of patient may be chronic or acute superimposed on chronic (adrenal crisis).

Long term treatment in chronic disease is treated with glucocorticoids and mineralocorticoids.

Glucocorticoids includes hydrocortisone (cortisol) and prednisolone, mineralocorticoids include fludrocortisones. Hydrocortisone, at 15-25 mg/day divided into 2/3rd in the morning and 1/3rd in the afternoon orally is the mainstay of glucocorticoids replacement therapy. If hydrocortisone not available, prednisolone 7.5 mg/day (5 mg on waking and 2.5 mg in the afternoon) is also given in some patients. After glucocorticoids therapy no need to monitor plasma cortisol level.

Fludrocortisones is usually need for primary adrenal insufficiency, with doses of 0.05-0.1 mg/day orally given. Doses of mineralocorticoids should be titrated to normalize the sodium, potassium and renin levels and to maintain normal blood pressure without postural changes.

Androgen replacement with Dexahydroepiandrosterone 50mg/day is usually indicated in females with primary adrenal insufficiency who have symptoms of reduced libido but side effects of androgen replacement therapy lead to growth of unwanted hairs and acne.

During adrenal crisis, if patient is critically ill or hypotensive, high dose hydrocortisone (10mg/hr continuous intravenously or 100mg bolus intravenously 3 times/day) should be given intravenously or intramuscularly together with intravenous 0.9% saline. When patient start improving and afebrile, the dose can be tapered by 20-30% daily to usual replacement doses. When patient become stable then oral steroid is started (initially hydrocortisone 20mg 8 hourly, reducing to 20-30 mg in divided doses over few days, than start original replacement therapy as mentioned in long term management). Acute hypoglycemia is corrected by given 10% glucose intravenously and hyperkalemia by intravenous calcium gluconate, salbutamol.

If tuberculosis is suspected or present anti-tuberculosis chemotherapy therapy should be given.

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