CUSHING SYNDROME

Dr. Muhammad Sarfraz

Abstract: It is defined as clinical condition in which there are increased free circulating glucocorticoides casused by excessive activation of glucocorticoids receptors. Most common cause of cushing syndrome is latrogenic, others causes being over production of cortisol by adrenal glands or excessive production of ACTH by pituitary tumor or ectopic ACTH production. Clinical features include central obesity, moon like face, easy bruisibility, pinkish stria, acne, amenorrhea etc. Diagnosis of cushing syndrome is two steps procedure.[1] Patient is suffering from cushing syndrome or not.[2] The underlying cause of cushing syndrome. Management-Prognosis very poor in untreated patient, Management includes medical therapy, external pituitary irradiation and surgical removal.

Key words: Glucocorticoides, ACTH, Metabolic alkalosis, Hypokalemia, Corticotrophin releasing hormone.

DEFINITION:

Cushing syndrome is defined as clinical condition in which there are increased free circulating glucocorticoids caused by excessive activation of glucocorticoids receptors.

AEITIOLOGY & PATHOPHYSIOLOGY:

The most common cause of Cushing syndrome is iatrogenic (due to administration of glucocorticoids for therapeutic reasons e-g asthma or arthritis). Other common cause is endogenous Cushing syndrome due to chronic over production of cortisol by adrenal glands (either by adrenal tumor or excessive production of ACTH by pituitary tumor or ectopic ACTH production). Endogenous Cushing syndrome is classified into ACTH-dependent 80%, non-ACTH-dependent 20%, and hypercortisolism due to other causes (referred as pseudocushing syndrome).

There are two main causes of ACTH-dependent endogenous Cushing syndrome, bilateral adrenal hyperplasia (or bilateral primary pigmented nodular hyperplasia BPPN) secondary to hypersecretion of ACTH by pituitary or ectopic. Pituitary adenoma is 70% four times common in females than males and ectopic ACTH syndrome 10% more common in males than females. Causes of Non-ACTH-dependent endogenous Cushing syndrome includes, adrenal adenoma 15%, adrenal carcinoma 5% and McCune-Albright syndrome. Pseudocushing syndrome is caused by alcohol excess, major depression, illness and primary obesity.

DIFFERENTIAL DIAGNOSIS:

Differential diagnosis of Cushing syndrome includes pituitary adenoma, adrenal

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carcinoma, ectopic ACTH due to bronchial or bronchus carcinoid lesion, adrenal adenomas and McCune Albright syndrome.

CLINICAL FEATURES:

Commonest clinical features are central obesity (like lemon on tooth picks), easy bruising, purple striae on lower abdomen, proximal myopathy, thin fragile skin on arms and legs, fat deposition in face and nuchal area (buffalo hump over seventh cervical vertebrae and moon facies) acne, virilization and amenorrhea.

Associated diseases include hypertension, osteoporosis and diabetes.

Careful drug history should be taken if suspected Cushing syndrome because glucocorticoids can induced Cushing syndrome.

Hypokalemia and metabolic alkalosis are more specific to ectopic ACTH syndrome. Hypokaelmia and metabolic alkalosis aggravates myopathy and hyperglycemia (by inhibiting insulin secretion).

Cachexia associated when tumors induces the ACTH secretion.

In case of pituitary adenoma there is excess corticosteroid secretion due to increased ACTH. As already mentioned it is four times common in females as males. This termed as Cushing disease.

INVESTIGATIONS:

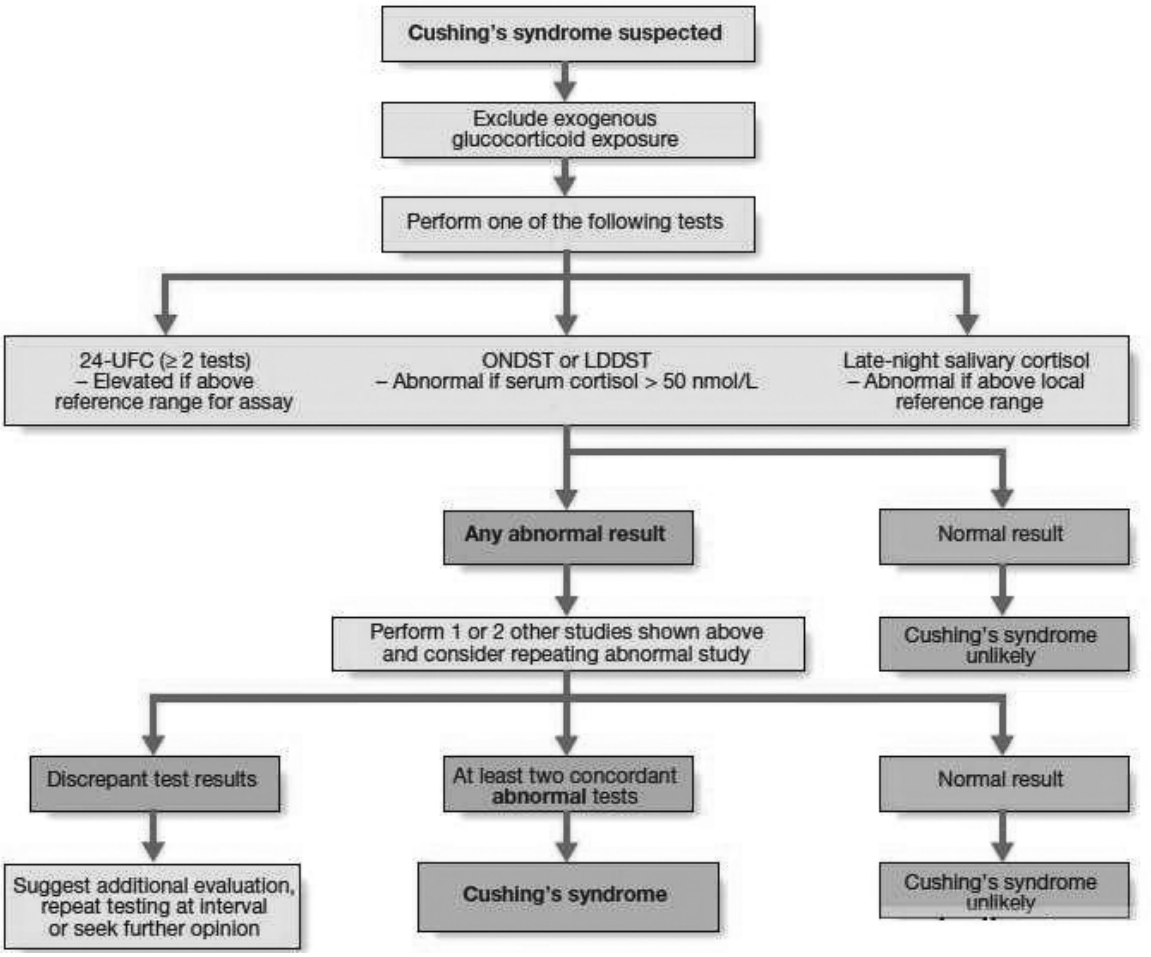
Before going to investigate patient of suspected Cushing syndrome always first rule out any acute illness, because this activates the HPA axis and causing spurious results.

Diagnosis of Cushing syndrome is two steps procedure) I is patient suffering from Cushing syndrome or not) II the underlying cause of Cushing syndrome (i-e differential diagnosis of its cause).

Diagnosis requires demonstration of increased cortisol production and abnormal cortisol suppression in response to dexamethasone. Initially 24 hr measurement of urinary cortisol, the 1 mg overnight dexamethasone test [8:00 A.M plasma cortisol < 1.8 µg/dL (50 nmol/L)], or late night salivary cortisol is most appropriate to measure. For the confirmation of Cushing syndrome revision or more than one investigations are required. Definitive diagnosis is made after failure to suppress serum cortisol with low doses oral dexamethasone [plasma cortisol < 5 µg/dL (140 nmol/dL) after 0.5 mg dexamethasone every 6 hr for 48 hrs], loss of normal circadian rhythm of cortisol with inappropriate increased level late night serum or salivary cortisol and increased 24 hr urine free cortisol [< 10 µg/dL (25 nmol/dl)].

When diagnosis is made plasma ACTH level is measured to find out underlying cause of Cushing syndrome. Low level of ACTH (below 1.1 pmol/L) suggest adrenal adenoma or carcinoma, abnormally higher level of ACTH indicate pituitary or ectopic source.

(ACTH = adrenocorticotrophic hormone; AIMAH = ACTH-independent macronodular adrenal hyperplasia; BIPSS = bilateral inferior petrosal sinus sampling; CRH = corticotrophin-releasing hormone; HDDST = high-dose dexamethasone suppression test; PPNAD = primary pigmented nodular adrenal disease)



Sequence of investigations in suspected spontaneous Cushing's syndrome.
A serum cortisol of 50 nmol/L is equivalent to 1.81 µg/ dL.
(LDDST = low-dose dexamethasone suppression test; ONDST = overnight dexamethasone suppression test; UFC = urinary free cortisol)
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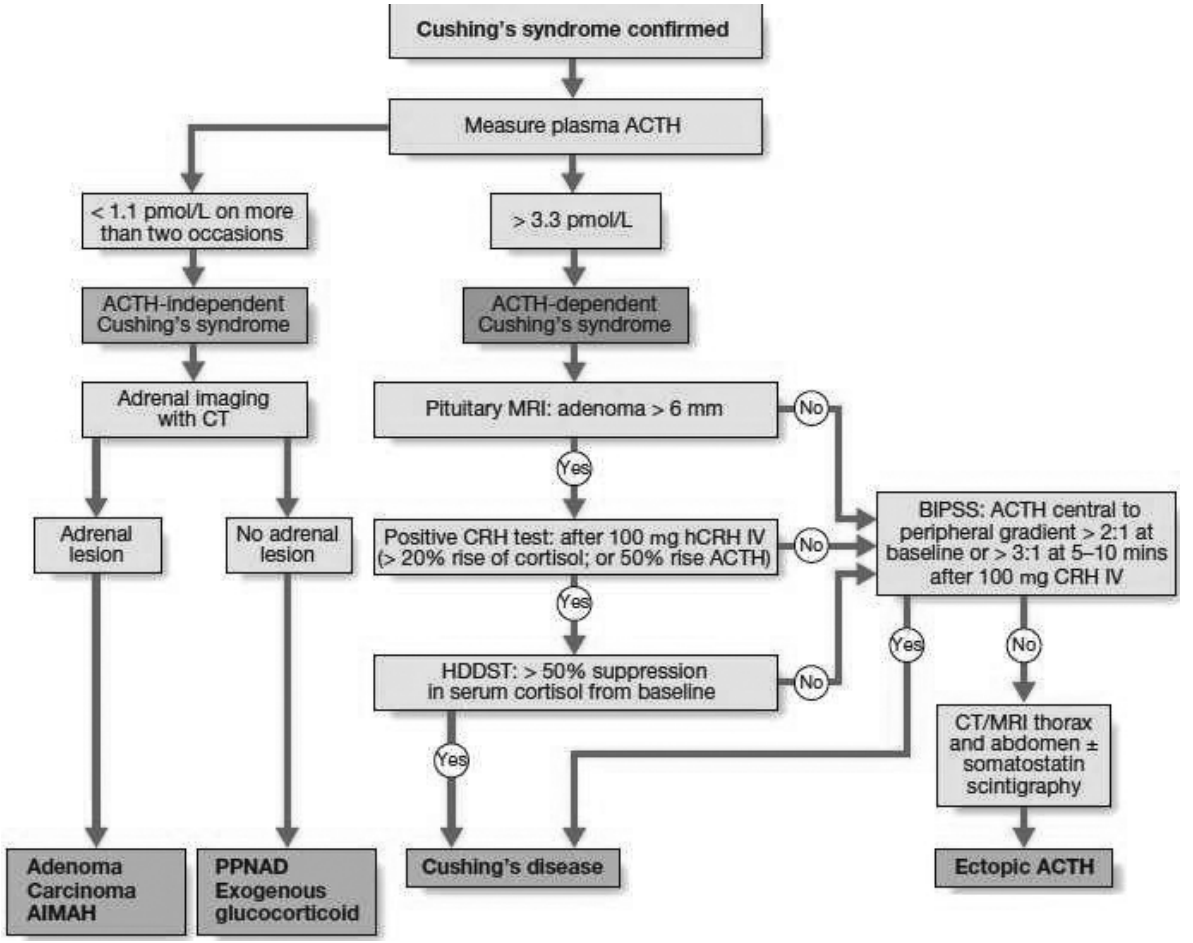
Thus, in pituitary-dependent Cushing's disease, ACTH secretion is suppressed by high dose dexamethasone and ACTH is stimulated by corticotrophin-releasing hormone (CRH). In a high-dose dexamethasone suppression test (HDDST), serum cortisol is measured before and after administration of 2 mg of dexamethasone 4 times daily for 48 hours. In more than 90% of ACTH-producing pituitary microadenomas, cortisol production is suppressed by high-dose dexamethasone 2 mg every 6 hr for 48 hr). Imaging techniques are used to localize tumors secreting ACTH or cortisol. MRI is used to confirm pituitary microadenomas secreting ACTH. If tumor is less than 6mm than bilateral inferior petrosal sinus sampling (BIPPS) with measurement of ACTH is best



Determining the cause of confirmed Cushing's syndrome.

to confirm the Cushing's disease. MRI and CT scan detects adrenal carcinoma greater than 5cm. Imaging of chest and abdomen is required to localize the source of ectopic ACTH production.

MANAGEMENT:

Prognosis is very poor in untreated patient and has 50-55% mortality in 5 year.

Management includes medical therapy, external pituitary irradiation and surgically removal. Medical treatment is used to improve clinical state prior to surgery or if source of ACTH cannot be resected. Medical management includes ketoconazole (600-1200 mg/d), metyrapone (2-3 g/d) or mitotane (2-3 mg/d) relieve clinical manifestations of cortisol excess. These dose of these corticosteroid biosynthesis inhibitors best titrated against serum cortisol levels or 24 hr urine cortisol. Surgical management includes trans-sphenoidal surgery and bilateral adrenalectomy. Trans-sphenoidal surgery with selective removal of adenoma is treatment of choice for

pituitary ACTH-secreting microadenomas (long term follow up required because these tumors reoccur). When surgical cure is not achieved, radiation therapy can be used and children respond better to radiation therapy. If there is bilateral adrenalectomy in patients of pituitary adenomas, they develop most common complication named as Nelson's syndrome (aggressive pituitary adenoma enlargement). Laproscopic adrenal surgery is treatment of choice for adrenal adenoma. Stress doses of glucocorticoids pre and post operatively must be given when surgical removal of adrenal adenoma and carcinoma going to be done. Metastatic adrenal carcinoma is treated with mitotane in doses gradually increased to 6g/d in three or four divided doses. In case of ectopic ACTH syndrome (bronchial carcinoid) removed surgically and before surgery its severity is reduced by medical therapy.

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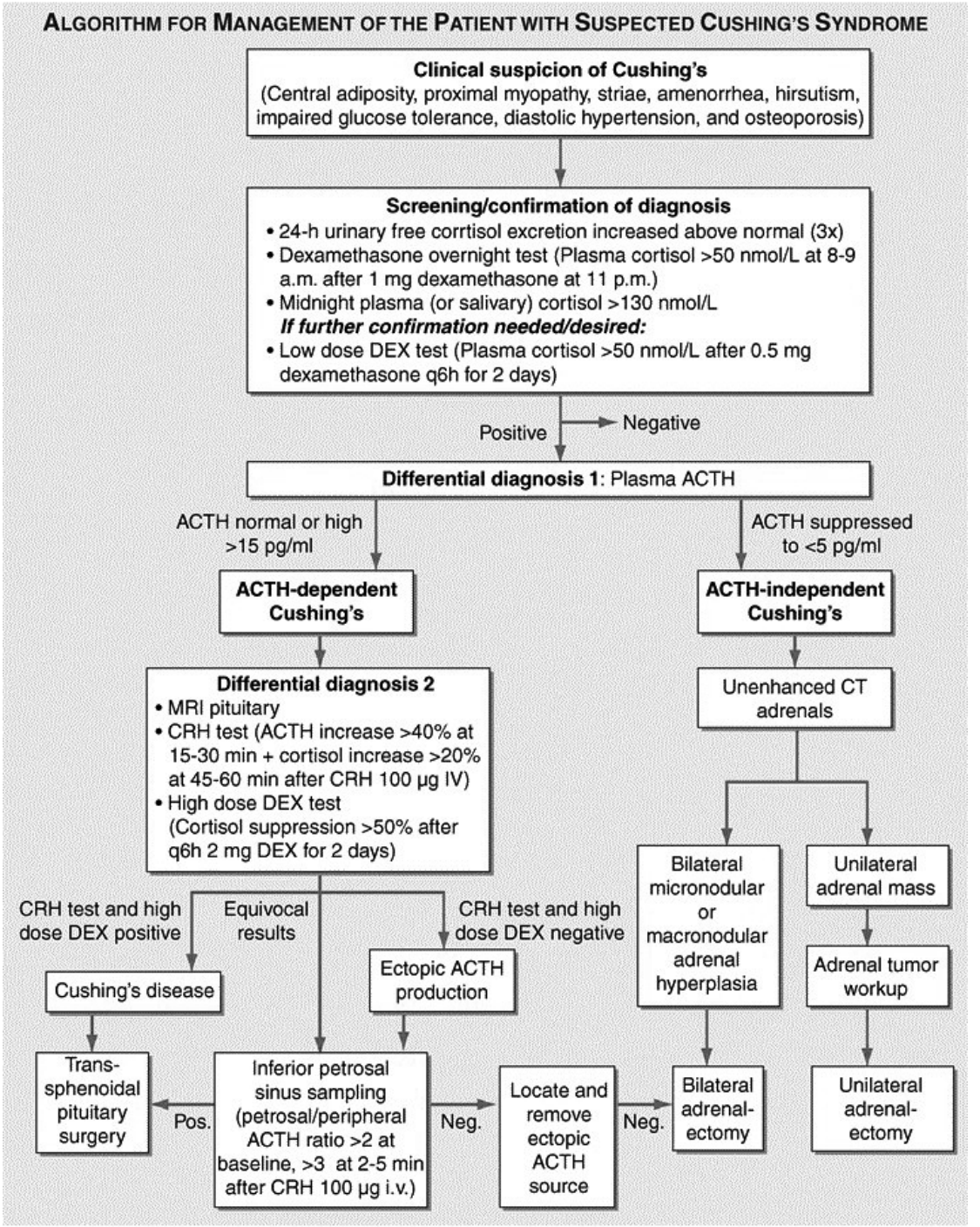

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