Original Article

Etiology and clinical profile of patients with Cushing's syndrome: A single center experience

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ABSTRACT

Background: There is little published literature on the profile of patients with Cushing's syndrome (CS) from India. The aim of this study was to compile data of CS patients treated at this hospital. **Materials and Methods:** Patients referred to the endocrine services of this hospital for diagnosis/treatment of CS from January 1985 to July 2012 were the subjects for this study. All patients had detailed medical history, physical examination and biochemical and hormonal assays (which changed with availability of tests and changing views). Assays for plasma adrenocorticotropic hormone (ACTH) (late 90s), salivary cortisol estimation, IJV sampling for ACTH and corticotrophin releasing hormone stimulation tests were added on later. Imaging included computed tomography (CT), magnetic resonance imaging (since the late 80's) and ^{68}Ga DOTA-TOC/FDG PET-CT (2008). **Results:** Three hundred sixty-four patients (250 females, 114 males, age 6 months to 65 years, mean 28 years + 12 years) were diagnosed to have CS during this period. Two hundred and ninety-three patients (80.5%) were ACTH dependent (CD 215, ectopic ACTH syndrome 22, occult ACTH source 56) while 71 (19.5%) were ACTH independent (adrenal carcinoma 36, adenoma 30, primary pigmented nodular adrenal disease 4, AIMAH 1). Pituitary macro adenoma was seen in 14% of the CD cases. The most common presenting complaints were hypertension and diabetes mellitus. A total of 63% patients complained of weight gain while 15% had lost weight. Myopathy, infections, skeletal fractures and psychiatric problems were the other common observations in our patients. **Conclusion:** The clinical spectrum was broad. CD was the most common cause for CS.

Key words: Adrenal adenoma, adrenal carcinoma, adrenocorticotropic hormone, adrenal cushing's, cushing's disease, cushing's syndrome, ectopic adrenocorticotropic hormone syndrome

Introduction

Cushing's syndrome (CS) is a complex endocrine disorder with potential for serious consequences if not adequately treated.[1] The incidence of CS varies in different studies from 0.7 to 2.4 per million populations per year.[1-3] A more recent study reported a prevalence of 79 per million and incidence of 1.8 per million per year for CS.[4] Nearly 80% of the cases of endogenous hypercortisolism are adrenocorticotropic hormone (ACTH) dependent, the ACTH source being pituitary in about 70-80% and ectopic in 10-15%.[5-9] The ACTH source may remain occult in few cases for many years in spite of extensive investigations. Primary adrenal disease (adrenal adenoma, adrenal carcinoma) accounts for about 15-20% of cases. CS is more common among certain high-risk groups, e.g., 2-5% among patients with type 2 diabetes mellitus with poor blood glucose control[10] and 0.5-1% among hypertensive patients.[11] CS patients experience significant clinical burden as a result of the physical illness, associated comorbidities like hypertension, diabetes mellitus, vulnerability to infections and associated psychopathology. Identification and management of this complex problem poses a greater challenge in a resource-poor country like India. Presented here is the profile of patients with CS attending this Tertiary Care Center since 1985.

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Materials And Methods

Patients referred to the endocrine services of this hospital for evaluation/management of CS, from January 1985 to July 2012, are included in this study. All subjects had detailed clinical evaluation, including review of past medical records and medications. The protocol for evaluation of patients with suspected CS has changed considerably during the study period. In the 80s, patients with suspected CS had plasma cortisol measurement 6 h for 2 days to assess diurnal variation followed by low-dose (0.5 mg 6 h for 2 days) dexamethasone suppression test. Plasma cortisol urine 17 hydroxy steroids were measured. Cortisol was measured with fluorimetric assays. Those confirmed to have hypercortisolism underwent computed tomography (CT) scan of the adrenal glands to exclude adrenal pathology. Those without an adrenal mass lesion underwent high-dose dexamethasone suppression test (HDDST) with 8 mg dexamethasone (2 mg 6 h for 2 days). Those who showed more than 50% suppression underwent CT (or magnetic resonance imaging (MRI) since the late 80's, 0.5 Tesla) scan for pituitary gland.[12] Those with non-suppressible cortisol on HDDST and those without a lesion on CT/MRI underwent further investigations to exclude an ectopic ACTH source. Those who had an adenoma (micro or macro) underwent pituitary surgery while those without a lesion underwent bilateral total adrenelectomy. MRI became available in this hospital during the late 80's. Radioimmunoassay for ACTH and cortisol became freely available (on a commercial basis during the mid 80's) in this hospital from the year 2000. Subsequently, late night salivary cortisol estimation,[13] intravenous HDDST, ^{68}Ga DOTA-TOC/FDG PET-CT scan[14] and bilateral internal jugular vein sampling for ACTH and corticotrophin releasing hormone (CRH) stimulation test have been added.[15]

Now (after year 2000), two or more screening tests (ONDST, LDDST, late night salivary cortisol) are performed in addition to measurement of basal serum cortisol and plasma ACTH. Those with discordant results and those with low serum cortisol in the absence of history of steroid use are re-evaluated subsequently to exclude the possibility of cyclical hypercortisolism. ACTH dependent CS (plasma ACTH >10 pg/mL) patients underwent HDDST and MRI of pituitary (1.5 Tesla since 2007) with dynamic sequences with gadolinium. ACTH dependent CS patients with normal or inconclusive (lesion <5 mm) findings on MRI sella were further investigated to localize the ectopic source of ACTH with contrast-enhanced CT scan of the neck, chest, abdomen and pelvis. CRH stimulation test, bilateral internal jugular vein sampling for ACTH and ^{68}Ga DOTA-TOC/FDG PET-CT scan were performed as additional tests for the more recent cases.

Subjects with ACTH dependent CS where no pituitary or ectopic ACTH producing tumor could be identified were explained the pros and cons of pituitary exploration, bilateral adrenalectomy and medical therapy and given the option for choosing one of these modalities of treatment. They were subsequently followed-up for an evolving pituitary or ectopic ACTH source. Some patients with Cushing's disease who were severely symptomatic (significant myopathy, multiple vertebral fractures, etc.,) had bilateral adrenelectomy as a life-saving measure. These patients underwent pituitary surgery 6-12 months later. All treated patients were advised life-long follow-up.

At present, cortisol and ACTH are measured by the ECLISA technique.[16] The measuring range for cortisol is 0.018-63.4 μg/dL. Estimation of plasma ACTH is performed using two monoclonal antibodies specific for ACTH (ACTH: 9-12 and ACTH: 36-39). The measuring range of ACTH assay is 1-2000 pg/mL with inter-assay and intra-assay CV <6%. MRI is performed on a 1.5T scanner (Siemens Avanto or Sonata, Erlangen, Germany). T1W spin echo sequences are obtained in the coronal and sagittal planes using thin slices (3 mm). Additional T2 fast spin echo sequences are performed in the coronal plane. Patients receive an intravenous gadolinium compound at a dose of 0.1 mmol/kg. Post-contrast T1W images are obtained in the coronal plane. Following contrast administration, both dynamic and routine images are performed. For dynamic imaging, fat-suppressed fast spin echo sequences are used.

There are no ethical issues regarding this study. Permission/waiver was obtained from the Institute Ethics Committee. SPSS version 15, Illinos Chicago, USA was used. Besides descriptive statistics, the two groups were compared by applying the Student *t*-test for continuous data. Qualitative data were compared by applying the Chi-square/Fishers test, $P < 0.05$ was considered as significant.

Results

Three hundred and sixty-four patients were diagnosed to have CS (250 females and 114 males, age ranging from 6 months to 65 years [28 years + 12 years]) during these 27 years. Most of these patients were from Delhi and other parts of India. There were few patients from Afganisthan, Nepal and Bangladesh. Figure 1 shows the age and gender distribution of these patients. Nearly 70% of the patients were in the 10-40 year age group [Figure 1]. Female gender preponderance was seen after 10 years of age.

One hundred and twenty-one of these patients were diagnosed prior to 2000 (88 females and 33 males, age ranging from 6 months to 56 years [mean 27.08±12]) [Table 1]. Among them, 25 patients had ACTH independent hypercortisolism (13 adrenal carcinoma, 11 adenoma and one primary pigmented nodular adrenal disease [PPNAD]). Five patients had ectopic ACTH syndrome (EAS) (four diagnosed during initial evaluation and one during follow-up). Among the other 91 patients, 61 had CD (12 pituitary macroadenoma, 42 microadenoma and seven normal pituitary on imaging [developed pituitary tumor during follow-up after bilateral adrenelectomy]); source of ACTH excess could not be established in 30 patients. Eleven of the twelve with pituitary macroadenoma had pituitary surgery as the initial therapy, seven of them required radiotherapy (external irradiation in five, Gamma knife in two) and six of these seven required bilateral adrenelectomy. One of these 12 patients underwent external irradiation for pituitary and bilateral total adrenelectomy at another center. One patient with microadenoma had a cerebellopontine angle tumor and another had breast carcinoma with secondaries; the other 40 patients underwent pituitary surgery. Bilateral total adrenalectomy was performed subsequently in 17 of these, four required additional pituitary surgery and/or radiotherapy. Nineteen of the thirty patients with normal pituitary had bilateral adrenalectomy, two died of septicemia with chest infection and nine were lost to follow-up.

Table 1: Cushing's syndrome patients evaluated during different periods

Time period	1985-1999	2000-2009	2010-2012	Total
Number of patients	121	191	52	364
Female/male	88/33	131/60	34/18	250/114
Female %	73	69	65	69
ACTH dependent (%)	96 (79)	151 (79)	46 (88.5)	293 (80.5)
CD	61 (50)	121 (63)	33 (63)	215 (59)
(macroadenoma) (%)	12 (20)	14 (11.5)	4 (12)	30 (14)
EAS (%)	5 (5)	13 (11)	4 (8)	22 (7.5)
UK (%)	30 (31)	17 (11)	9 (17)	56 (19)
ACTH independent (%)	25 (21)	40 (21)	6 (11.5)	71 (19.5)
Adrenal adenoma	11	15	4	30
Adrenal carcinoma	13	23		36
PPNAD	1	1	2	4
Macronodular adrenal hyperplasia		1		1

ACTH: Adrenocorticotropic hormone, CD: Cushing's disease, EAS: Ectopic adrenocorticotropic hormone syndrome, UK: Unknown, PPNAD: Primary pigmented nodular adrenal disease

One hundred and ninety-one patients were diagnosed to have CS (131 females and 60 males, age ranging from 2 years to 65 years [28.7±11.8]) between January 2000 and December 2009. Of these, 151 were ACTH dependent while 40 were ACTH independent. Among the ACTH dependent, 121 were due to CD (14 macroadenoma), 13 EAS (11 during initial evaluation and two on follow-up) and 17 occult ACTH source. Part of this is published.[17] Among the 40 patients with adrenal CS, 23 were adrenal carcinomas, 15 were adrenal adenoma, one was AIMAH and one was PPNAD.

Fifty-two patients (34 females and 18 males, age ranging from 12 years to 55 years [26.7 ± 11.16 years]) were diagnosed to have CS between January 2010 and July 2012. Forty-six patients had ACTH dependent CS while six had ACTH independent hypercortisolism (four adrenal adenoma and two PPNAD). Among the 46 ACTH dependent CS patients, four had EAS (one thymic carcinoid and three bronchial carcinoid), 33 CD (four macroadenoma) and nine with occult ACTH source.

Altogether 293 (80.5%) were ACTH dependent CS, 71 (19.5%) were ACTH independent [Table 2]. Among 293 ACTH dependent cases, 215 (73%) were due to CD (30 [14%] pituitary macroadenoma), 22 (7.5%) were due to EAS and in 56 (19%), the ACTH source could not be identified (occult ACTH source). Figure 2 shows the etiology for CS in the different age groups. Number and size of macroadenomas were higher during the earlier period. Figure 3 shows the CT scan of a patient of CD diagnosed in 1998. Source of EAS was bronchial carcinoid (seven cases), thymic carcinoid (six cases), pancreatic neuroendocrine

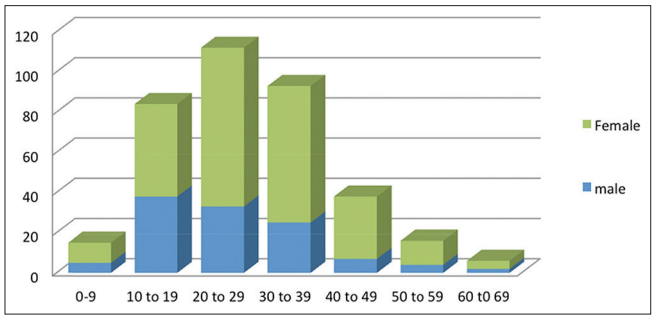

Figure 1: Age and gender distribution of patients in different age groups

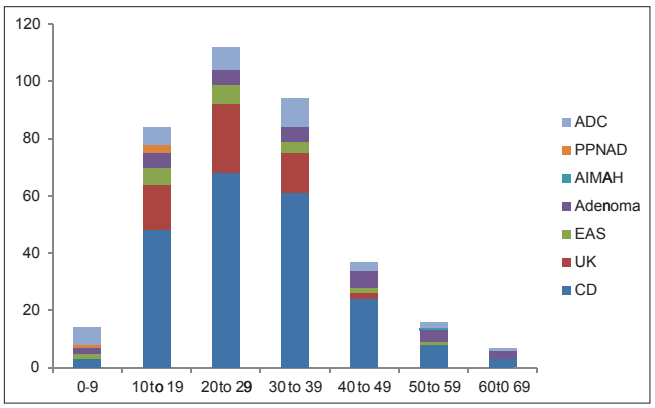

Figure 2: Etiology of Cushing's syndrome in different age groups

tumor (four cases including one case of insulinoma), MEN 2 (medullary ca thyroid with ectopic ACTH secretion) (one case) and four cases of metastatic carcinoma (one each of squamous cell carcinoma, adenocarcinoma, small cell carcinoma and metastatic neuroendocrine tumor with unknown primary [tumorlets]). Figure 3 shows the etiology of EAS in the different age groups. Adrenal carcinoma (36), adrenal adenoma (30), PPNAD (4) and ACTH independent macronodular adrenal hyperplasia (1) accounted for the 71 ACTH independent CS cases. Figure 4 shows the age and gender distribution of patients with adrenal adenoma and adrenal carcinoma.

Hypertension and diabetes mellitus were the predominant presenting symptoms. Age and clinical profile of CD patients with pituitary macroadenoma was not significantly different from those with smaller pituitary lesions [Table 2]. Prevalence of hypertension, diabetes mellitus and obesity were 77%, 57% and 60%, respectively, among CD patients with pituitary macroadenoma, while it was 72%, 67% and 72% among those with pituitary microadenoma. Mean plasma ACTH was higher [Figure 5] and a lower number of patients showed >50% suppression with HDDST in the group with macroadenoma (not statistically significant).

Obesity was less common among EAS and adrenal carcinoma patients. Psychiatric manifestations were more common among EAS patients. Plasma ACTH was higher

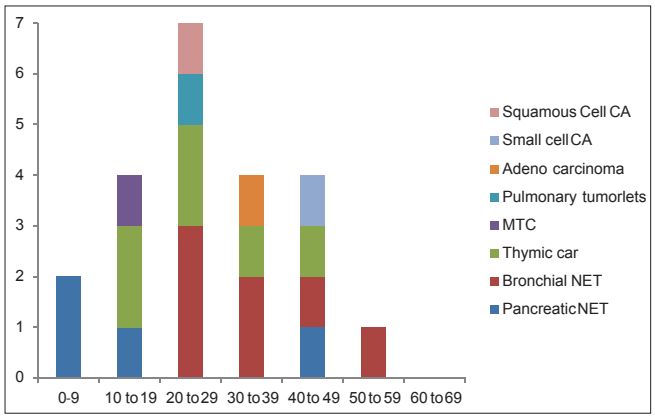

Figure 3: Etiology of ectopic adrenocorticotropic hormone syndrome in different age groups

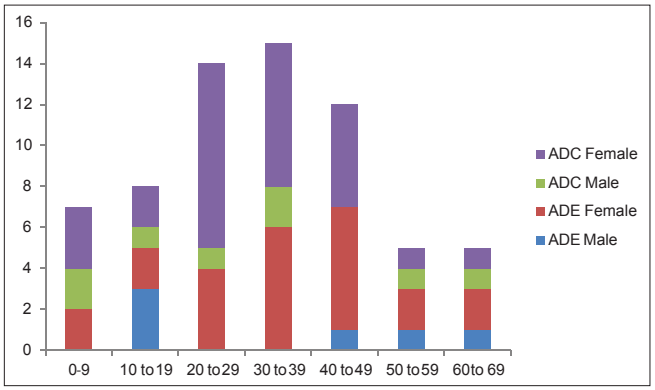

Figure 4: Age wise distribution of cases of adrenal adenomas and carcinomas

Table 2: Profile of patients with Cushing's syndrome

Parameters	Micro adenoma (*N*=185)	Macro adenoma (*N*=30)	*P* value C1 versus. C2	Unknown (*N*=56)	Ectopic C3 (*N*=22) *P* value (C1+C2) versus. C4	Adrenal adenoma (*N*=30)	Adrenal carcinoma (*N*=36) *P* value C5 versus C6	*N*=359
Column	C1	C2	-	C3	C4 p	C5	C6 p	
F/M	122:63	20:10	NS	42:14	12:10 NS	24:06	28:08 NS	248:111
Age (mean±SD) years	27.6±11.5	26.9±8.3	NS	27±11	26.7±11.9 NS	34.76±16.3	29.36±15.8 NS	27.8±12
Duration	3.2 years	3.10 years	NS	3.3 years	2 years NS	2.44 years	1.79 years NS	
*Obesity (%)	134 (72.40)	18 (60)	NS	35 (62.5)	6 (27.7) <0.01	18 (60)	14 (38.8) NS	225 (62.6)
HTN (%)	133 (71.80)	23 (76.60)	NS	39 (69.6)	12 (54.4) NS	23 (76.60)	28 (77.7) NS	258 (71.8)
DM (%)	124 (67)	17 (56.60)	NS	37 (66)	13 (59) NS	15 (50)	21 (58.30) NS	227 (63.2)
Fractures (%)	47 (25.4)	6 (20)	NS	11 (19.6)	7 (31.8) 0.01	4 (13.30)	5 (13.8) NS	80 (22.2)
Psychiatric manifestation (%)	57 (31)	5 (16.60)	NS	20 (35.7)	13 (59) 0.01	6 (20)	8 (22.2) NS	109 (30.3)
Striae (%)	113 (61)	19 (63.30)	NS	34 (60.7)	10 (45.4) NS	18 (60)	12 (33.3) <0.05	206 (57.3)
Hirsutism (%)	98 (80.3)	16 (80)	NS	35 (83.3)	11 (91.6) NS	16 (66.6)	26 (92.8) NS	202 (81.4)
Menstrual irregularity (%)	111 (91)	20 (100)	<0.01	42 (100)	7 (58.3) <0.01	12 (50)	22 (78.5) NS	229 (92.3)
Myopathy (%)	129 (70)	22 (73.3)	NS	35 (62.5)	15 (68) NS	20 (66.6)	27 (75) <0.01	248 (69)
Morning cortisol μg/dl	31.95±14.8	30.8±11.2	NS	33.4±13.8	34.6±22.7 NS	27.6±6.8	34.8±11 NS	
Evening cortisol μg/dl	25.6±10.3	30.2±9	<0.05	20.37±10	36.4±24.8<0.01	25.13±8.6	30.9±9.6 NS	
ACTH pg/ml	60.3±43	74.3±54	NS	80±32	103.8±87.3<0.01	5.91±14.5	2.7±3.7 NS	
Cortisol on LDDST μg/dl	22.7±12.3	22.9±12.4	NS	25.8±12	27.3±15.2 NS	24.6±6.6	30.8±8.4<0.01	
Cortisol on HDDST μg/dl	17.2±16.3	17.5±10.6	NS	18.3±15.8	28.3±14<.01	29.6±5.6	34±12.9 NS	
HDDST>50% suppression	77/141 (54.6%)	11/24 (45.8%)	NS	4 (7%)	2 (9%)	0	0	

HDDST: High dose dexamethasone suppression test, LDDST: Low dose dexamethasone suppression test, NS: Not significant, ACTH: Adrenocorticotropic hormone, HTN: Hypertension, DM: Diabetes mellitus, F: Female, M: Male, SD: Standard deviation

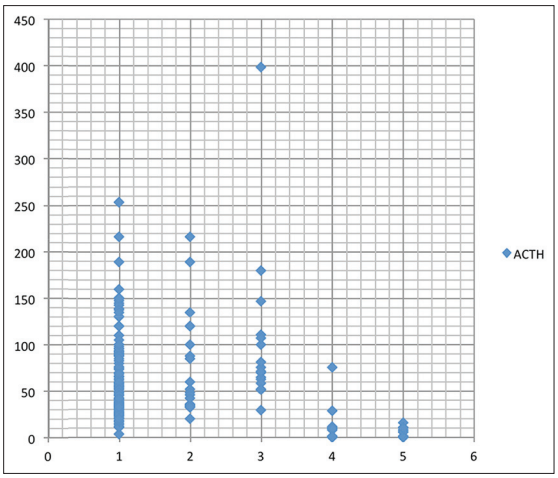

Figure 5: Plasma adrenocorticotropic hormone (pg/mL) in Cushing's syndrome patients with pituitary micro adenoma (1), macro adenoma (2), EAS (3), adrenal adenoma (4) and adrenal carcinoma (5)

among patients with EAS compared with patients with CD. Among CD patients, ACTH was higher among patients with pituitary macroadenoma. However, these were not statistically significant. Evening plasma cortisol was significantly higher among patients with EAS and adrenal carcinoma.

Ninety-one (26%) patients had skin infections, 15 patients had wound infections, nine patients had chest infection and four of these died of septicemia prior to any surgical intervention. Fifteen patients had tuberculosis, which included two adrenal tuberculosis and two intestinal tuberculosis with perforation and peritonitis. One of the patients with adrenal tuberculosis was misdiagnosed as adrenal adenoma and subjected to adrenalectomy. Histopathology revealed caseating granulomas with acid fast bacilli in addition to diffuse cortical hyperplasia. Five patients had herpes zoster.

Sixty-four patients had fractures, which included fracture hip in one patient, multiple rib and vertebral fractures. Two patients with vertebral fractures had paraparesis and one had paraplegia; all three were males with age ranging from 13 years to 26 years. Seven patients had avascular necrosis of bone, and the most common site was head of femur, others being head of humerus and carpel bones.

There were three patients with CD who developed pituitary apoplexy, two of them required surgery for hypercortisolism while one was asymptomatic without surgery.

Complaints were of cyclical nature in three patients (two F, one M), with length of cycles ranging from 2 weeks to 2 years. The first patient had normal cortisol levels during evaluation at our hospital, and MRI revealed pituitary microdenoma with hemorrhage. The second patient had several such episodes during a 6-year period, where she had weight gain followed by symptomatic hypocortisolism and weight loss of 16-20 kg. We observed one episode when her plasma cortisol was undetectable with low ACTH. She lost 25 kg (103-78 kg) during the next 1 year, which was followed by weight gain and increase in plasma cortisol and ACTH. The third patient was a 19-year-old male admitted with overt features of CS and no history of steroid use. Initial evaluation revealed low plasma cortisol, but repeat evaluation few weeks later revealed ACTH dependent hypercortisolism. Source of ACTH could not be identified in both these patients; they underwent bilateral adrenalectomy and are on follow-up.

Two women with CS (one with CD and another with unknown ACTH source) had venous thrombosis. The first patient had axillary vein thrombosis some years after cure of hypercortisolism while the other had a large thrombus extending from the inferior vena cava to the right atrium at the time of diagnosis of CS. X-ray of the chest of this patient showed miliary shadows that were mistaken for miliary tuberculosis. One young male patient had dialated cardiomyopathy, which recovered within 1 year of bilateral adrenalectomy.

One patient had carcinoma breast with secondaries in the liver at the time of diagnosis of CS and two women developed breast carcinoma several years after cure of hypercortisolism. Two of them had CD while the third had adrenal adenoma. Two patients with CD had acoustic neuromas.

Discussion

Introduction of sensitive assays for ACTH and cortisol, higher resolution imaging techniques and better understanding of the etiology have changed the diagnostic and therapeutic strategy for patients with CS. Availability of ACTH assay has made it possible to distinguish between ACTH dependent and ACTH independent CS. However, identifying the ACTH source (pituitary versus ectopic) still continues to be a challenge. The present study included 364 CS patients evaluated during the last 27 years in the Endocrine services of this hospital. Seventy-one (19.5%) had primary adrenal disease while 293 (80.5%) were ACTH dependent. Unilateral adrenal disease (adrenal carcinoma 36, adenoma 30) accounted for most of the adrenal CS. There were four cases of PPNAD and one case of AIMAH. Among the cases of ACTH dependent CS, 215 (73.4%) were due to CD, 22 (7.5%) were due to EAS and 56 (19.1%) had occult ACTH source.

CD was the most common cause (59%) for CS in the present study, although it was less than in other published series.[5-8,10] Table 3 compares the profile of CS patients in the present study with some large published series. Our patients were younger compared with CS patients in the Italian multicentric study[6] and the Euro Cushings registry[9] (mean age 28 years vs. 36 years and 43 years). Duration of symptoms prior to diagnosis was 3.2 years, which was longer compared with 29 months in the Italian multicenter study. Macroadenomas are reported in 4-10% of the cases with CD.[18] In the present study, 30 (14%) of the 215 patients with CD had pituitary macroadenoma, proportion of patients with macroadenoma was higher among the earlier group (20% vs. 12%) compared with patients diagnosed more recently. There was a significant female preponderance in all etiological groups except EAS, like other published series. The number of patients diagnosed CS per year (8 vs. 19) and percentage of patients with EAS (5 vs. 17) was more after year 2000. The percentage of patients with pituitary macroadenoma among CD patients was higher (20% vs. 12%) during the earlier period. The size of the tumors was also bigger in the earlier group.

Common co-morbidities with CS are obesity, hypertension, diabetes mellitus, osteoporosis, infections and neurocognitive dysfunction. Hypertension and diabetes mellitus were the most common problems in the present study group. Prevalence of obesity was 65%, while 15% had weight loss. Those with weight loss were patients with a very long duration of symptoms, uncontrolled diabetes mellitus and infections like tuberculosis. About one-fifth of the CS patients had some infection. We did not observe significant difference in the clinical profile of patients with different etiology for cortisol excess except that obesity was less common among the EAS and adrenal carcinoma group and psychiatric problems were more common among EAS compared with the other groups.[19-22]

ACTH independent CS is mostly due to unilateral adrenal tumors; adenomas are more common than carcinomas. In this present study, there were 66 patients with adrenal tumors; 30 adenomas and 36 carcinomas. There were more patients with adrenal carcinoma than with adrenal adenoma in our study. Shah *et al*.[10] also observed a similar trend. It is difficult to say whether adrenal carcinoma is more common among Indian patients or if this is a reflection of referral bias.

Cyclicity/periodic hormonogenesis have been reported, although rarely, in patients with CS.[23] Some of the hypotheses suggested to explain this phenomenon are episodic hemorrhage, synchronous growth and death of tumor cells, fluctuations in the hypothalamus–pituitary–adrenal axis, etc., Cyclicity has been defined as occurrence of three peaks and two troughs of hypercortisolemia.[24] This is often difficult to establish as the intercycle period may be variable. There were three patients in this group with cyclical symptoms.

Skeletal fractures, avascular necrosis of bones, venous thrombosis,[25] and cardiac dysfunction[26] are well documented in patients with CS. One of our patients had extensive IVC thrombosis with miliary shadows in the lungs that was mistaken for milliary tuberculosis. One young man with CS had reversible dilated cardiomyopathy. Three patients had breast carcinoma (one at the time of diagnosis and two during follow-up) and two had accoustic neuroma. It is not possible to say whether there is a causal link or whether it is a coincidence, as these are not uncommon diseases.

Tubercular infection of adrenal glands causing adrenal insufficiency is well recognized.[27,28] It has not been reported in patients with CS. Two CS patients in this study had unilateral adrenal tuberculosis.

The strength of this study is the large number of patients studied at a single center by the same investigators and the

Table 3: Etiology of Cushing's syndrome: Comparison with some published series

Different studies	Bertagna[5] *et al.*	Newell-price *et al.*[8]	Invitti *et al.*[6]	Erem *et al.*[7]	Shah *et al.*[10]	Euro cushings registry[9]	Present study
Number of patients	809	150	426	55	100	481	364
Year	-	1970-1994	1979-1999	1983-2000	2004	2000-2010	1985-2012
Pituitary (%)	550 (68)	110 (73)	288 (68)	39 (71)	69	317 (66)	215 (59)
Ectopic (%)	58 (07)	12 (09)	25 (06)	-	8	24 (5)	22 (6)
Unknown (%)	-	08 (05)		-	13		56 (15)
Adrenal (%)	Adenoma=111 (14) Carcinoma 88 (11)	17 (11)	80 (18)	13 (24) carcinima 3 (5)	Adenoma 2 Carcinoma 8	130 (27)	Adenoma 30 (8) Carcinoma 36 (10)
PPNAD (%)			24 (06)			5	4 (1)
AIMAH (%)	02 (0.2)	03 (02)	09 (02)	-		4	1
Cyclical						1	3*

*All ACTH dependent Cushing's syndrome, AIMAH: ACTH independantmacronodularadrenal hyperplasia, PPNAD: Primary pigmented nodular adrenal disease, ACTH: Adrenocorticotropic hormone

long-term follow-up. Some important diagnostic tools were not available during the major part of this study. That is one possible reason for the higher number of cases with occult ACTH source.

Conclusion

Cushing's disease was the most common cause for CS; 14% patients with CD had pituitary macroadenoma. Etiology of ACTH/cortisol excess could not be established in 56 (15%) CS patients. Patients in this study were young, had long duration of illness, multiple metabolic abnormalities and coexisting infections.

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