Neurocognitive Functions and Brain Volume in Patients with Endogenous Cushing’s Syndrome Before and After Curative Surgery

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Abstract

Introduction: Cushing’s syndrome (CS) leads to various neuropsychiatric manifestations due to structural and functional changes of the brain and contributes significantly in the impairment of health-related quality of life. Aim and Objective: This study is conducted with aims to evaluate neurocognitive functions and brain volume in patients with endogenous Cushing’s syndrome before and after curative surgery. Methods: The diagnosis of CS was made by clinical features, abnormal cortisol dynamics, ACTH levels, and imaging studies. Neuropsychiatric tests (Beck depression Index, Spatial span test, PGI memory scale, Color trail test, Verbal fluency test), and Brain volume (Bi-caudate and third ventricular diameter) were done before and after curative surgery. Results: Fifteen patients of CS were included for the study; all patients underwent curative surgery, neuropsychiatric assessment, and brain volume measurements. Nine patients were followed successfully till remission and repeat evaluation of these patients was done. Depression was the most common neuropsychiatric illness. Severity of depression positively correlated with 0800 h plasma cortisol and ACTH. Patients with higher severity of depression had maximum improvement after curative surgery. Significant decrease in the third ventricular, as well as bicaudate diameter, was observed after curative surgery \( (P < 0.01) \). Conclusion: Neuropsychiatric functions and structural brain changes reverse after curative surgery in patients with endogenous CS, however, long term follow-up is required to know whether these changes reverse completely or not.

Keywords: Brain volume, Cushing’s syndrome, neuropsychiatry

INTRODUCTION

Endogenous, adrenocorticotropic hormone (ACTH) dependent Cushing’s syndrome (CS) is mostly due to corticotrope pituitary adenoma in 80–85% of patients, while in 20% of the patients it is due to ACTH independent causes. Chronic endogenous cortisol excess leads to metabolic complications such as visceral obesity, insulin resistance with glucose intolerance and diabetes mellitus, dyslipidemia, cardiovascular complications such as systemic arterial hypertension, atherosclerosis, thromboembolism, osteoporosis, infective complications, ranging from an increased susceptibility to infections to fatal sepsis and neuropsychiatric disorders.1–4 The first description of neuropsychiatric disturbances was described by Harvey Cushing’s in 1932 in his original description in a series of 12 patients of CS and highlighted the presence of emotional disturbances as a pathologic feature of CS.3 Various neuropsychiatric disorders like major depression, mania, anxiety, neurocognitive disorders characterized by impairment of memory and concentration are present in patients of CS which contribute significantly in the impairment of health-related quality of life. Glucocorticoid receptors are present ubiquitously in the central nervous system with more concentration in the hippocampus. Glucocorticoids mediate

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its harmful effects by increasing the excitatory amino acids, decreases the synthesis of neurotrophic factors, inhibits the long term potentials, suppression of neurogenesis, and altering the glucose metabolism. All these factors lead to structural changes in different areas of the brain and ultimately functional disturbances leading to neuropsychiatric manifestations.\(^{[6-9]}\)

**Aims and Objective**

This study is conducted with aims to evaluate neurocognitive functions and brain volume in patients with endogenous Cushing’s syndrome before and after curative surgery.

**Methods**

**Study setting**

The study was carried out in the department of Endocrinology of Post Graduate Institute of Medical Education and Research (PGIMER) Chandigarh, a tertiary care hospital of north India. The patients with Cushing’s syndrome who were admitted from October 2012 to December 2013 for corrective surgery were included for the study. Fifteen patients of endogenous Cushing’s syndrome (ACTH dependent/ACTH independent) confirmed on cortisol dynamics of age between 15 years and 60 years, who could read and write Hindi and English were included for the study. Patients with a history of chronic alcoholism, smoking, history of cerebrovascular accidents, and previous radiotherapy were excluded.

**Procedure**

Diagnosis of Cushing’s syndrome was established based on clinical features, abnormal cortisol dynamics {at least two abnormal screening tests out of the following—elevated late-night plasma cortisol, 24 h urinary free cortisol, non-suppressible 1 mg overnight dexamethasone suppression test (ONDST), low dose dexamethasone suppression test (LDDST)}. Fourteen patients had Cushing’s disease while one patient had Cushing’s syndrome secondary to adrenal adenoma. The duration of symptoms ranges from nine months to nine years.

**Neuroimaging**

These patients underwent contrast-enhanced MRI (CEMRI) of the sella and brain (Siemens Magnetom Aera 1.5 T, Erlangen). For sellar imaging thin high resolution coronal T2, T1, post-contrast dynamic T1, and sagittal pre- and post-contrast T1 fat-saturated images were acquired. For brain screening, T2 axial, and 3D-T1 weighted images of the whole brain were acquired. The axial images were obtained from 3D-T1 weighted volumetric data of the whole brain with angulation according to bicommissural line.

The analysis of bicaudate diameter and third ventricular diameter was performed manually on the high-resolution axial images by two experienced radiologists. The third ventricle diameter was measured as the maximum diameter of the third ventricle at the level of the foramen of Monroe [Figure 1a (before surgery), and b (after surgery) in the same patient]. Bicaudate diameter is the distance between the heads of the two caudate and was measured as the largest distance between the midportion of the head of the caudate, manually on axial images [Figure 1c (before surgery) and d (after surgery) in the same patient]. Inter-Rater CV for pre-operative and post-operative Bicaudate diameter was 0.94, while for third ventricular diameter was 0.82.

**Neuropsychiatric assessment**

Neuropsychiatric assessment using battery of tests (Beck depression test, color trail test, memory–PGI memory scale, verbal fluency test, and standard progressive matrices) was done during their admission.

**Neuropsychological tests**

**Beck depression index**

The Beck Depression Inventory is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for measuring the severity of depression. In its current version, the questionnaire is designed for individuals aged 13 years and above, and is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The patients were classified according to score 15–20 as mild, 21–29 as moderate, and >29 as severe depression.\(^{[10]}\)
Color trail test
This was used for measuring visual scanning, divided attention, and motor speed. This test is an analog of trail making test. It has two parts. Part 1 measures sustained attention, perceptual tracking, and simple sequencing. The subject has to join circles containing consecutive numbers. Part 2 additionally assesses mental flexibility. The subject has to join numbers in ascending order but in alternating colors. The subject is ordered to connect the circles in the correct order as quickly as possible without lifting the pencil from the paper. Scoring is done by noting down the time taken to complete both parts and the number of errors.\[12,13\]

Memory–PGI memory scale
The PGI memory scale is a part of the PGI battery of brain dysfunction, developed at PGIMER, Chandigarh, India. The battery is administered in Hindi, the first language of most subjects, and has been developed and validated for use in the Hindi-speaking population. It measures 10 subscales of memory function, i.e., recent, remote, mental balance, attention and concentration, delayed recall, immediate recall, retention for similar pairs, retention for dissimilar pairs, visual retention.

Verbal fluency test
Controlled oral word association test
This test is used to measure phonemic fluency. The subject generates words based on phonetic similarity. In Indian adaptation, the subject is asked to generate words (in Hindi) commencing with consonants “pa” “aa” “sa”. The subject is expected to spontaneously produce words as instructed. Proper names and nouns should be excluded. The same word should not be repeated with a different suffix. The duration for each consonant is 60 s. Scoring is done by adding the total number of acceptable new words generated in the stipulated time. The average new words generated over three trials form the score.\[12,13\]

Animal naming test
The animal fluency test generally involves the patient naming as many animals as possible within a 60 s time period. The clinician records the number of animals named. If the patient named 15 or fewer animals within the 60 s time frame this may indicate early stages of dementia or the development of a cognitive impairment. The subject score is the number of animals correctly named. Preservation and intrusions are recorded.\[14\]

Standard progressive matrices
It measures Spearman’s general intelligence factor in individuals aged between 6 and 80 years. It is available in five black and white sets of 12 problems each and can be completed in 20–45 min. The scale is designed to provide a reliable estimate of a person’s capacity to think clearly when allowed to work steadily at his or her own speed from beginning to end without interruption. The total score provides a measure of individual capacity. The total number of problems solved correctly is the total score obtained by the subject. From the tabulated raw scores Wechsler adult intelligence scale (WAIS) equivalent IQ is determined by using the table devised for the same.\[15,16\]

Spatial span test
This test is done to assess the visuo-spatial working memory. This is a test of the participant’s ability to retain spatial information and to manipulate remembered items in working memory. It is a visual analog of the familiar finger span test. The spatial span board features 10 cubes, with numbers 1–10 printed on the side of the cube facing the examiner. Two trials for each sequence length are administered.\[17,18\]

Transsphenoidal surgery was done to remove the adenoma with an attempt to preserve the normal pituitary by the same neurosurgeon for all the patients with Cushing’s disease. One patient underwent unilateral adrenalectomy for adrenal adenoma. All the patients were regularly followed-up on an outpatient basis for clinical and biochemical remission. After achieving biochemical remission patients were subjected to repeat CEMRI of brain and neuropsychiatric analysis.

Criteria’s for remission/cure of the Cushing’s syndrome were:-
1. Patients having a 0800 h cortisol level of less than 150 nmol/L in the first-week post-surgery or those who are requiring cortisol replacement post-surgery.
2. A repeat cortisol 0800 h was done at the time of repeat imaging and the cure was defined as
   a) <100 nmol/L – these patients were directly recruited
   b) 100-350 nmol/L – these patients were subjected to 250 microgram ACTH stimulation test followed by ONDST, if ONDST was suppressible they were recruited
   c) >350 nmol/L – ONDST was done, if ONDST was suppressible they were recruited.

All the patients were hypocortisolic or eucorticisolic postoperatively and were in remission on follow up. Those who were not in remission were excluded from the final analysis. The mean interval duration of eucoortisolema was 7 months ± 28 days.

Statistical analysis
Statistical analysis was done using SPSS 16 version. Descriptive statistics like mean and median were calculated. The data of the third ventricular diameter and bicaudate diameter obtained pre-operatively was compared with the data post-operatively. The data obtained from neurocognitive studies of Cushing’s patient pre-operatively was also compared with the post-operatively data. Statistical analysis to identify differences between values before and after surgery was performed by Wilcoxon signed-rank test. Spearman’s correlation coefficient was used to evaluate the relationship between variables. The level of significance was set at 0.05 for all statistical tests.

The study was approved by the institutes ethic committee.

Consent: Informed written consent was taken from each patient participating in the study.
RESULTS
Fifteen patients of Cushing’s syndrome were enrolled for the study, (Cushing’s disease (CD)-14, Adrenal adenoma-1). Out of 15 patients (Male-3, CD-3), (Female-12, CD-11, Adrenal adenoma-1) were part of the study. Out of fourteen patients of CD, two patients were postoperative cases of CD but were still having active disease. Twelve patients underwent trans-sphenoidal surgery. One patient with adrenal adenoma underwent unilateral adrenalectomy. Two patients were lost to follow up. Thirteen patients had follow up of a mean duration of 7 months ± 28 days after surgery. Nine patients, all of which were having CD (Male-3, Females-6) were followed up successfully till remission and underwent repeat evaluation (CEMRI sella/brain and neuropsychiatric assessment).

Depression of varying degrees was the most common neuropsychiatric illness. In pre-operative group 4 patients had minimal depression, 3 had mild depression, 2 patients had moderate depression, and 1 patient had severe depression. Patients with moderate and severe depression were treated for depression. Two patients with suicidal tendencies showed the maximal improvement in depression following surgery. The maximal improvement was seen in the patients with moderate and severe depression.

Correlation of pre-operative 0800 h serum cortisol and ACTH with neuropsychiatric tests, third ventricular diameter, and bicaudate diameter was done to study the effect of serum cortisol on these parameters [Table 1]. No significant correlation between 0800 h serum cortisol and brain volume parameters was found. Among neuropsychiatric tests, Beck’s depression index showed significant correlation with 0800 h serum cortisol and ACTH.

There was improvement in all the neuropsychiatric tests performed postoperatively [Table 2], i.e., BDI, Spatial span test, IQ as measured by the standard progressive matrices, animal naming test, COWAT score, color trail test 1 and 2, and PGI memory scale; which suggests that following curative surgery of CS most of the neurocognitive functions improves significantly.

There was significant reduction in the third ventricular (−1.08 mm, P-0.008) and bicaudate nucleus (−1.27 mm, P-0.008) diameter from baseline after curative surgery; which are surrogate marker of increase in brain volume, thus suggesting an increase in brain volume after curative surgery [Figure 1].

DISCUSSION
Neuropsychiatric disorders like major depression, mania, anxiety, impairment of memory, and concentration are present in patients of CS due to structural and functional changes in the brain leading to impairment of health-related quality of life. These changes partially or completely reverse after curative surgery or treatment of CS. [6-20] We performed the neuropsychiatric tests and imaging studies of the brain to study the effect of curative surgery on the structural and functional parameters of the brain in the patients of CS.

Mild to severe degree of depression was found in most of the patients (12 out of 15) in our study group; while two patients had also suicidal tendencies using the Beck depression scale. Major depression was the most common neuropsychiatric comorbidity in patients of CS. Several studies have shown that the incidence of depression ranges from 50 to 81% in patients of endogenous CS and the degree of severity varies from minimal to severe depression and can be associated with suicidal tendencies. [16-20]

Female gender, older age, and levels of cortisol have been associated with a higher incidence of depression. In our study number of females was higher as CS is more common in females but we did not find any gender differences in the incidence of depression, however; the incidence of depression was similar to the reported literature. Levels of cortisol have been associated with severity of depression; in our study, we also found 0800 h cortisol and ACTH were positively correlated with the severity of depression. We also that found after curative surgery maximal improvement was seen in patients who had severe depression particularly suicidal tendencies were improved significantly and most of the patients had minimal or mild depression on follow up. [21-25]

Curative surgery leads to improvement in the clinical, metabolic, and neuropsychiatric manifestations but whether these changes are completely or partially reversed is still controversial, however many studies have shown that there is a significant or complete improvement in the clinical as well as neuropsychiatric profile of patients who have curative surgery. [26-30]

Long term follow-up has shown that there is long-lasting impairment in many areas of cognitive functions such as attention, reasoning, alerting memory, reading, verbal fluency,
Table 2: Neuropsychiatric tests

| Test                                      | Score (mean±standard deviation) | Before surgery | After surgery | P    |
|-------------------------------------------|---------------------------------|----------------|---------------|------|
| BDI                                       | 18.89±9.77                      | 10.78±3.96     | 0.008         |
| Spatial span test                         | 10.11±1.96                      | 11.89±1.90     | 0.016         |
| PGIMS                                     | 30.11±8.16                      | 46.33±6.42     | 0.008         |
| Standard progressive matrix (IQ test)     | 94.89±9.57                      | 104.44±8.14    | 0.008         |
| Animal naming test                        | 10.44±2.06                      | 14.44±2.24     | 0.007         |
| COWAT score                               | 15.67±6.78                      | 24.78±5.44     | 0.007         |
| Color trail test 1 (milliseconds)         | 6475.11±1281.90                 | 5024.22±1288.54| 0.008         |
| Color trail test 2 (milliseconds)         | 13066.22±1245.17                | 10425.67±2004.60 | 0.011     |

BDI, Becks Depression Index; COWAT, Controlled Oral Word Association Test; PGIMS, Post Graduate Institute Memory Scale; IQ, Intelligence quotient

and executive functions in patients of CS after curative surgery.[31-33] In our study there was improvement in all the parameters of cognitive functions such as spatial span test, PGI memory scale, standard progressive matrix (IQ test), animal naming test, COWAT score, color trail test-1, and color trail test-2, suggesting that there is an improvement in the cognitive functions after curative surgery in patients of CS; however long term follow-up is required to know the extent of improvement in the cognitive functions.

Cerebral and cerebellar atrophy, reduction of hippocampal, parahippocampal, temporal lobe, and amygdala volumes have been implicated in the neurocognitive decline in patients of active CS.[34-36] In a study by Bourdeau et al., 22 patients of CS were followed after cure, and imaging done at 39.7 ± 34.1 months revealed significant improvement of the third ventricle diameter (P < 0.001) and bicaudate diameter (P < 0.0005).[37] In a study by Merke et al. in the pediatric age group; they showed that after one year of following after curative treatment for CS, the structural abnormalities were normalized, however; cognitive dysfunctions persisted.[38] Studies using proton magnetic resonance spectroscopy have shown that even after long term biochemical cure of CS, neuronal dysfunctions persists and regeneration process like glial proliferation also continues.[39]

We studied the third ventricular and bicaudate nucleus diameter, which are surrogate markers of reduction in the brain volume. We found that there was a significant (P < 0.01) reduction in the diameter of both these parameters, suggesting that curative surgery in patients with CS leads to a reversal of structural changes of the brain.[40-41] However, studies with long term follow-up are required to know that these changes are completely reversed and neuropsychiatric manifestations revert to normal after structural changes normalized.

Small sample size and relatively short follow up are the limitation of our study; however, because of the rarity of the disease, this sample size is enough to compare the neuropsychiatric outcome after the cure of CS. Comprehensive evaluation of the patients by a battery of neuropsychiatric function tests and structural brain changes are strengths of our study.

To conclude, neuropsychiatric functions and structural brain changes reverse after curative surgery; however; long term follow-up is required to know whether these changes reverse completely or not. Functional imaging like magnetic resonance spectroscopy can be more helpful in studying the structural brain changes in these group of patients.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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