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General Medicine

SECONDARY ADRENAL INSUFFICIENCY DUE TO THE ABUSE OF SYSTEMIC CORTICOSTEROIDS-A GROWING MENACE IN THE ELDERLY-A RETROSPECTIVE STUDY

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ABSTRACT

BACKGROUND: Corticosteroids are beneficial and often life-saving in many diseases. Yet its misuse has resulted in life-threatening adverse effects. Secondary adrenal insufficiency due to abrupt withdrawal of corticosteroid after prolonged use is one of the most feared complications. Its presentation is non-specific and in the absence of a history of corticosteroid intake, it can be misdiagnosed with serious consequences.

AIMS: This study was done to highlight the various non-specific presentations of secondary adrenal insufficiency and create an awareness of this problem.

METHODS: This was a retrospective study conducted in the geriatric medicine unit of our hospital between 2014 January and 2016 September. Charts of patients discharged with a diagnosis of chronic steroid abuse and secondary adrenal insufficiency due to hypothalamo-pituitary-adrenal axis suppression were retrieved and studied.

RESULTS: The charts of 29 patients with secondary adrenal insufficiency were analysed. Patients were aged 60–95 years (mean 70.4 years -SD 8.53). Male: female ratio was almost equal (1.07:1). Corticosteroid use was definitely documented in 11 patients (37.93 %) and duration of use varied from 1 year to 40 years with route of administration being parenteral or oral. Presenting symptoms were non-specific in all patients. The morning (AM) cortisol was less than or equal to 5mcg/dl in 21 patients and above 5 mcg /dl upto 7.5 mcg /dl in 8 patients. Mean serum cortisol was 3.28 mcg /dl (SD=2.52), median value of 2.49 mcg /dl.

CONCLUSION: Secondary adrenal insufficiency due to misuse of corticosteroids has a non-specific presentation and we need to consider it in the differential diagnosis of every critically ill patient.

KEYWORDS :

INTRODUCTION:

Introduction of corticosteroids in the treatment of various medical conditions[1] has been a great boon to medical science, saving lives and alleviating the suffering of many. Yet its misuse has resulted in life-threatening adverse effects[2,7,8]. There is an increasing incidence of corticosteroid overuse especially in respiratory, rheumatologic and skin diseases[3,4,5]

Adrenal insufficiency is one of the most feared complications of abrupt withdrawal of prolonged corticosteroid therapy. The symptoms[1] of chronic adrenal insufficiency are non-specific like anorexia, nausea, vomiting, weakness, myalgia, and weight loss. Hyperpigmentation of skin and mucosa that is typical of Addison's disease is not present, since pituitary secretion of ACTH is inhibited. In severe cases, a life-threatening acute adrenal crisis may occur and shock is refractory to therapy with vasopressors until normal level of glucocorticoids is restored. Suppression of HPA (hypothalamo pituitary adrenal) axis is inevitable in patients taking an equivalent of more than 30 mg of hydrocortisone, 7.5mg of prednisolone or 0.75 mg of dexamethasone per day for over 3 weeks.

Adverse effects of prolonged ingestion of corticosteroids[1,7] other than suppression of the hypothalamo-pituitary-adrenal axis are Cushing's syndrome, glaucoma and cataracts, thinning and bruising of the skin, infections from immune-suppression, psychiatric and cognitive disturbances, myopathy, gastric ulcer with perforation and hemorrhage and osteoporosis.

Some features like increased intra-ocular pressure, cataracts, benign intracranial hypertension, aseptic necrosis of femoral head, osteoporosis and pancreatitis are more common in iatrogenic Cushing's syndrome than in endogenous Cushing's syndrome whereas hypertension, hirsutism and menstrual disturbances are less prevalent in the former.

Very low early morning serum cortisol (less than 5 mcg/dl) is highly suggestive of adrenocortical insufficiency but lacks sensitivity. Sensitivity is increased by raising the cut-off for presumptive diagnosis to 10 mcg/dl but decreases the specificity. Morning (AM) cortisol more than 15 mcg/dl makes the diagnosis unlikely. To assess the function of the HPA axis[6], ACTH (adrenocorticotrophic hormone) stimulation test is done. Here, base-line cortisol is drawn and 250mcg of synthetic ACTH (Cosyntropin) is given IV or IM and the level of cortisol at 30minutes, and 60 minutes is measured. A normal response is a post-stimulation serum cortisol more than 20mcg/dl. In the absence of a normal response, ACTH levels should be measured to distinguish primary from secondary adrenal insufficiency.

NEED FOR THE STUDY:

In our practice, we observed that oral and parenteral corticosteroids were being chronically abused for COPD, chronic skin conditions, osteoarthritis of the knees and non-specific complaints like body aches which did not warrant steroids. Sudden withdrawal of corticosteroids often resulted in the patient presenting with life-threatening complications like refractory shock. Chronic adrenal insufficiency presented with multiple non-specific symptoms. Most often the history of corticosteroid ingestion is absent and so the diagnosis is missed by even an astute physician, with disastrous consequences. Despite the large number of cases we see in our practice, there are hardly any reports of secondary adrenal insufficiency due to indiscriminate steroid abuse from India. The dermatologists and pulmonologists are campaigning against the use of topical[3] and inhaled steroids[4,5], yet there is no mention made of the large scale indiscriminate use of potent oral and parenteral corticosteroids. We felt the need to create awareness of this problem and hence we conducted this study.

MATERIAL & METHODS

This was a retrospective study conducted in the division of geriatric medicine of our hospital between 2014 January and 2016 September. The admission/discharge register was scanned for the following diagnoses –'HPA axis suppression', 'chronic steroid abuse', 'steroid withdrawal', 'adrenal insufficiency' and 'iatrogenic Cushing's syndrome'. Charts with the above diagnoses were retrieved and details

of cases of secondary adrenal insufficiency due to withdrawal of exogeneous steroid use were obtained as per the performa.

Serum cortisol was estimated by fully automated chemiluminescence methodology using Siemens Advia Centaur (with the intra assay coefficient of variation 3.8 percent and inter assay coefficient of variation 9.1 percent).

Morning serum cortisol <10mcg/dl was considered as low. ACTH stimulation was done using twenty five units of injection ACTH (Acton Prolongatum -Ferring pharmaceuticals corticotropin) intramuscular. Serum cortisol was estimated at baseline and 60 minutes after ACTH. Subjects with one hour post- ACTH serum cortisol < 20 mcg/dl were diagnosed as having adrenal insufficiency.

STATISTICAL METHODS:

Clinical and demographic characteristics measured as categorical variables were reported using numbers and percentages, continuous variables were reported as mean and SD. SPSS 21.0 version was used for data analysis.

RESULTS:

We identified 41 patients with suspected secondary adrenal insufficiency due to exogeneous steroid abuse (2.94 % of admissions to geriatric unit). Among 41 patients, 9 patients who had no record of serum cortisol and 3 patients who had morning serum cortisol > 10mcg/dl were eliminated. The remaining 29 patients were analysed.

Table 1: Characteristics of study patients

Patient characteristics	N (%)
Gender Male Female	15 (51.7%) Male:Female (1.07:1). 14(48.3%)
Age (range 60-95 yrs)	Mean 70.4 yrs (SD 8.53)

Although all 29 gave a history of chronic use of medications either oral or parenteral for their complaints, corticosteroid use was definitely documented in 11 patients (37.93 %) who brought us the medication or the prescriptions; 6 were taking potent long-acting corticosteroid (betamethasone or dexamethasone), 3 were on prednisolone and 2 were on depot steroid (depomedrol) injections. The duration of intake varied from 1 year to 40 years and route of administration was IM, IV or oral.

Table 2: Reasons for corticosteroid use in study patients

Reason for Corticosteroid use	Number of patients	%
Respiratory (COPD)	14	48.3
Non-specific aches and pains	9	31
Osteoarthritis knees	8	27.6
Rheumatoid arthritis	4	13.8
Dermatological condition	1	3.4
Reason not documented	2	6.8

Note: Some patients had multiple reasons for abusing corticosteroids. Presenting symptoms were non-specific in all patients and they are listed below with their frequencies.

Table 3: Presenting symptoms in study patients

Presenting complaint	No. of patients (of n=29)	Percentage
Nausea & vomiting	10	34.5
Fatigue	9	31
Anorexia	8	27.6
Loose stools	7	24.1
Abdominal pain	3	10.3
Giddiness	1	3.4

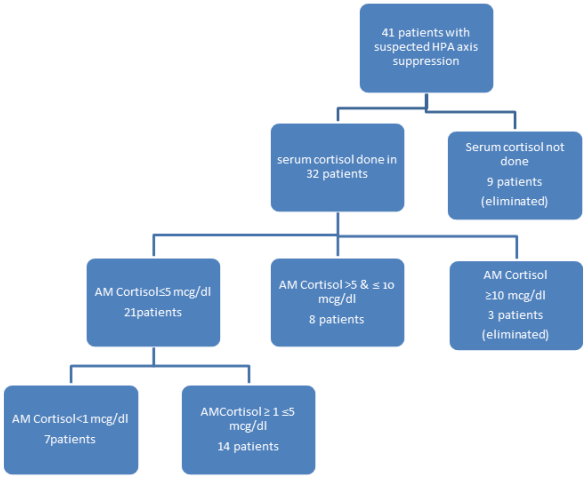
Table 4: Adverse effects of chronic steroid abuse.

Adverse effect	No. of patients (of n=29)	Percentage
Hypertension	19	65.5
Infections	17	58.6
Diabetes	14	48.3
Cushingoid features(central obesity, moon face, buffalo hump etc)	8	27.6
Hyponatremia	7	24.1
Pedal edema	6	20.7
Cataract	5	17.2
Hypotension	4	13.8
Osteoporosis	3	10.3
Peptic ulcer	2	6.9
Proximal myopathy	1	3.4
Hypoglycaemia	1	3.4

All patients had HPA axis suppression.

The morning cortisol of the 29 patients ranged from 0.2 -7.5 mcg/dl. Serum cortisol was less than or equal to 5mcg/dl in 21 patients (serum cortisol was below 1 mcg/dl in 7 patients and between 1-5 mcg/dl in 14 patients). Serum cortisol was above 5 mcg /dl upto 7.5 mcg /dl in 8 patients. Mean serum cortisol was 3.28 mcg /dl (SD=2.52), median value of 2.49 mcg /dl. ACTH stimulation test was documented in only 4 patients (3 patients with serum cortisol above 5 and less than 10 mcg/dl and one with serum cortisol less than 5mcg/dl and all were suggestive of adrenal insufficiency.

Diagram: Flow chart of AM cortisol of study patients



DISCUSSION:

We identified 29 elderly patients with chronic steroid abuse and secondary adrenal insufficiency. The mean age of the study group was 70.4 years and male to female ratio was equal. Definite evidence of taking corticosteroids was present in 11 patients (37.93 %) while the majority did not give any history of corticosteroid use although there was history of taking 'some' injections and tablets for years for their condition. The reason for taking corticosteroids was chronic obstructive lung disease (48.3%, n=14), osteoarthritis knees (27.6%, n=8), non-specific aches and pains (31 %, n=9), rheumatoid arthritis (13.8 %, n=4), dermatological complaints (3.4 %, n=1) and no reason was documented in two (6.8 %). All the patients presented with non-specific symptoms like anorexia, nausea, vomiting diarrhea and fatigue.

Four patients (13.8%) came with hypotension. Hyponatremia was seen in 7 (24.1 %). None had abnormal serum potassium. Hypoglycaemia (41 mg/dl) was noted in one patient. Infection was documented in 17(58.6%) patients – cellulitis, oral candidiasis, urinary and respiratory infections.

This study was done to draw attention to the high prevalence of secondary adrenal insufficiency due to misuse of exogenous corticosteroids in our country[7,8]. When there is a definite history of steroid use for a definite indication like a connective tissue disorder, the diagnosis of secondary adrenal insufficiency is straight-forward. But when no such history is forth-coming a high degree of suspicion is required. It should be considered in the differential diagnosis of patients coming with refractory hypotension and unexplained non-specific symptoms like anorexia, vomiting and fatigue and unexplained hyponatremia. In all patients with COPD, osteoarthritis especially of the knees and chronic skin conditions a zealous search of prescriptions and medications should be made.

The relevance of this condition to geriatrics is worth emphasizing

1) Elderly are a vulnerable population with multiple comorbidities and hence make multiple visits to doctors.
2) Aging already predisposes them to diabetes, hypertension, cataracts and osteoporosis. Steroids increase their risk for the same.

3) Age results in poor immune response and corticosteroids add to the risk of serious infections in them
4) Memory impairment, depression and psychosis which are features of chronic adrenal insufficiency may be thought of as part of normal aging and overlooked in elderly.
5) Orthostatic hypotension can be seen in 5-30 % of healthy elderly. Drugs and diseases increase this risk and so does secondary adrenal insufficiency.
6) Falls risk is increased in elderly who abuse corticosteroid by causing proximal myopathy, bone disease and cataracts and hypotension.
7) Glucocorticoid-induced osteoporosis (GIO) can occur with a daily steroid dose of more than 5 mg of prednisolone for over a month. This is especially relevant in elderly and more so in post-menopausal women.
8) Symptoms of chronic adrenal insufficiency are overlooked as they are non-specific and overlap with many symptoms of aging and disease. For example, non-specific musculoskeletal complaints could be due to various reasons ranging from vitamin D deficiency and hypothyroidism to depression and osteoporosis. As there are already multiple reasons for the older patients' symptoms, adrenal insufficiency will not be suspected by the uninitiated.

Basal cortisol level in low to normal range cannot be used to exclude the diagnosis. A basal cortisol more than 14.5 mcg/dl invariably indicates an intact hypothalamo-pituitary-adrenal (HPA) axis. In practice rather than wait for insensitive basal tests, all patients with suspected adrenal insufficiency should have an ACTH stimulation test. This was one of the limitations of the study wherein only 4 out of 29 had an ACTH stimulation test. But if adrenal crisis is suspected one should treat immediately and test later.

Some of the reasons that we have high prevalence of steroid abuse in our country are as follows

1. In India most corticosteroids are cheap and available over-the-counter. There is inadequate policing of medical shops and even prescription drugs can very often be bought from medical shops without an actual prescription from the doctor. We are aware that salespersons at chemist counters are prescribing and there are no policies to take punitive action against those who prescribe without a license.
2. There is high rate of illiteracy and lack of awareness of the public.
3. Patients want instant relief and corticosteroids are magical drugs. With their anti-inflammatory and euphoric effects they provide instant gratification for the patient and the "practitioner" is described as a demigod. This encourages further abuse of corticosteroids and education of the public alone can break this cycle. Patients should be made aware that although there is subjective benefit, not only is there no objective improvement in the underlying disease but on the other hand serious adverse effects can result.

We have to start a powerful campaign against misuse of steroids. We need to take measures to educate the public (eg. before projection of popular movies in theatres), street plays, and education programs in schools, colleges and hospitals. There should be policies to prevent abuse of corticosteroids especially by those who prescribe medicines without labels and without a license to practice.

In conclusion, misuse of corticosteroids is more common than has been reported. This article highlights the non-specific presentation and the need to consider secondary adrenocortical insufficiency in the differential diagnosis of every critically ill patient.

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