

Psychiatric Disorders in Patients with Cushing's Disease Before and After Neurosurgery



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SUMMARY

Objective: Cushing's disease which is a consequence of ACTH-secreting pituitary adenoma leads to hypercortisolism. Cushing's disease is associated with several psychiatric disturbances. The aim of the present study was to identify which psychiatric disorders were present in patients with Cushing's disease over a 2-year period and to monitor their general psychiatric condition. Additionally, the study aimed to examine the relationship between the duration of Cushing's disease, and the severity of psychiatric conditions based on psychiatric rating scales.

Method: The study included 39 patients with Cushing's disease that underwent neurosurgery for ACTH-secreting pituitary adenomas. The transsphenoidal approach (the standard microsurgery technique) was performed in all patients. ACTH-secreting pituitary adenomas were confirmed based on immunohistochemistry in all patients. Psychiatric conditions in the patients were identified using the Clinical Global Impression Scale (CGI) and ICD 10 diagnostic criteria at 3 time points: prior to surgery, and 6 and 48 months post surgery.

Results: The Cushing's disease patients exhibited statistically significant improvement in their psychiatric condition, according to the CGI, 6 and 48 months post surgery. There wasn't any significant correlation between the duration of Cushing's disease and psychiatric status, as measured by the CGI prior to surgery, 6 months post surgery, or 48 months post surgery.

Conclusion: Patients with Cushing's disease had a significant level psychiatric disturbance that remitted after surgery. There wasn't a significant correlation between the duration of Cushing's disease and psychiatric status.

Key Words: Cushing's disease, psychiatric disorders, longitudinal follow up, neurosurgery

INTRODUCTION

Cushing's disease which is a consequence of ACTH-secreting pituitary adenoma leads to hypercortisolism. Cushing's disease is a rare and complex endocrine disorder associated with several psychiatric disturbances (Sonino and Fava, 2001). Some researchers have reported that prolonged exposure to increased levels of cortisol in most patients leads to significant psychopathology, primarily depression, irritability, and a generally poor psychiatric status (Musselman and Nemeroff, 1996; Sonino et al., 1996; Sonino et al., 1998). Studies on psychiatric complications in Cushing's syndrome, which has been extensively investigated, continue to increase in num-

ber; however, to date, few studies on psychiatric pathology in patients with Cushing's disease have been carried out. One study examined the prevalence of depression in Cushing's disease patients and reported that 54% had a depressive disorder (Sonino et al., 1998). Another study reported that 79% of Cushing's disease patients had an anxiety disorder, 68% had a depressive disorder, and 53% had panic disorder (Loosen et al., 1992), while a third study showed that 56% of patients had a depressive disorder (Hudson et al., 1987).

To the best of our knowledge no follow-up studies examined psychopathology in Cushing's disease patients or changes in the severity of psychopathology after surgical removal of the

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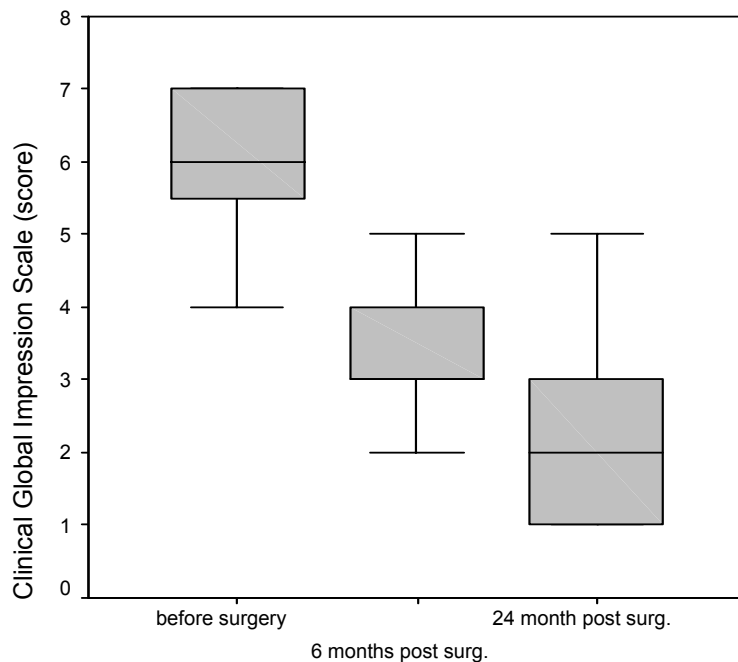


FIGURE 1. CGI scores in the Cushing's disease patients prior to surgery, and 6 and 48 months post surgery

tumor. Accordingly, the aim of the present study was to investigate which psychiatric disorders were present and to monitor the general psychiatric status of Cushing's disease patients over a 2-year period: prior to surgery, and 6 and 48 months post surgery. In addition, we aimed to examine the relationship between the duration of Cushing's disease and the severity of psychiatric conditions based on psychiatric rating scales.

METHODS AND MATERIAL

Patients

This study was conducted at the Multidisciplinary Center of Neuroendocrinology and Pituitary Diseases of the Sestre milosrdnice University Hospital, Zagreb, Croatia. From 1984 to 2009 more than 1300 tumors of the sellar region were operated; among them there were 60 adenomas with ACTH hypersecretion and clinical picture of Cushing's disease. From among these 60 patients, 39 were included in the study. Some patients were excluded because they were no longer available for follow-up due to the disintegration of the former state of Yugoslavia and because they relocated outside Croatia. Other patients were excluded because they did not undergo psychiatric evaluations during the entire follow-up period, they had incomplete medical documentation, or their surgery was unsuccessful. Criteria for surgical success were clinical improvement, normal plasma ACTH values, and/or normal urine cortisol values (Trainer and Grossman, 1991).

The final sample included 39 Cushing's disease patients that underwent surgery for an ACTH-secreting pituitary adenoma (1 patient had a macro adenoma and 38 had a micro adeno-

ma) between 1991 and 2007. Among the 39 patients included in the follow-up, 10 were male and were 29 female. Mean age of the patients was 35.4 ± 7.2 years (range: 8-55 years). There were 7 patients (18%) 8-14 years old, 2 patients (5%) were 15-18 years old, and 30 (77%) patients were >18 years old. The duration of Cushing's disease ranged between 1 and 4 years (mean: 2.9 ± 1.1). All patients were operated by the same neurosurgeon using the standard microsurgery transsphenoidal approach (Ludecke et al., 2001; Gnjidić, 2004; Gnjidić et al., 2006). ACTH-secreting adenoma was confirmed based on immunohistochemistry in all the patients. None of the patients had a psychiatric disorder in anamnesis prior to developing Cushing's disease. The Ethics Committee of Sestre milosrdnice University Hospital approved the study protocol and all the patients provided informed consent.

Evaluation of the patient's psychiatric status

Psychiatric evaluations were performed in all the patients by the same consultation-liaison psychiatrist (Karlović D.) at the Multidisciplinary Center of Neuroendocrinology. Psychiatric diagnoses were based on ICD 10 criteria and were determined before neurosurgery, and 6 and 48 months post surgery (World Health Organization, 1992). The psychiatric condition of each patient was monitored using a scale for the evaluation of general clinical impression of psychiatric functioning - the Clinical Global Impression Scale (CGI) (Guy, 1976). The CGI is a standardized assessment tool clinicians use to rate the severity of illness, changes over time, and the efficacy of treatment, taking into account the patient's clinical condition and the severity of side effects. The CGI scale is widely used in clinical tre-

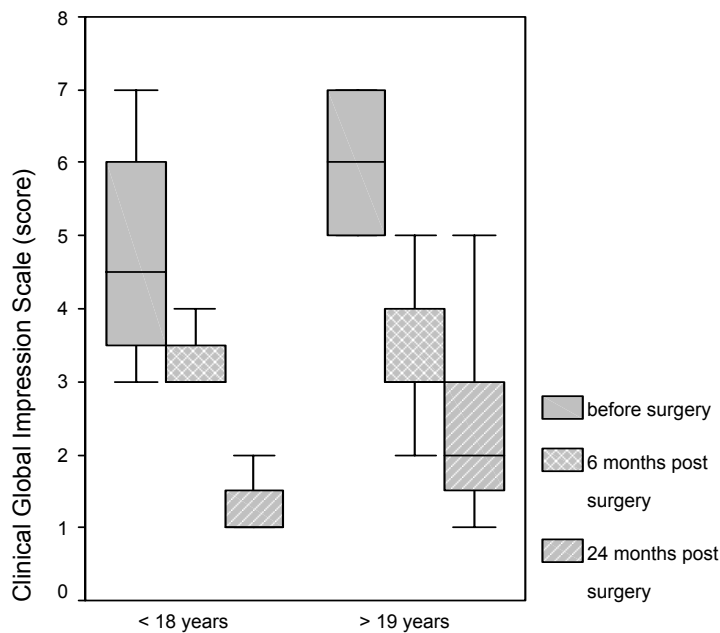


FIGURE 2. CGI scores in the Cushing's disease patients 6 and 48 months post surgery, according to age group (<18 years of age and >19 years of age).

atment trials as an outcome measure. In the present study the CGI was administered prior to surgery, and 6 and 48 months post surgery by a psychiatrist trained in its use.

Statistical methods

The research results were first analyzed using the Kolmogorov-Smirnov test to determine the normality of data distributed over individual variables (CGI results prior to surgery, and 6 and 48 months post surgery). None of the variables were distributed normally; therefore, in order to evaluate changes in CGI scores we used the non-parametric Friedman test, which measures a sample's possible changes in statistical significance across 3 points in time. The Mann-Whitney U test was used to compare possible differences in CGI scores between patients <18 years of age and those >19 years of age. The relationship between the duration of Cushing's disease, and the severity of psychiatric symptoms before surgery, and 6 and 48 months post surgery was explored using Spearman's correlation analysis. Statistical significance was considered $P < 0.01$. Statistical analysis was performed using SPSS v. 11 (SPSS, Inc., Chicago, IL).

RESULTS

The Cushing's disease patients exhibited statistically significant psychiatric improvement, based on CGI scores, both 6 and 48 months post surgery (Friedman test: 70.886; $df = 2$; $P < 0.01$). CGI scores were lowest prior to surgery (mean: 6.9 ± 0.8 ; range: 4-7; mean rank: 2.99), somewhat better 6 months post surgery (mean: 4.3 ± 1.3 ; range: 2-7; mean rank:

1.81), and were highest 48 months post surgery (mean: 3.1 ± 1.3 ; range: 2-6; mean rank: 1.2). The psychiatric status of the patients, according to CGI scores, is illustrated in Figure 1. Psychiatric diagnoses in the Cushing's disease patients before neurosurgery, and 6 and 48 months post neurosurgery are shown in Table 1.

When we separated the sample according to age (<18 years of age [children/adolescents] and >19 years of age [adults]) we did not observe any statistical differences (Figure 2) between them before surgery (mean: 4.7 ± 1.5 ; range: 3-7; mean rank: 12.1 versus mean: 6.1 ± 0.9 ; range: 5-7; mean rank: 22.0, respectively; Mann-Whitney U test: 60.5; $P = 0.021$), 6 months post of surgery (mean: 3.4 ± 1.2 ; range: 2-6; mean rank: 18.9 versus mean: 3.4 ± 0.3 ; range: 1-6; mean rank: 20.1, respectively; Mann-Whitney U test: 115.1; $P = 0.742$), or 48 months post surgery (mean: 1.4 ± 0.3 ; range: 1-3; mean rank: 12.01 versus mean: 2.4 ± 0.3 ; range: 1-5; mean rank: 22.1, respectively; Mann-Whitney U test: 59.9; $P = 0.02$).

We did not observe a significant correlation between the duration of Cushing's disease and the severity of psychiatric status as measured by the CGI prior to surgery (Spearman's correlation: 0.133; $P = 0.419$), 6 months post surgery (Spearman's correlation: 0.110; $P = 0.504$), or 48 months post surgery (Spearman's correlation: 0.073; $P = 0.66$).

DISCUSSION

The present results show that the general psychiatric condition of the Cushing's disease patients in the children/adolescent and adult groups, as measured by the CGI, significantly

TABLE 1. Psychiatric diagnoses, according to ICD 10, in patients with Cushing's disease patients before neurosurgery, and 6 and 48 months post neurosurgery.

	Before neurosurgery	6 months post neurosurgery	48 months post neurosurgery
Organic depressive disorder	21	9	2
Organic mixed affective disorder	9	4	1
Organic anxiety disorder	4	1	0
Organic emotionally labile disorder	3	1	0
No psychiatric diagnosis	2	24	36

improved after the correction of hypercortisolism via surgical removal of their pituitary adenomas. Additionally, we did not observe a statistically significant correlation between the duration of Cushing's disease and CGI score. The majority of the patients had an organic psychiatric disorder that regressed during the follow-up period.

To the best of our knowledge research on changes in the psychiatric condition of patients with Cushing's disease has not been previously conducted. To date, monitoring psychiatric changes has only been performed in patients with Cushing's syndrome; research on the influence of the duration of Cushing's disease on psychiatric status has not been carried out. In the present study we assessed the patients' psychiatric status according to ICD 10 classification, as we are legally bound to use it in the Republic of Croatia. As such, we had somewhat different diagnostic categories in our population in comparison to other studies (Hudson et al., 1987; Loosen et al., 1992; Sonino et al., 1996; Sonino et al., 1998).

The present study has some limitations, mainly because we measured only general psychiatric status using the CGI and did not correlate these findings with serum or urine hormone concentrations (cortisol, ACTH, and urine cortisol); this was done because the sample was collected over a 20-year period and the incompatibility of the hormone concentrations

measured during this period would have resulted in substantial methodological weakness. This is partially due to the fact that hormone levels, although studied in the same laboratory, were analyzed by different biochemical methods (from RIA to ELISA) and that hormone levels were reported in different units (mmol L^{-1} , ng L^{-1} , and international units). In our case, complete regression of hormone concentration within referent values was common for all the analyzed values. We focused on psychiatric disorders of organic origin, while numerous studies suggest that Cushing's disease and syndrome cause a wider spectrum of neuropsychiatric consequences, e.g. cognitive and morphologic disorders that are consequences of hypercortisolemia.

In the future, changes in individual psychopathological symptoms after surgery should also be monitored; for instance, depressive symptoms, anxious symptoms, obsessive symptoms, impulsivity, and even psychotic symptoms. In conclusion, we would like to reiterate that the general psychiatric status of the Cushing's disease patients prior to surgery was significantly poorer than post surgery. The psychiatric status of the patients improved with time post surgery. Additional research is necessary to evaluate the specific psychiatric disorders in Cushing's disease patients and to correlate the severity of specific psychiatric diagnoses with serum cortisol and ACTH concentrations over time.

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