Coll. Antropol. **32** (2008) 4: 1165–1170
Original scientific paper

Reversible »Brain Atrophy« in Patients with Cushing's Disease

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A B S T R A C T

During the past 25 years, we came across 60 patients with corticotroph pituitary adenomas and Cushing's disease. Neuroradiological examination showed prominent volume loss of the brain parenchyma, unexpected for the patient's age. This »brain atrophy« appeared to regress after surgical removal of pituitary adenoma and normalization of cortisol level. Observed difference between degree of »brain atrophy« in the Cushing's disease group and in the control group was statistically significant ($p<0.001$). The degree of »brain atrophy« correlated well with the duration of Cushing's disease. Partial reversibility of »brain atrophy« was noticed during the 2nd, 3rd and 4th year after surgery and normalization of cortisol level. Increased cortisol level is one of the causative factors in pathogenesis of »brain atrophy«. Loss of brain volume is at least partially reversible after normalization of cortisol levels.

Key words: *Cushing's disease, brain atrophy, pituitary ACTH adenoma, hypercortisolism, transsphenoidal surgery, CT, MRI, reversibility*

Introduction

Patients with Cushing's disease caused by ACTH-secreting pituitary adenoma, constitute a very complex group of patients with peculiar clinical symptoms and high number of potential complications associated with surgical treatment[1,2]. Due to anatomical and morphological characteristics of ACTH adenomas, especially their small size, commonly encountered are false-negative sellar computed tomography (CT) scans (67%), pituitary magnetic resonance (MR) imaging scans (48%), as well as cases with ectopic ACTH secretion[3,4]. Difficulty in obtaining accurate location of ACTH pituitary adenoma has been reported even after sampling of the inferior petrosal sinus[5,6]. Therefore, in majority of cases our decision for surgical treatment has been based on clinical manifestations and laboratory findings.

Analyzing the brain CT and MR scans of patients with Cushing's disease, we have noticed diffuse brain volume loss disconcordant with patient's age. Observed »brain atrophy« was so prominent, that in some cases with borderline clinical and laboratory findings, brain volume loss almost became a lead diagnostic tool.

Long-term follow-up of surgically treated patients with Cushing's disease caused by ACTH-secreting pituitary adenoma was conducted. Partial, or in some cases complete remission of brain atrophy after normalization of cortisol level was noticed on control postoperative CT and MR scans. In this report, a group of 39 patients with Cushing's disease was examined to assess the presence and degree of brain atrophy and its remission after surgery and normalization of cortisol level.

Systemic effects of hypercortisolism are well known and described[7]. However, the data on structural alterations of human brain in Cushing's disease are limited and not emphasized in the literature as a detectable manifestation of this disease. In 1971 Momose et al. described the presence of diffuse cerebral atrophy in 74% of patients with Cushing's disease using pneumoencephalography[8]. Starkman et al. found decreased hippocampal

Received for publication December 1, 2006

formation volume in 27% of 12 patients with Cushing's disease on magnetic resonance imaging[9]. Heinz et al. described a 9-year-old boy with Cushing's disease and apparent severe cerebral atrophy which recuperated almost completely after successful disease treatment[10]. Starkman et al. reported a mean 3.2% ± 2.5% increase in hippocampal formation and caudate nucleus volumes following treatment in 22 patients with Cushing's disease[11]. Decrease of cortisol levels, usually 16 months after surgery, is correlated with the volume increase in those two brain structures, with the increase of hippocampal volume being twice that of caudate nucleus. As evidence of the well-known dexamethasone antiedematous effect, the amount of water in the gray and white matter of the brain, including the hippocampus, increases with decreased cortisol levels[12,13]. Although changes in brain volume may be caused by variations in the amount of water in the brain, the fact that cortisol level normalization has stronger effect on hippocampus than on caudate nucleus indicates that an additional mechanism is likely to play a role[9,11]. Hippocampus in adults of different species has the ability to generate new granular neuronal cells and in humans the production of new neurons has been already proven[14]. Increase in hippocampal volume was shown to be directly associated with amelioration of cognitive functions[11,15].

Patients and Methods

Patients

Since 1980 we have operated on more than 1300 sellar tumors, including 60 patients with ACTH-secreting pituitary adenoma and clinical signs of Cushing's disease.

This retrospective study included 39 patients with Cushing's disease caused by an ACTH-secreting pituitary adenoma who had successful surgical treatment and whose medical data were available. The selection criteria for successful surgery and normalization of Cushing's disease were: 1) regression of clinical symptoms, and 2) postoperative normal plasma ACTH and cortisol levels and/or normal urinary free cortisol concentration. Analyzed group included 10 male and 29 female patients, ageing from 8–56 years old, median age 33.2 ± 13.9 years. There were 5 children (0–14 yrs), 5 adolescents (15–19 yrs) and 29 adults (≥20 yrs).

Out of the remaining 21 patients, who were not analyzed, 11 patients had an incomplete tumor removal, 3 patients died, 2 patients had incomplete medical records and 5 patients did not answer the call for investigation.

The control group consisted of 39 patients: 5 with growth hormone (GH)-secreting microadenoma, 5 with prolactin (PRL)-secreting microadenoma, 10 with hormonally inactive pituitary adenoma and 19 patients in who brain CT and/or MR scans were performed for conditions not related to intracranial masses, metabolic disorders, cerebrovascular disease or other conditions inducing brain atrophy. All patients within this group had normal ACTH and cortisol levels. They were 10–57 years old, with median age 40.1 ± 13.8 years. There were 12 men and 27 woman; 5 children, 2 adolescents, and 32 adults. The control group was necessary in order to demonstrate the difference in »brain atrophy« degree between patients with and without Cushing's disease.

Surgery

All patients with ACTH-secreting pituitary adenomas and with other pituitary adenomas from the control group were surgically treated using standard transsphenoidal approach. In all 39 patients an ACTH-secreting adenoma was diagnosed using pathohistological and immunohistochemical analysis.

Radiological examination

16 out of 39 patients had sellar CT using DRH Siemens with coronal 2mm thick sections, before and after administration of 60 mL contrasting agent (380 mg Jod/mL). The remaining 23 patients were evaluated using a 1.0 T Siemens-Harmony MR scanner. Magnetic resonance imaging included sagittal and coronal T1-weighted sequences before and after administration of paramagnetic contrast agent (0.1 mL/kg), coronal postcontrast dynamic T1-weighted image, as well as axial and coronal T2-weighted images, all with 3 mm slice thickness. Postoperative neuroradiological examinations were performed using same diagnostic devices as the preoperative scans, under same technical conditions so the scans taken before and after surgery could be compared. Neuroradiological evaluation was done for clinical purposes. Therefore, at our disposal we had CT or MR scan pictures with neuroradiological description, without electronic version of the scans. Therefore, we used judgment received from two neuroradiologists who were blinded to all patient data and who independently reviewed all imaging materials. Any disagreements were solved by consensus on an additional review. Using this procedure, we were able to avoid and test for subjectivity in assessing the degree of »brain atrophy«.

Statistical analysis

The degree of »brain atrophy« was measured and determined according to the scale proposed by Momose in 1971[8] and modified by Simmons in 2000[16], and classified as follows: 0 – no atrophy; 1 – minimal atrophy; 2 – moderate atrophy; 3 – severe atrophy. Data obtained from neuroradiologists were compared using Cohen's Kappa test. Data used in further analysis were obtained from a neuroradiologist who, in evaluating the brain atrophy in each case, used a higher degree. Patients were divided in subgroups according to the duration of the disease: one year or less, 2–3 years, 4–5 years, 6 and more years. Regression of the degree of brain volume loss was analyzed during 4 years after surgery.

Results are sorted in Table 1 and 2. Patients with Cushing's disease and patients from the control group were compared using χ^2 test. The degree of brain atrophy in different time period was analyzed with Stuart-Maxwell test[17,18].

Results

In our series there was significant discordance in evaluation of »brain atrophy« degree between two neuroradiologists (control group: $\kappa = 0.267$; Cushing's disease: $\kappa = 0.125$), but only for one degree, in four grade scale, in all cases.

Observed difference in the degree of »brain atrophy« in patients with Cushing's disease before operation and control group was statistically significant ($\chi^2 = 23{,}673$; $p < 0.001$, Table 1).

TABLE 1
DISTRIBUTION OF PATIENTS ACCORDING TO PREOPERATIVE ASSESSMENT OF BRAIN ATROPHY DEGREE IN CONTROL GROUP AND IN GROUP WITH CUSHING'S DISEASE

$\chi^2 = 23{,}673$; $p < 0.001$	Group	
	Cushing's disease n (%)	CONTROL n (%)
No atrophy	0 (0%)	16 (41.0%)
Minimal atrophy	25 (64.1%)	20 (51.3%)
Medium or severe atrophy*	14 (35.9%)	3 (7.7%)
Total	39 (100%)	39 (100%)

* In only two patients with Cushing's disease severe brain atrophy was observed

There was statistically significant difference in distribution of patients according to preoperative assessment of »brain atrophy« degree and disease duration ($\chi^2 = 8{,}344$; $p = 0.004$, Table 2 and Figure 1).

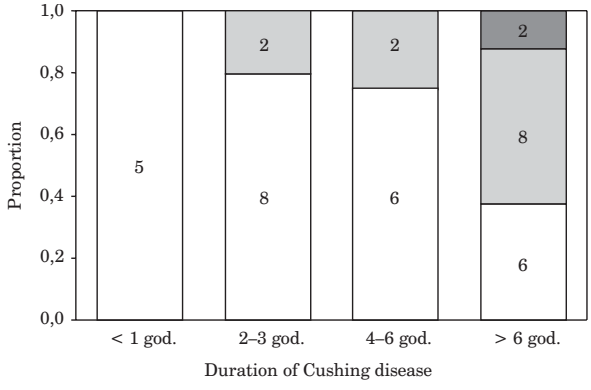

Fig. 1. Proportion of patients according to the duration of Cushing's disease: minimal atrophy (open bars), medium atrophy (dotted bars), severe atrophy (striped bars).

The »brain atrophy« degree before and one, two, three and four years after surgery was analyzed. No statistically significant difference was found in brain atrophy degree before and one year after surgery ($p=0.172$) but there was statistically significant difference in »brain atrophy« degree two, three and four years after surgery ($p=0.003$, 0.002 and 0.001 respectively, Figure 2).

TABLE 2
DISTRIBUTION OF PATIENTS ACCORDING PREOPERATIVE ASSESSMENT OF BRAIN ATROPHY DEGREE AND DISEASE DURATION

Disease duration (years)	Brain atrophy degree		
	Minimal	Medium + severe	
≤ 6	19	4	$\chi^2=8{,}344$
>6	6	10	p=0.004

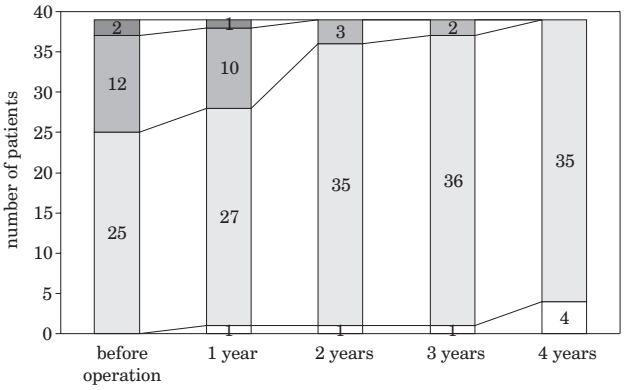

Fig. 2. The brain atrophy degree before, one, two, three and four years after surgery: no atrophy (open bars), minimal atrophy (doted bars), medium atrophy (wave bars), severe atrophy (striped bars).

Discussion

In our series, according to the χ^2 test, the »brain atrophy« degree was statistically significantly higher in patients with Cushing's disease when comparing with the control group ($p<0.001$), despite the fact that control group was, in average, slightly older. This result confirmed our empiric observation and justified further investigation. Similar results were presented by other authors who used comparable methodology[9,16]. The »brain atrophy« degree increased with preoperative duration of Cushing's disease. So, when Cushing's disease lasted one year or less, only minimal atrophy was observed and in case of prolonged Cushing's disease, proportion of »brain atrophy« degree changed in advantage of medium and severe atrophy. Statistical significance was noticed when comparing patients with disease duration of more or less than six years (Figure 3 and 4).

Despite the effort to precisely detect the beginning of the Cushing's disease it is highly possible that disease lasted longer before it was diagnosed. Other authors, especially Simmons et al. detected correlation between duration of hypercortisolism and degree of brain atrophy[16].

Analyzing the whole specimen, one year following the surgery and normalization of blood cortisol level, degree of brain atrophy showed improvement on control neuroradiological imaging in 5 patients and while the remaining 34 patients findings were unchanged. After surgery »brain atrophy« regressed, so already two years later

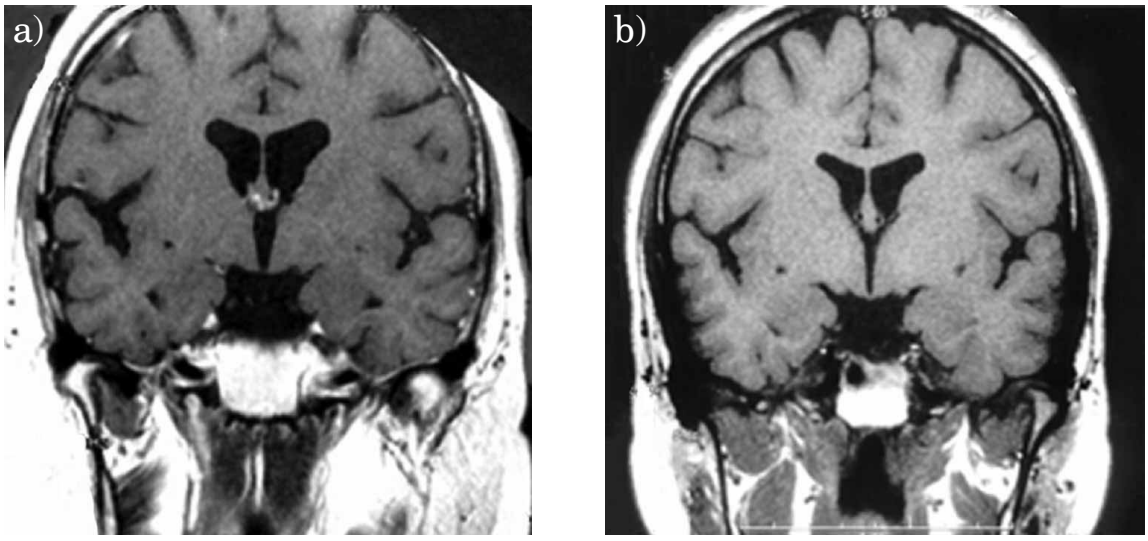

Fig. 3. Patient with Cushing's disease, operated 2 years after the onset of symptoms. a) Coronal T1-weighted image one year after surgery shows mild (Grade 1) brain volume loss, with prominent lateral ventricles and Sylvian fissures. b) Corresponding coronal T1-weighted image two years after surgery demonstrates interval improvement without significant (Grade 0) brain volume loss.

there was significant improvement in »brain atrophy«. Three and four years after surgery results were even better, clearly indicating positive effect of surgery on degree of »brain atrophy«.

Bourdeau et al. described a group of 38 patients with Cushing's syndrome and found a subjective loss of brain volume in 86% of patients with Cushing's disease and 100% of patients with adrenal Cushing's syndrome. Partial reversibility of anatomical modifications of brain volume was observed in most patients 40 months after cortisol level normalization what correlates with our results where four years after cortisol level normalization there was no further change in brain atrophy degree.

We have used the term »brain atrophy« because it was often used by the neuroradiologists. Quotation-marks were used due to the doubt of accuracy of this term. Bourdeau favors the term »loss of brain volume« over the term »brain atrophy« due to partial reversibility and lack of evidence for brain atrophy in patients with Cushing's disease. Partial reversibility of cerebral atrophy which correlates with hypercortisolism clearly indicates that the loss of brain volume is not only a consequence of neuronal cell death[19].

Bourdeau states that the loss of brain volume is a diffuse process, not limited to hippocampal formation, often seen in patients with Cushing's syndrome either pitu-

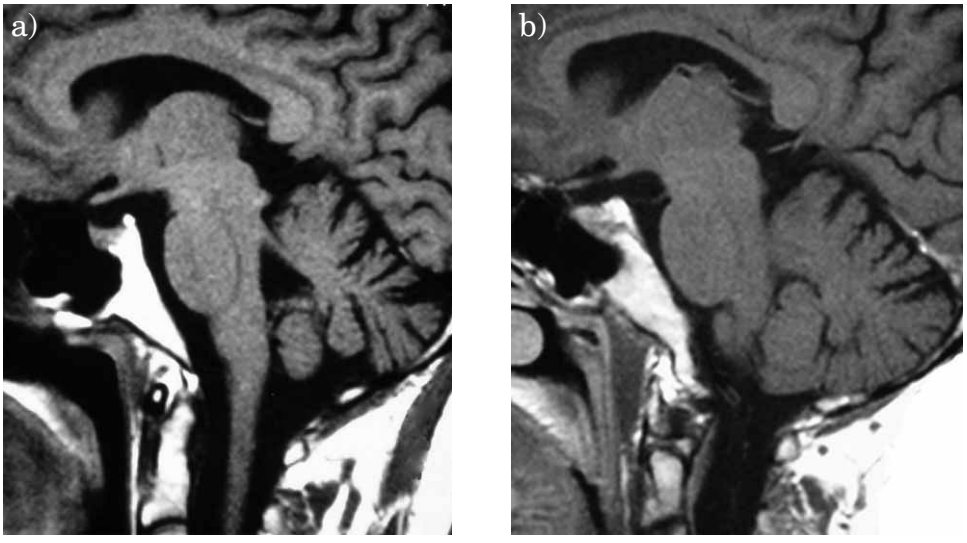

Fig. 4. Patient with Cushing's disease, operated 6 years after the onset of symptoms. a) Midsagittal T1-weighted image one year after surgery shows severe (Grade 3) volume loss, especially in the cerebellum with very thin vermian folia. b) Corresponding sagittal T1-weighted image three years after surgery reveals significant interval improvement with only mild (Grade 1) volume loss.

itary or adrenal etiology. Brain volume loss is finally partially reversible after cortisol level normalization indicating that ACTH is not responsible for structural changes in the brain. Brain volume loss is not associated with other pituitary lesions. These investigations correlate with the results of Starkman et al.[9,11,15]. Bordeau also stated that further studies are necessary in order to establish when complete recovery of brain volume loss is possible and how this recovery correlates with neuropsychological improvement[20]. According to the latest literature review there are four theories on mechanisms leading to glucocorticoid-induced brain atrophy and hippocampal changes[7]. These theories are: decreased utilization of glucose as glucocorticoids affect cellular glucose metabolism; increased actions of excitatory amino acid neurotransmitters such as glutamate; presynaptic reduction of neurotrophic factors leading to inhibition of long-term potentiation, and finally suppressed neurogenesis in the subgranular layer of the dentate gyrus leading to granular neurons and hippocampal volume loss[7].

The study of McEwen et al., on stress and cognitive function emphasized that occupation of mineralocorticoid receptors by physiological concentrations of cortisol in hippocampal cell cultures is essential for maintaining neuronal cell survival and function[21–28]. On the other hand, occupation of glucocorticoid receptors by supraphysiological values of cortisol initially leads to decreased cell excitability and reversible atrophy of apical dendrites of CA3 pyramidal neurons in culture.

Brain is a plastic structure with an ability to reverse its structural changes, which is confirmed by studies on effect of prolonged stress and prolonged exposure to excess glucocorticoids that suggest reversibility of changes in the neuronal cell structure, especially in hippocampus[24].

Partial recovery in brain volume loss in both studies suggests that some aspects of Cushing's syndrome cannot be completely reversible. Only detailed follow-up of these patients in future will determine reversibility of brain atrophy after surgical treatment.

Merke et al. analyzed changes in brain structure and cognitive function in children 8–16 years of age with endogenous Cushing's disease. They noticed that the effect of supraphysiological levels of glucocorticoids on children differs from that on the adults. Adults more commonly exhibit brain volume loss, memory disturbances, and depression with partial or complete remission following normalization of cortisol levels[29].

However, in our series there were 5 children (8–14 years) and 5 adolescents where the degree of brain atrophy was not smaller than in adult patients. In postoperative follow-up during four years there was no statistically significant difference in regression of brain atrophy degree between these two subgroups – young patients and adult patients.

The limitation of our study is its retrospective nature which did not allow us to conduct a randomized trial.

Cushing's disease is a good model for investigation of influence of high cortisol level on human brain. Pathogenesis of brain volume loss in chronic hypercortisolism is multifactorial. Changes in brain volume loss in the past treated as irreversible damage today seem to be reversible. Partial recovery in brain volume loss after prolonged hypercortisolism suggests that some aspects of neurological damage are not completely reversible.

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REVERZIBILNA »ATROFIJA MOZGA« U PACIJENATA SA CUSHINGOVOM BOLESTI

S A Ž E T A K

Unazad 25 godina liječili smo 60 pacijenata sa kortikotropnim adenomima hipofize i Cushingovom bolesti. Neuroradiološko snimanje pokazalo je značajan gubitak volumena moždanog parenhima, neočetkivan za pacijentovu dob. Izgleda da ta »moždana atrofija« regredira nakon kirurškog odstranjenja adenoma hipofize i normalizacije razine kortizola. Razlika u utvrđenoj razini »atrofije mozga« u Cushingovoj bolesti i u kontrolnoj skupini je statistički značajna ($p<0,001$). Stupanj »moždane atrofije« korelira dobro sa trajanjem Cushingove bolesti. Djelomično povlačenje »atrofije mozga« primijećeno je dvije, tri i četiri godine nakon kirurškog liječenja i normalizacije razine kortizola. Povišena razina kortizola je jedan od uzročnih faktora u patogenezi »moždane atrofije«. Smanjenje volumena mozga je djelomično reverzibilno nakon normalizacije razine kortizola.