Etiological aspects of Cushing's syndrome

Sir,

Cushing's syndrome, the clinical manifestation of chronic glucocorticoid excess or hypercortisolism, was first described 60 years ago. This condition may occur secondary to specific pathology within the pituitary and the adrenal glands, or ectopic adrenocorticotropic hormone (ACTH) or, rarely, corticotrophin releasing hormone (CRH) production from non-endocrine tumors. Cushing's syndrome is also seen in patients receiving large doses of the synthetic corticosteroids for various non-endocrine disorders (iatrogenic Cushing's syndrome). Most Cushing's syndrome is iatrogenic because of the common therapeutic use of high dose glucocorticoids. Eighty three subjects were evaluated for Cushing's syndrome in the Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir (India) from January 1986 to December 1996. The records of these subjects were reviewed for clinical, diagnostic, and therapeutic details. Adequate data could be retrieved in only 70 cases. Clinical data recorded included presence of obesity, moon facies, coarsening of skin, purple striae, hirsutism, ecchymoses, hyperpigmentation, proximal myopathy, hypertension, diabetes mellitus, osteoporosis, menstrual irregularities etc. Particular stress was laid on history of consumption of glucocorticoids for any systemic disease, type of steroid used and duration of intake. Routine investigations performed included complete hemogram, urine examination, and blood chemistry including serum cholesterol, electrolytes (sodium, potassium), calcium and phosphorous, alkaline phosphatase and oral glucose tolerance test (as recommended by WHO). Radiological investigations performed included x-rays of chest, pelvis, and skull. Abdominal sonography and computerized tomography of pituitary and adrenal glands was routinely performed in all cases of suspected Cushing's syndrome. Only a few patients underwent magnetic resonance imaging. Hormonal investigations included: basal plasma cortisol (8 am and 6 pm), dexamethasone suppression tests, and ACTH stimulation test. Seventy subjects, who constitute the subject material of this study, after proper clinical assessment and extensive investigations were classified into 3 groups. Group 1 - This group consisted of 27 patients who had iatrogenic Cushing's syndrome because of intake of supraphysiologic doses of glucocorticoids over prolonged periods for non-endocrine disorders. Group 2 - This group comprised of 13 patients in whom endogenous Cushing's syndrome was confirmed; 7 of these patients had pituitary (ACTH-dependent) Cushing's, whereas 6 patients had adrenal lesions. Group 3 - This group comprised of 30 subjects in whom the diagnosis of Cushing's syndrome could not be substantiated after detailed investigations.

Mean age (±SD) of the patients was 32.74 ± 0.79 years, 33.15 ± 0.79 years and 29.83 ± 13.91 years in groups 1, 2 and 3 respectively. On comparison, these groups did not exhibit any significant difference in their age. There was a female predominance in all the groups, being most marked in group 3 (5:1). Central obesity, expectedly, was more often seen in patients in group 1 and 2 as compared to those in group 3, who more frequently had generalized obesity. Hypertension, diabetes mellitus, hirsutism, and purple striae were more common in patients with endogenous Cushing's syndrome. Serum electrolytes were normal in most of the subjects, however, serum cholesterol showed a borderline or marked increase in 53.7% of patients in group 2. Of the 27 patients with iatrogenic Cushing's syndrome, glucocorticoids had been prescribed for some form of collagen vascular disease in 13 (48.1%), dermatological disorders in 6 (22.2%), chronic bronchial asthma in 5 (18.5%) and other miscellaneous disorders in 3 (11.1%). In 10 patients, ACTH stimulation test demonstrated adrenal stimulation, while adequate adrenal stimulation could not be demonstrated in 17 patients. Seven patients were documented to have Cushing's disease; 4 underwent pituitary surgery whereas 3 underwent bilateral adrenalectomy. Out of 6 patients with adrenal tumors, one patient had adrenal carcinoma, while 5 had adenomas. In these patients, disease was satisfactorily eradicated after adrenalectomy.

Cushing's syndrome results from exposure of tissues to excessive cortisol. The diagnosis of this disorder cannot be made unless both clinical features and biochemical abnormalities are present. Advances in diagnostic modalities and medical and surgical procedures over the past 2 decades have greatly changed the management of Cushing's syndrome. The advent of bilateral petrolas sinus sampling for corticotrophin coupled with advances in microsurgery have had a major impact on the diagnosis and treatment of Cushing's disease. Microadenomas in Cushing's disease may not be visualized even with the most sophisticated contemporary imaging techniques. Suppression tests continue to be the backbone in the evaluation of Cushing's syndrome although, both false negative and false positive results may occur. In approximately 20% of patients with Cushing's disease the 2 day high-dose dexamethasone does not suppress cortisol production, and some patients may require up to 32 mg of dexamethasone for
Letters to the Editor

suppression to occur. Most of the patients with Cushing’s disease in our series behaved predictably except for one patient, who needed 16 mg dexamethasone for suppression of cortisol.

The true incidence of Cushing’s syndrome is not known. Iatrogenic cases probably account for the majority of cases because of widespread therapeutic use of high dose synthetic glucocorticoids. In our series, exogenous steroid intake was the cause in 27 (67.5%) cases of Cushing’s syndrome. Of the endogenous Cushing’s syndrome, more than 70% of cases are classified as Cushing’s disease in Europe and the United States, whereas, in Japan 50.9% cases are caused by adrenal adenomas. The majority of corticotrope adenomas (70%) are less than 10mm in diameter and are difficult to identify by computed tomography (CT) and magnetic resonance imaging (MRI). The use of MRI with gadolinium as contrast agent improves detection of microadenomas. MRI with gadolinium enhancement has virtually supplanted CT in the diagnosis of pituitary adenomas, especially for lesions causing Cushing’s disease. Out of our 7 patients with Cushing’s disease, CT scan demonstrated pituitary microadenomas in only 3. Two patients with normal CT scan underwent bilateral adrenalectomy with gratifying results, while as pituitary microadenoma was documented in another patient with contrast enhanced MRI. One patient was lost to follow up. Computed tomography has great utility in localizing the adrenal lesions in subjects who have biochemical evidence of adrenal tumor. In addition, if the CT scan shows evidence of necrosis, the tumor is likely to be a carcinoma. All the 6 patients in our series with biochemical evidence of adrenal disease were documented to have adrenal tumor on CT scanning. In our small series, pituitary disease was slightly more common than adrenal disease causing Cushing’s syndrome. Cushing’s syndrome of adrenal or pituitary origin is 4 to 6 times more common in women than men. Our series also documents a female preponderance. Ectopic ACTH secretion is the only cause of Cushing’s syndrome that is more common in men. Central obesity, facial plethora, ecchymoses, proximal muscle weakness, osteopenia, and hypertension are good discriminant indices for Cushing’s syndrome. In our series, patients with Cushing’s syndrome had high incidence of central obesity, diabetes mellitus, purple striae, proximal myopathy, ecchymoses, and osteoporosis. Patients with endogenous Cushing’s syndrome had higher incidence of hypertension, hirsutism and menstrual irregularities. Purple striae more than one centimeter in diameter are virtually pathognomonic of Cushing’s syndrome. Emotional and cognitive changes, depressed mood, decreased libido, insomnia, anxiety, and impaired memory are seen in most patients.

Because of the common occurrence of iatrogenic Cushing’s syndrome, it is recommended that synthetic glucocorticoids should be prescribed for non-endocrine disorders only when other options have not proved effective. This is particularly important in developing and under developed countries of the world, such as ours, where patients have a tendency to continue taking medicines beyond the prescribed dosage and time limits.

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