CUSHING'S DISEASE

A Thesis

Submitted for partial fulfilment of M. S.

(Medicine)

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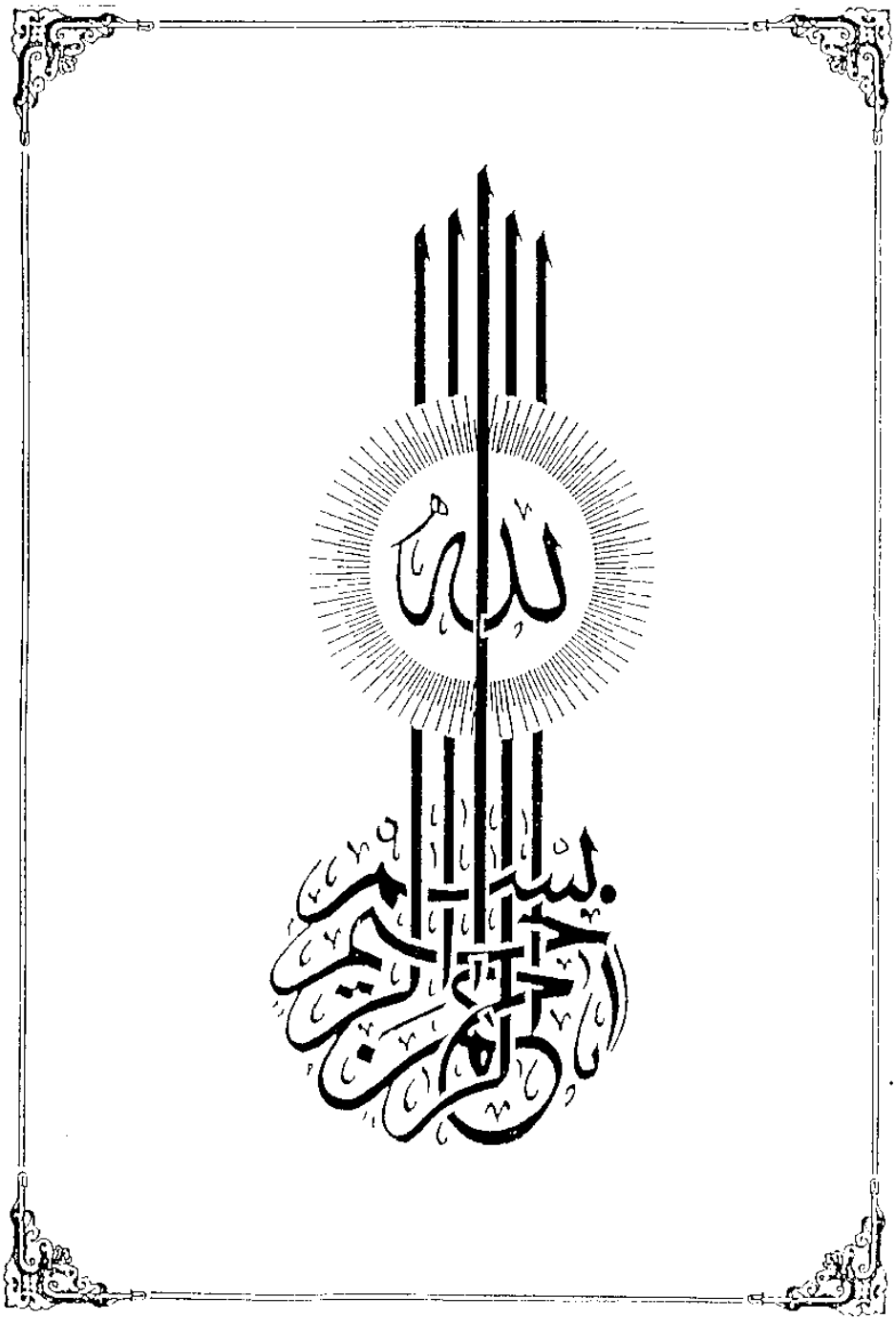
1976

ACKNOLEDGMENT

I would like to thank Dr. A. M. Ghareeb for his advice to complete this article and allowing me to measure plasma cortisol and A.C.T.H. in the endocrine laboratory as well as the referances which were forwarded to me to complete this work.



CONTENTS

	Page
1. Historical Review	1
2. Aetiology	1
3. Metabolic Aspects	2
4. Clinical picture	5
5. Diagnosis	8
6. Managment	14
- Cushing's syndrome	14
- Cushing's disease	20
- Ectopic A C T H syndrome	25
7. Cushing's syndrome in children	27
8. Virilism & Mineralocorticoid excess associated with Cushing's syndrome	29
9. Special problems related to Cushing's Syndrome .	30
- Recovery from pictuitary-adrenal suppression .	30
- Pituitary tumours following bilateral adrenalectomy	31
- Aetiology of hyperpigmentation in Cushing's disease and Ectopic A C T H syndrome	32
10. References	34

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CUSHING'S DISEASE

Historical Review :

Harvey Cushing. The first to describe the disease, studied medicine at Harvard - then a student of Halsted in Baltimore, became a leader in neurosurgery. Early in his career, he worked with kocher in Bern, where he demonstrated the relationship between intracranial pressure and blood pressure. Back to States, he described the relationship between pituitary tumours & infantilism. In 1912 he published a monograph on the pituitary body, and in 1932 described hypophyseal basophilism known since as Cushing's disease.(1)

Aetiology :

Cushing's syndrome is mainly due to chronic excess of cortisol"hypercortisolism". This cortisol excess may be due either to adrenal tumour "adenoma or carcinoma" or to excessive stimulation of the adrenals by excessive amounts of ACTH which may be of pituitary "basophil adenoma or chromophobe adenoma" or of ectopic sites.(2)

With wide use of cortisone & its long list of derivatives down to dexamesathone, in the treatment of various chronic aliments, "iatrogenic" cushing's is frequently encountered in clinical practice. Cushinoid features occassionally occur during pregnancy or after long term treatment with Salicylates.(1)

Metabolic Aspects :

The main metabolic changes in Cushing's syndrome, whatever its cause may be, are due to hypercortisim.(2)

Carbohydrate Metabolism :

Cortisol excess produces hyperglycaemia, glycosuria, increased resistance to insulin, and an increase in liver glycogen. Cortisol accelerates gluconeogenesis in the liver, mainly by favouring glycogen formation from amino acids formed by protein breakdown. This protein comes mainly from muscles, bone materix and subcutaneous tissues. Cortisol also inhibits glucose uptake by the tissues. The blood pyruvate level rises.(4)

Protein Metabolism :

Cortisol promotes catabolism of proteins, excess of cortisol causes a negative nitrogen balance accompained by retardation of growth, wasting of muscles, thining of the skin, osteoporosis & reduction in lymphoid tissues. Break down of muscles increases creatine excretion, and dissolution of lymphocytes increases uric acid excretion in the urine.(4)

Lipid Metabolism :

Cortisol excess raises blood lipids and the plasma cholesterol level. This leads to atherosclerosis which is a feature of Cushing's syndrome.(4)

Electrolyte & water metabolism :

Cortisol promotes retention of Na^+ and usually of Cl-, and excretion of K^+ by the kidney. When excessive, it will lead to hypokalaemia and hypertension.(4)

Blood : Eosinopenia, lymphopenia, neutrophil leucocytosis and polycythaemia occur in Cushing's syndrome. Excess of cortisol causes lysis of fixed lymphoid tissue of the thymus, spleen and lymph nodes. Cortisol causes lymphopenia by interfering with DNA synthesis, and by promoting destruction of lymphocytes. The eosinophil count is lowered by sequestration of eosinophil is in the lungs & spleen, and by destruction in the circulating blood. The basophils undergo a similar change. Cortisol increases the platelet count and shortens blood clotting time.(4)

Immunologic effects :

Overproduction of cortisol results in profound damage to the circulating "T" lymphocytes - "B" lymphocytes & leucocytes are less sensetive to endogenous over production of cortisol and γ globulin level is normally produced by mature "B" lymphocytes. This renders patients with Cushing's syndrome more liable to infection, especially fungal.(7)

Cortisol excess reduces the formation of granulation tissue and delay wound healing by inhibiting the production of ground substance by collagen-producing cells.(4)

Cardiovascular system : In excess, cortisol may raise the blood pressure above normal, it increases the production of angiotensinogen which could lead to enhanced formation of angiotensin and this in turn to increased secretion of aldosterone.(4)

Gastro-intestinal tract : Cortisol increases gastric acidity & pepsin production.(4)

Bone metabolism : Cortisol excess impedes the development of cartilage, and causes thining of the epiphyseal plate and inturruption of growth "in children". There is a defect in the synthesis of the protein matrix and decreased deposition of calcium. There is also decreased absorption of calcium from the gut; cortisol antagonizes vit. "D", and increased loss of calcium in the urine.(4)

Muscle power : Muscle weakness result, from the negative nitrogen balance due to loss of protein & creatine from muscles - also hypokalaemia leads to muscle weakness.(4)

Central nervous system : Cortisol excess lowers the threshold for electrical excitation of the brain and tends to promote fits in epileptic subjects. Euphoria is a feature of Cushing's syndrome.(4)

Clinical picture :

Cushing's syndrome occurs sporadically in all races, all ages and both sexes, but it is most common in women between the ages of 20 and 60. Typically it is charcterized by weight gain which is due principally to accumulation of adipose tissue, particularly in the facial, nuchal, truncal, and girdle areas. This is sometimes referred to as centripetal or "buffalo" obesity.(1)

Another charcter of cushing's syndrome is evidence of protein loss. In mild cases or those of only a few months duration, this may amount to nothing more than tendency to bruise easily. In more sever, chronic cases, the skin may be so thin and fragile that it is denuded by removal of a strip of adhesive tape or some other trivial injury. Insignificant trauma may result in formation of ecchymosis. Because the weakned skin is stretched by underlying accumulation of adipose tissue, it may become so thin that streaks of capillaries become visible - the pink or purple striae

of classic Cushing's syndrome. Muscle wasting may result in sever muscle weakness. Generalized osteoporosis is more common in the vertebral column where the weakening of the vertebral bodies may permit bulging of intervertebral discs, giving rise to the "cod fish vertebrae" appearance in x-ray. Spontaneous fractures may occur with anterior wedging of the vertebral bodies, resulting in kyphosis, loss of hight, and backache. Pathologic fractures may occur in the extremities in more sever cases.(2)

Osteoporosis may lead to a mild type of hyper calciuria, with urinary calcium values of 150-200 mg. pe. day. Renal stones occur in about 20 % of cases.(2)

Superficial wounds heal slowely and frequently infected & ulcerated - this is especially common on pretibial areas.

In children and adolescents, growth is arrested, for if the epiphyses of long bones close before the Cushing's syndrome is corrected, shortened stature will be inevitable. So, if an obese child is growing rapidly - he has no Cushing's syndrome, but the syndrome must be suspected in obese children who grow slowely.(2)

In addition to centripetal obesity and protein wasting,

the patient with Cushing's syndrome usually has impaired glucose tolerance.(4) The usual pattern is not that of frank diabetes mellitus with glycosuria and elevated fasting blood glucose, but rather a failur of blood glucose to return to fasting levels during a second and third hours of a standerd glucose tolerance test. Approximately 90 % of patients with Cushing's syndrome will have at least impairment of glucose tolerance.(2)

The majority of patients with Cushing's syndrome have high blood pressure. They may have left ventricular hypertrophy and increased susceptibility to occlusion of major arteries. Edema and hypokalaemia occur in only a minority of patients with Cushing's syndrome.(2)

Other common manifestations of Cushing's syndrome include moon face, hirsutism, oligomenorrhea, mild erythrocytosis, lymphopenia and eosinopenia. About 30 % have superficial fungal infections such as tinea versicolor. Serum gamma globulin concentrations and serum protein - bound iodine concentrations are often slightly subnormal. Many patients with Cushing's syndrome are emotionally labile and easily irritated. A few are psychotic, and the psychotic patterns have most frequently resembled schizophrenia, hypomania, or depression.

In the past, death commonly resulted among patients with Cushing's syndrome from infections with pyogenic organisms, hypertensive arteriosclerotic cardiovascular disease, and suicide.

Many patients with hypercortisolism have some associated excess of adrenal androgen, but it is not so extreme, with only some hirsutism in androgen sensetive areas, acne, and oligomenorrhea. Extreme excesses of adrenal androgen might result in temporal hair recession, coarsening of the voice, and clitoral hypertrophy.(2)

Diagnosis :

Two problems are faced in the diagnosis of Cushing's syndrome. The first is to confirm that adrenocortical hypersecretion is present and the second is to determine the underlying pathological cause of the increased glucocorticoid secretion because this influences treatment.

If the disease is suspected, it should be confirmed by showing increased blood levels of cortisol. The estimation of plasma 11-hydroxycorticosteroids which include cortisol , corticosterone is a rapid & simple method of assay. It depends chemically on fluorscence which is not

produced by synthetic compounds such as prednisone or dexamethasone. The normal range in a blood sample taken between 9 and 10 a.m. is 5.7 - 23.7 microgm/100 ml. with a mean of 14.7/100 ml. The values varies during the day being higher in the early morning than late at night. This is called Circadian rhythm - and is almost always disturbed in patients with Cushing's syndrome and a midnight plasma 11 OHCS level is not as low as normal and exceeds 5 - 8 mg/100 ml.(3)

Determination of 11-hydroxycorticosteroids - Fluorimetric Method "Mattingly 1962" :

Reagents :

1. Methylene chloride.
2. Ethanol.
3. Concentrated sulphoric acid.
4. Fluorescence reagents : to 3 volumes ethanol add 7 volumes sulphoric acid slowely under cooling in ice bath.
5. Cortisol standerds : Prepared as follows :
   a) Stock standerd : dissolve 5 mg. of cortisol in 50 ml. ethanol and keep at -20°C. till need.
   b) Semidiluted standard : to 1 ml. of stock standerd add 99 ml. ethanol and keep at 2 - 4°C.

c) Warking standerd : to 1 ml. of semidiluted standard add 9 ml. of distelled water.

Procedure :

1. Into glass stoppered tube pipette 2 ml. hepa inized plasma and 15 ml. of methylene chloride, in another tube add 2 ml. distelled water and 15 ml. methylene chloride as blank, and in another tube 1 ml. Warking standard, 1 ml. distelled water and 15 ml. methylene chloride as standard. Cover the tubes, then shake all the tubes for 30 times, remove the supernatent by suction.

2. Add 10 ml. of the extract to 5 ml. of fluorescnce reagent in a glass stoppered tube and shake vigorously for 20 seconds. Carfully suck off the methylene chloride layer and read in "Ratio fluorometer" at 450 mm. after 10 minutes of mixing with 1 minute between each sample and another.

Calculation : µg "Cortisol" per 100 ml. plasma =

$$= \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 1,0 \times 50 \qquad (13)$$

If it is proved that plasma cortisol value is high - the next step is to determine the site of excess of cortisol :-

1. Iatrogenic cases are excluded from the history - most of them are asthmatics, or suffer from rheumatoid arthritis, or using the drug as an immunosuppressive.

2. Plain x-ray to skull for sella turcica, to lungs for branchogenic lesions, to spine etc.....

3. Retroperitoneal air insufflation which may show either :
   a) Unilateral or bilateral hyperplastic glands.
   b) Unilateral tumour.

4. If measurment of ACTH is available, this is raised in ectopic cases as will as in pituitary lesion.

5. The final stop is to resort to the dexamethasone suppression test.

Dexamethasone suppression test :

The suppressive action of dexamethasone on ACTH secretion as reflected by lowering of the plasmal cortisol level or the urinary excretion of 17-oxogenic steroids is of particular value in establishing the diagnosis of Cushing's syndrome and also in deciding whether the syndrome is caused by adrenal hyperplasia, an adrenal adenoma or carcinoma, or an ACTH- producing non endocrine tumours.