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CASE REPORT

# Psychosocial morbidity in Cushing disease: a study from India

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**Abstract** The main objective of this article is to study the psychosocial profile of patients of Cushing disease (CD) in a developing country setting. Eighteen patients with CD underwent a cross-sectional assessment regarding their socio-demographic and clinical profile, life events, social support, coping, dysfunction, quality of life, and psychiatric morbidity. Twenty-two demographically group-matched healthy participants (free from psychological morbidity) acted as the control group. The CD group had predominance of females (71.5%) with mean age at onset of 20.38 (range 8–38) years, and mean duration of illness of 65.33 (range 4–260) months. Six subjects (i.e., GHQ positive group) scored positive on the General Health Questionnaire-12 giving a psychological morbidity rate of 33.33%, with one having an ICD-10 diagnosis. There was no difference between GHQ positive and GHQ negative groups on number of life events, social support, quality of life and dysfunction. However, GHQ positive group used significantly more of internalizing coping strategies. Psychological morbidity occurs in a significant percentage of patients with CD. Presence of psychological morbidity is associated with internalizing coping strategies.

**Keywords** Cushing disease · Psychological morbidity · Quality of life · Coping · Dysfunction

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## Introduction

With a prevalence of endogenous Cushing syndrome at 2–13 per million cases [1, 2], the Cushing disease (CD) is a chronic debilitating illness with neuropsychiatric manifestations in 85–100% cases [3, 4] and often marked disturbance in physical appearance [3, 5]. Among psychiatric manifestations, the common ones are emotional instability, depression, anxiety, sleep disruption, and cognitive impairments [3, 4, 6, 7] and rare ones are psychosis and mania [8, 9]. The depression seen in CD is quite frequently has atypical manifestations [7]. The psychiatric manifestations may be attributable to the hormonal/biochemical changes [10–12], but the role of psychosocial stress induced by the pervasiveness of clinical features and body disfigurement may be equally or more important.

CD has been reported to impact everyday living and impair marital, family, and work functioning [3], and affect the quality of life [13]. The available research being sparse and almost all from the western or developed countries, and the psychosocial milieu of the developing countries possibly being more severely stigmatizing for disfigurement [14], this research was planned as a cross-sectional study of psychosocial profile of CD in India, a developing country.

## Materials and methods

### Setting

The study was carried out at the Postgraduate Institute of Medical Education and Research, Chandigarh, a multi-speciality teaching tertiary-care referral hospital providing services to a major area of north India and catering to approximately 40 million people.

## Design

Cross-sectional assessment.

## Sample

All the subjects were recruited on the basis of a written informed consent assuring confidentiality and freedom of choice of participation. The patients were recruited between August 1999 and March 2001 on the basis of a purposive sampling and specified inclusion and exclusion criteria. The sample comprised two groups: Cushing disease (CD) group ($N = 18$) and Healthy Controls (HC) group ($N = 22$).

The CD group included subjects who were seeking outpatient or inpatient treatment under the endocrinology services of the Institute. The diagnosis was made by the clinical features of protein catabolism, e.g., striae, ecchymosis, proximal myopathy, hirsuitism and amenorrhoea, and biochemical features of increased basal plasma cortisol, loss of circadian rhythm in cortisol secretion, and non-suppressibility with dexamethasone. Imaging of the pituitary or adrenal area was used to substantiate the etiology. The patients taking exogenous steroids were excluded. The endocrinology consultant (AKB) identified and listed from the existing records of the endocrinology department patients of CD of either gender and in the age range of 20–50 years, most of whom were on active follow-up and treatment. For the purpose of this study, they were contacted during their routine follow-up visits or by writing letters to them if they missed such visits. In addition, new patients reporting with disease/syndrome for the diagnosis and treatment were also included in the study.

The HC group comprised of subjects recruited from the attendants/relatives of the patients attending the dermatology outpatient department of the Institute. They were group-matched with the CD group for gender and education, and were to be free from any major physical or psychiatric illness. The psychological morbidity was determined by administration of General Health Questionnaire-12 Item (GHQ-12) as explained in the next section. A matched HC group was taken, so as we could conclude that the psychological morbidity is not just a function of sociodemographic variables. Initially, it was thought to blind the assessor for the diagnosis of CD, but in view of the physical appearance of CD patient, it was not possible.

## Instruments

The following instruments, as required, were used in the two groups:

1. *Sociodemographic profile sheet*: A proforma, specially designed for this study, was used to record the relevant sociodemographic data (age, gender, marital status, and education) for both the groups.
2. *Clinical profile sheet*: A proforma, specifically constructed for this study, was used to record the following clinical details about the CD: Duration of illness; age at onset; cortisol levels—basal AM and PM, and Post dexamethasone AM and PM; and receiving or not receiving ketoconazole.
3. *Dysfunction Analysis Questionnaire* (DAQ) [15]: Developed at PGIMER, this questionnaire assesses the dysfunction as compared to the pre-illness level of functioning across five areas—social, vocational, personal, family, and cognitive. Five-point scaling of 50-items gives a possible disability score range of 46–100 for individual domains and 206–500 for the total, a higher score indicating a higher dysfunction. With a proven validity and reliability (test–retest reliability of 0.77–0.92 for various domains), this questionnaire in Hindi language provides norms for the local population and has been widely used in India on different clinical populations.
4. *WHO Quality of Life Scale-Bref—Hindi* (WHOQOL-B) [16]: WHOQOL-B, available in the Hindi language, is a self-administered psychometrically sound cross-cultural generic questionnaire derived from WHOQOL-100 scale which was developed in 15 centers across developing and developed countries [17]. It profiles the subjective evaluation (rather than the objective status) of the functioning in the past 2 weeks for four domains: physical health, psychological health, social relationships, and environment. The 26 items are scored 1–5 to give domain scores and a total score range of 26–130, a higher score indicating a better QOL.
5. *Coping Strategies Check List—Hindi* [14] (CSCL): CSCL [18] is a self-administered yes/no checklist with high reliability that lists coping strategies used by people to deal with the situations which trouble them. The checklist covers all stressors and is not disease-specific. The 36 strategies have been factored into 5 factors: denial, internalize, externalize, emotional outlet, and anger. A higher score indicates greater use of coping strategies. A Hindi translation with Cronbach's $\alpha$ of 0.64 was developed and used in our center earlier [14].
6. *Presumptive Stressful Life Events Scale* (PSLES) [19]: Based on Stressful Life Events Scale of Holmes and Rahe [20], PSLES has been standardized with 51 life events relevant to the Indian setting. Based on their data, the authors reported that an adult in India experienced an average of 10 events (mean + SD 10.34 + 5.40) in a lifetime and 2 events (mean + SD 1.90 + 2.62) in the past one year without suffering

any physical or psychological disturbance. In this study, the number of life events was recorded for the lifetime before onset and after onset of the CD.

7. *Social Support Questionnaire* (SSQ) [21]: A Hindi language adaptation of Social Support Questionnaire [22] assesses the perceived social support. It has 18 items, rated 1–4, with maximum score of 72; higher the score better the social support. It has a test–retest reliability of 0.59 and correlation with clinician's assessment at 0.80 and with items of social support from Family Interactions Pattern Scale [23] at 0.65.
8. *General Health Questionnaire-12* (GHQ-12): GHQ-12 is a derivative of GHQ that was developed as a valid and reliable self-administered 60-item screening measure for psychological problems in primary care and community settings [24]. GHQ-12 used in this study is based on the Hindi translation of the 60-item GHQ that has been standardized in India and in Indian population [25, 26] and has been used in our center earlier in research with patients with vitiligo and psoriasis [27–29]. In this study, to define a case with possible psychiatric morbidity a score >2 was used. This is because GHQ score of 2 is considered as the best cutoff or threshold for psychiatric diagnosis [30].
9. *Comprehensive Psychopathological Rating Scale* (CPRS) [31]: CPRS assesses the full range of psychopathology with a high reliability. Each of its 65 items is explicitly described and scored 0–3 with each scale step being operationally defined on the basis of intensity, frequency, and duration of the symptoms. Two indices have been derived from the CPRS: Anxiety Index (AI) with 7 items [32] and Depression Rating Scale (MADRS) with 10 items [33].
10. *International Classification of Diseases—10th revision* (ICD-10) [34]: (ICD-10) was used to arrive at the possible clinical diagnoses based on a detailed psychiatric evaluation.

### Procedure

The consultant endocrinologist (AKB) made the initial recruitment and assessment of demography and clinical profile (instruments 1 and 2). Thereafter, the psychologist (RM) completed the psychosocial assessment (instruments 3–8) on the same day over a maximum of two sessions of 1–2 h each. For those with GHQ score >2, the consultant psychiatrist (NG) conducted a semistructured clinical interviewed to determine the presence and the severity of the psychiatric illness using ICD-10 & CPRS (instruments 9 and 10). The psychologist (RM) also recruited the control group satisfying the inclusion/exclusion criteria and assessed it for demography and possible psychiatric illness (instruments 1 and 8).

### Ethical considerations

The Research Ethics Committee of the Institute had cleared the study and all the subjects were recruited on the basis of a written informed consent assuring confidentiality and freedom of choice of participation.

### Statistical analysis

Descriptive statistics in terms of percentage were used for categorical variables; mean and SD were calculated for the continuous variables. The categorical variables were compared using either Chi-square analysis, while the continuous variables were compared using Students' *t*-test by using two tailed analysis. SPSS version-14 was used for data analysis.

## Results

### Demographic profile

As shown in Table 1, the CD and HC groups had similar sociodemographic profiles.

**Table 1** Sociodemographic profile of Cushing disease and Healthy Control groups

| Variable | Cushing cases ($N = 18$) | Healthy Controls ($N = 22$) | Comparison statistics | *P* value |
|---|---|---|---|---|
| Age in years (Mean ± SD) | 25.6 ± 9.9 | 30.7 ± 7.8 | *t*-value = 1.77 | 0.084 |
| Sex | | | | |
| Male | 04 | 09 | Chi square with Yates correction = 0.839 | 0.360 |
| Female | 14 | 13 | | |
| Education in years (mean ± SD) | 9.5 ± 3.3 | 10.4 ± 4.2 | 1.62 | 0.303 |
| Marital status | | | | |
| Unmarried | 09 | 14 | 7.53 | 0.385 |
| Married | 09 | 08 | | |

As shown in Table 1, the sample comprised of mainly females (71.5%) and urban (78.6%) subjects with equal number being married and unmarried. The mean age of the sample was 25.66 (range 10–42) years with education of 9.5 (range 2–14) years.

The mean age of onset of illness was 20.38 (range 8–38) years and the mean duration of illness was 65.33 (range 4–260) months (Table 2). As is shown in Table 2, the reported dysfunction was low-to-moderate with the means ranging from 40.00 (family) to 45.00 (personal) for individual domains and 209.66 for the total. The perceived social support was moderately high with a mean of 48.55. The number of reported lifetime life events was relatively fewer with a mean of 6.22. The subjective QOL reported was quite poor ranging from a mean of 5.83 to 21.66 for different domains and 72.66 for the total. The number of coping strategies used was also low ranging from mean of 1.22 for emotional to 5.11 for denial and 14.27 for all strategies together.

Eight of the 18 subjects were operated about 1 year back and 7 were receiving ketoconazole at the time of assessment. The hormone levels, available for only 12 cases, showed the following mean ± SD values (nmol/l): basal serum cortisol—AM 786.33 ± 251.90 (range 372–1200), basal serum cortisol—PM 699.08 ± 186.57 (range 460–1060), post-dexamethasone serum cortisol—AM 713.50 ± 244.43 (range 230–1100), Post-dexamethasone serum cortisol—PM 546.83 ± 284.23 (range 107–1060).

## GHQ positive versus GHQ negative subgroups

By study design, none of the HC group subjects was GHQ positive. Out of 18 subjects of CD, 6 were GHQ positive (scores > 2), giving a psychological morbidity prevalence of 33.33% (Confidence interval 0.162–0.565). The two subgroups—GHQ positive and GHQ negative—had a comparable sociodemographic profile except that the GHQ positive subgroup had no males. The two subgroups were comparable for quality of life, dysfunction, social support, number of life events, and coping strategies, except that the GHQ positive subgroup used significantly more coping of internalization compared to GHQ negative subgroup.

The ICD-10 diagnostic assessment of all GHQ positive subjects revealed that one subject was suffering from

**Table 2** Psychological profile of cases of Cushing disease

| | Whole group ($N = 18$) (mean ± SD) | Median | First quartile | Third quartile |
|---|---|---|---|---|
| Age at onset (in years) | 20.3 ± 8.5 | 18 | 14 | 25 |
| Duration of illness (in months) | 65.3 ± 76.4 | 36 | 17 | 33.7 |
| DAQ—social | 42.4 ± 8.4 | 40 | 40 | 40 |
| DAQ—vocational | 41.3 ± 4.7 | 40 | 40 | 40 |
| DAQ—personal | 45.0 ± 5.0 | 44 | 40 | 48 |
| DAQ—family | 40.0 ± 0.0 | 40 | 40 | 40 |
| DAQ—cognitive | 40.9 ± 2.8 | 40 | 40 | 40 |
| Total DAQ score | 209.7 ± 20.0 | 204 | 200 | 208 |
| Social support scores | 48.5 ± 6.9 | 48 | 44 | 54 |
| Life events before diagnosis (No.) | 4.1 ± 3.7 | 2.5 | 1 | 7 |
| Life events after diagnosis (no.) | 2.0 ± 1.9 | 1 | 0.7 | 3.25 |
| Total life events (No.) | 6.2 ± 4.5 | 5.5 | 2 | 9.2 |
| QOL—physical health | 19.7 ± 2.6 | 20 | 18 | 21 |
| QOL—psychological health | 17.1 ± 2.7 | 17.5 | 14.7 | 19.2 |
| QOL—social relationship | 08.3 ± 1.4 | 9 | 7.5 | 9 |
| QOL—environmental health | 21.6 ± 4.2 | 22.5 | 17.5 | 24.5 |
| QOL—general well-being | 05.8 ± 1.2 | 6 | 5 | 6.25 |
| QOL—total score | 72.6 ± 11.0 | 73.5 | 62.5 | 80.0 |
| Coping denial | 5.1 ± 2.0 | 5 | 3 | 7 |
| Coping internalize | 3.6 ± 1.8 | 3 | 2 | 5 |
| Coping anger | 2.83± 1.5 | 2.5 | 2 | 3.25 |
| Coping externalize | 1.5 ± 0.9 | 2 | 1 | 1 |
| Coping emotional | 1.2 ± 0.8 | 1 | 1 | 2 |
| Coping total | 14.2 ± 5.6 | 15 | 9 | 17 |

*DAQ* Dysfunction Analysis Questionnaire; *QOL* quality of life

severe depressive episode with psychotic symptoms with scores of 46 for CPRS and MADRS, and 6 for ASI; all other 5 cases did not fulfill any syndromal diagnosis.

## Discussion

The comparability of the CD and the HC groups on sociodemographic variables suggests that the psychological morbidity is not a function of sociodemographic variables. More than 70% of our sample comprised of females, which is similar to the reported prevalence of pituitary dependent adrenal hyperplasia, i.e., F:M ratio of 3:1. Most of our subjects coming from urban areas are partly reflective of the fact that the urban subjects avail health services much more than the rural subjects [35].

Our sample reported a trend for more life events before rather than after the diagnosis. Many authors have also reported 'psychological stress' to be a possible pathogenic factor in their case series of Cushing syndrome [36, 37]. Sonino et al. [38, 39] investigated for stressful life events in the year before the first signs of onset of CD in 66 consecutive and 66 healthy subjects matched for sociodemographic variables using Paykel's [40] interview for Recent Life Events. CD patients reported significantly more loss, undesirable, and uncontrolled events than the controls and the results did not differ between patients with and without major depression. Our finding also provides credence to the stress as an etiological factor in the CD.

Though sparse, western research on QOL in CD has shown SF-36 measured QOL as seriously compromised even when patients are hormonally well [41–43]. Using a different measure (WHOQOL), we too found QOL to be poor in CD in all domains—physical, psychological, social, environmental, and general well-being. Our finding of significant impairment in the physical domain is similar to the findings of Van Aken et al. [13] and Gotch [3] who reported reduced QOL especially for items concerning fatigue and physical ability.

Our finding of psychological morbidity at the rate of 33.33% is relatively low compared to the studies from the West [44–46]. One explanation for this difference could be that while the Western studies have evaluated lifetime psychiatric morbidity, we focused only on current psychological and psychiatric morbidity.

Our GHQ positive subgroup comprised of only females. If not a chance finding, we speculate that female subjects find the disfigurement as more stigmatizing and therefore, are more prone to develop psychological morbidity. The similarity of our GHQ positive and GHQ negative subgroups on quality of life, dysfunction, social support, and number of life events suggests that the psychological morbidity may be related to the impact of the disease on the person and not to the demographic and other clinical variables.

The diagnostic assessment of all GHQ positive subjects revealed that only one subject was suffering from depression, giving a prevalence rate of 5.5%, which is significantly less as compared to Western data. The possible reasons for this lower prevalence could be that majority of our subjects were operated within last 1 year and nearly 40% of the cases were receiving ketoconazole, a drug known to inhibit biosynthesis of cortisol by causing enzymatic blockade of C17, 20-lyase, 11-hydroxylase, and 17-hydroxylase [47]. Studies have shown that corticosteroid levels are high in subjects with depression and drugs like ketoconazole improve depressive symptoms in subjects with CD [47, 48]. The one subject diagnosed with depression was neither operated nor was receiving ketoconazole at the time of assessment.

Cushing syndrome leads to significant physical morbidity and impacts the QOL. Physicians taking care of these patients should address psychological morbidity and quality of life issues and should refer these patients to a psychiatrist, if required.

Our study was limited by the small sample size. Further, we took both incidence and prevalence cases of CD. Hence, our results—particularly those related to the life events (especially after the diagnosis, in incidence cases)—need to be interpreted in this background.

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