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Assessment of brain and hippocampal volume in patients with Cushing's disease

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Abstract

Introduction: The purpose of this study was to assess the volumes of the hippocampus, grey matter, and the whole brain in patients with active Cushing's disease compared to a control group.

Material and methods: We included 36 patients diagnosed with Cushing's disease, with pituitary magnetic resonance imaging (MRI) performed as a standard preoperative assessment. The sample size of the control group was 26 persons. MRI studies were acquired with a 3.0 Tesla MR scanner equipped with a 24-channel head coil. The MRI study protocol included a pre-contrast 3D T1-weighted gradient sequence. Volumetric segmentation of the brain structures was performed using version 6.0 of the FreeSurfer software.

Results: We observed statistically significant reduction in the grey matter volume in the study group as compared to the control group ($p < 0.001$), with no significant differences in the volume of the whole brain ($p = 0.104$), left hippocampus ($p = 0.790$), and right hippocampus ($p = 0.517$). There was a strong positive correlation between grey matter volume and brain volume ($r = 0.75$, $p < 0.001$), independent of the study group.

Conclusions: The study showed unevenly distributed brain atrophy in patients suffering from Cushing's disease, with no significant hippocampal atrophy. Significant atrophy was observed within the grey matter, potentially constituting a preliminary stage of whole-brain atrophy. **(Endokrynol Pol 2022; 73 (5): 823–830)**

Key words: *Cushing's disease; hypercortisolism; hippocampal atrophy; brain atrophy; magnetic resonance imaging*

Introduction

The problem of hypercortisolaemia affects not only patients with Cushing's disease (CD), with an incidence of 40 cases per million, but also about 1% of the population that are currently undergoing long-term treatment with various corticosteroid preparations [1]. The anti-inflammatory, anti-allergic, and immunosuppressive effects of corticosteroids are part of pharmacotherapy. They are also used to replenish hormone deficiencies in the body.

Cortisol, called a stress hormone, like adrenaline, is a steroid hormone that has a complex and wide-ranging effect on the metabolism. It also acts within the central nervous system (CNS). The influence of hypercortisolaemia on the CNS is of great interest to both clinicians and radiologists. Cortisol receptors are found in various regions of the brain, including the structures of the limbic system, the reticular formation, and the cortical and subcortical regions. Cortisol supports complex functions, both conscious and unconscious, related to cognition, emotions, memory, and learning.

The mechanisms through which hypercortisolaemia can affect the CNS include reduction in neurogenesis and synthesis of neurotrophic factors, resulting in reduced numbers of neurons, decreased density of the dendritic network and changes within the synapses. The energy processes are also disturbed, the concentration of the brain-derived neurotrophic factor (BDNF) is reduced, and the N-methyl-D-aspartic acid (NMDA) dependent cytotoxicity is activated [2–7].

The hippocampus, as part of the limbic system, plays a significant role in the processes of learning and memory. It contains numerous glucocorticoid (GC) receptors. This makes it particularly sensitive to increased concentrations of these hormones, caused by endogenous overproduction in the course of various diseases, under the influence of stress [8], depressive episodes [9], and in the elderly [10], as well as by their exogenous supply.

Magnetic resonance imaging (MRI) is currently the best method of structural assessment of the brain. The high spatial and tissue resolution of 3T MRI sys-

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tems enables accurate volumetric measurements of both the volume of the whole brain, and the cortical and subcortical grey matter, including the hippocampal volume.

There are few studies available in the literature that assess the volumes of the hippocampus and the brain in patients with active CD. Their results are inconclusive. The author expects that the study performed on the world's largest group of patients with active CD (36 patients), based on scans made with a 3T MRI system and using automatic volumetric methods, will provide a significant contribution to the determination of the effect of GC on the volumes of the hippocampus and the brain.

Material and methods

Patient selection

The Research Ethics Committee of the Military Institute of Medicine in Warsaw approved the protocol of this single-centre prospective study. Prior informed consent was obtained from all participants.

The study group consisted of 36 patients diagnosed with CD. Adrenocorticotropic hormone (ACTH)-induced hypercortisolaemia was established based on disease course, characteristic clinical picture, and commonly recognized laboratory tests. Pituitary MRI was performed as a standard preoperative assessment.

The sample size of the control group was 26 persons. Subjects were recruited among patients with suspected multiple sclerosis, whose brain MRI revealed no abnormalities. They had no history of diabetes mellitus, GC exposure, or signs of hypercortisolaemia.

MRI protocol

Patients with a brain pathology visualized on MRI (except pituitary adenoma in study group) or MRI artefacts that hindered credible volumetry were excluded from the study.

MRI studies were acquired with a 3.0 Tesla MR scanner (GE Discovery MR750) equipped with a 24-channel head coil. The study protocol included a pre-contrast 3D T1-weighted gradient sequence in the sagittal plane, with the following settings: TR 6 msec, TE 2.4 msec, matrix 192 × 192, FOV 24 cm, slice thickness 1.0 mm, and scan time 3:24 min. All T1-weighted images were visually inspected for motion artefacts and grey/white matter intensity contrast.

Volumetric assessment

Volumetric segmentation of the CNS structures was performed using version 6.0 of the FreeSurfer software, which is available for free download online (http://surfer.nmr.mgh.harvard.edu). Automated brain segmentation utilized the T1-weighted gradient isovolumetric sequence.

This process includes multiple steps [11]: motion correction and averaging of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (including hippocampus), intensity normalization, tessellation of the grey matter/white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the grey/white matter and grey matter/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and field strengths [12–14].

The volume of the whole brain (total brain volume — TBV), grey matter volume (GMV), right and left hippocampus (hippocampal volume right and left — HVR and HVL), and total intracranial volume (TIV) were gathered for statistical analysis.

Statistical analysis

Data analysis was undertaken based on R 4.0.2 software. Prior to analysing HVR, HVL, GMV, and TBV, the parameters were adjusted to TIV by dividing the parameter value for a given participant by his or her TIV value. Thus, the HVR, HVL, GMV, and TBV parameter values reported below represent proportions with respect to TIV.

Welch's t test (a variation of the t test, which does not assume equal variances) was used to compare mean parameter values between two independent groups (e.g. control *vs*. study group), and Cohen's d was used as an effect size measure for this test. To test for a linear relationship between two continuous variables (e.g. age and GMV) Pearson's r coefficient was used. Use of the parametric tests was motivated by the continuous nature of the parameters and their symmetrical distributions, as indicated by low skewness values (i.e. $|\text{skewness}| < 1$). Finally, multivariate linear regression was used to test for a relationship between the patients' group in parameter values while controlling for sex and age. The conventional level of $\leq 5\%$ was used to infer significance in the results.

Results

Characteristics of the studied patient population

The control and study groups did not differ significantly in respect to average age and proportion of males to females (Tab. 1). In both groups, about 90% of the samples

Table 1. *The characteristics of the control and study groups*

Variable	Level	n (%)	Group		Statistic	p	Effect size
			Control	Study			
			26 (41.94)	36 (58.06)			
Age	M (SD)	–	38.04 (12.11)	40.36 (13.51)	–0.71	0.481	–0.18
Sex	Female	56 (90.32)	24 (92.31)	32 (88.89)	0.2	0.7	0.06
	Male	6 (9.68)	2 (7.69)	4 (11.11)			

Note: for age, statistic, p and effect size are t value, corresponding significance level and Cohen's d, respectively. For sex, the columns are χ^2 value, corresponding significance, and Cramer's V; M — mean; SD — standard deviation

Table 2. *The clinical characteristics of the study group*

	Study group (n = 36)
Serum ACTH [pg/mL]	72.0 ± 62.5
Urinary free cortisol [μg/24 h]	624.7 ± 194.1
Duration of symptoms [months]	44.6 ± 26.5
BMI	30.3 ± 9.1

ACTH — adrenocorticotropic hormone; BMI — body mass index

were from females, and the average age was approx. 40 years.

The clinical parameters assessed in the study group included serum ACTH concentration, amount of free cortisol in the urine, duration of symptoms, and body mass index (BMI) (Tab. 2).

Comparison of the study group and the control group

We observed that average HVL, HVR, and TBV did not differ significantly between the control and study groups (Tab. 3). However, the average GMV was significantly and moderately lower among patients with CD compared to the control group (Tab. 3, Fig. 1).

The results of the correlation analyses between age and the study parameters indicated that no significant associations were present between age and HVL ($r = 0.04$, $p = 0.772$), HVR ($r = 0.03$, $p = 0.818$), and TBV ($r = –0.23$, $p = 0.069$). Age was significantly, moderately, and negatively related to GMV ($r = –0.56$, $p < 0.001$), indicating that lower grey matter volume was associated with older age (Fig. 2).

Because we had observed a significant relationship for GMV with age, as the next step of the analyses we conducted multivariate linear regression with standardized GMV as the dependent variable and standardized age, sex, and group as the predictors. We used orthogonal sum-to-zero contrast for sex and group with –0.5 and 0.5 values, thus the regression weights for these variables represent differences between groups on a standard normal scale. The analysis allowed us to test the difference in average GMV between the con-

Table 3. *Results of Welch's t tests*

Parameter	Group	M	SD	LI	UI	Sk.	t	df	p	d
HVL										
Control		0.0024	0.0002	0.0023	0.0024	–0.43	–0.27	57.47	0.790	0.07
Study		0.0024	0.0002	0.0023	0.0024	–0.14				
HVR										
Control		0.0024	0.0002	0.0023	0.0025	–0.42	–0.65	54.81	0.517	0.17
Study		0.0024	0.0002	0.0024	0.0025	–0.33				
GMV										
Control		0.45	0.02	0.44	0.46	0.29	3.46	58.75	0.001	0.86
Study		0.43	0.02	0.42	0.44	0.13				
TBV										
Control		0.78	0.03	0.77	0.79	–0.07	1.65	60.00	0.104	0.40
Study		0.76	0.04	0.75	0.77	–0.05				

M — mean; SD — standard deviation; LI and UI — lower and upper intervals of the 95% confidence interval of the mean; Sk. — skewness; t — Welch t statistic; df — degrees of freedom; p — significance of the t statistic; d — Cohen's d; HVL — hippocampal volume left; HVR — hippocampal volume right; GMV — grey matter volume; TBV — total brain volume

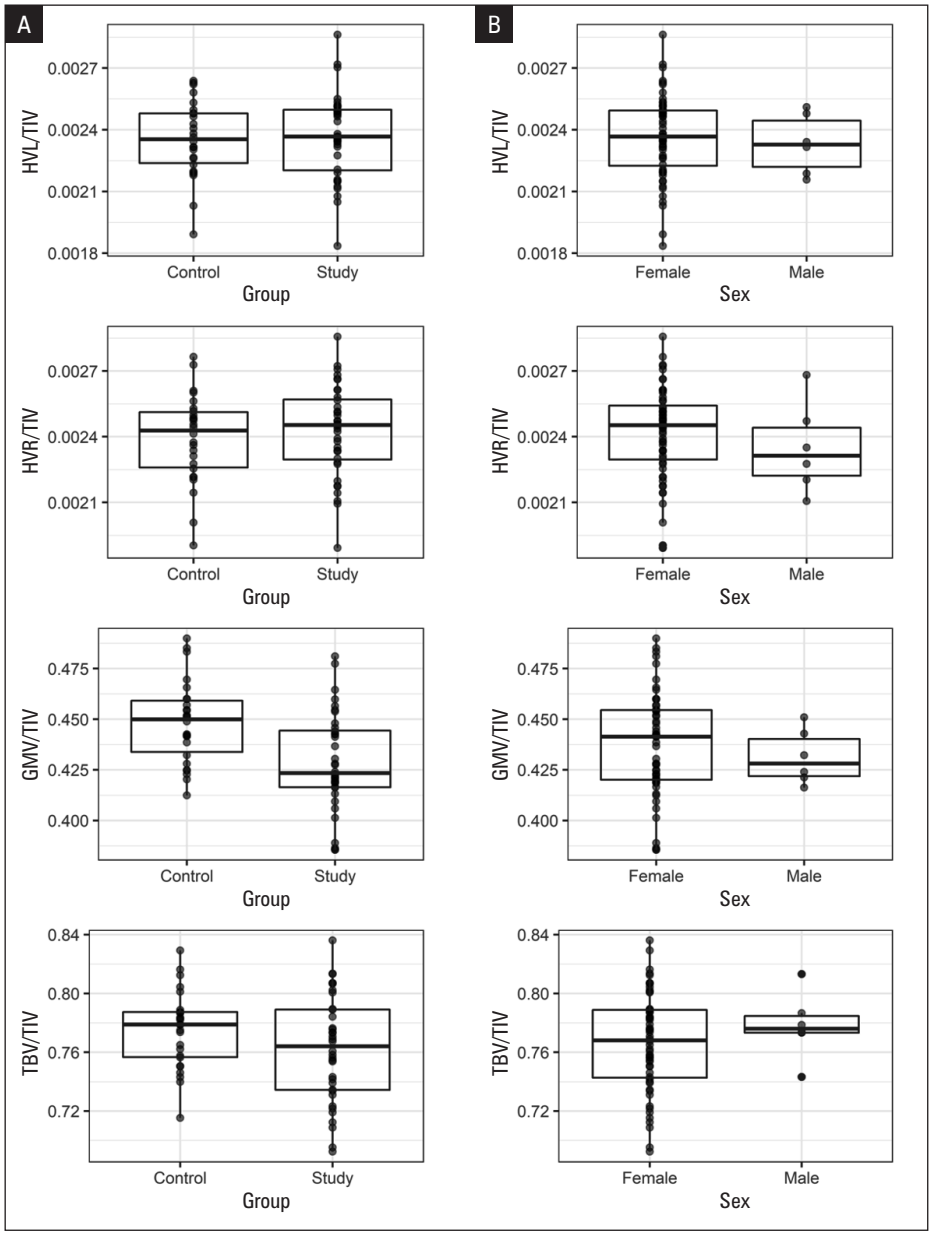

Figure 1. *Total intracranial volume (TIV) adjusted hippocampal volume left (HVL) and right (HVR), grey matter volume (GMV), and total brain volume (TBV) as a function of patient's group (***A***) and sex (***B***). Single point is one participant*

trol and study groups while controlling for association with age. We observed that age and group were still statistically significant and moderately strong predictors of the GMV while controlling for each other and sex (Tab. 4).

The relationship between adjusted TBV and adjusted GMV was tested separately for the control and study groups with Pearson's r coefficient. We observed a strong, positive association between the variables in both groups [study group: r = 0.81, 95% confidence interval (CI): 0.66–0.90, p < 0.001; control group: r = 0.61, 95% CI: 0.30–0.81, p < 0.001; Fig. 3]. To determine if the relationship between TBV and GMV in the study group was significantly stronger than in the control group, we compared the R-squared change between the regression with TBV as the dependent variable and GMV and group as the predictors, and the analogous regression but including the GMV and group interaction. The change in R-squared was not statistically significant (F = 2.63, p = 0.11), indicating that the relationship between TBV and GMV was not statistically different between the groups.

Discussion

Key results

The study did not demonstrate hippocampal atrophy in patients with CD. In the study group, the hippo-

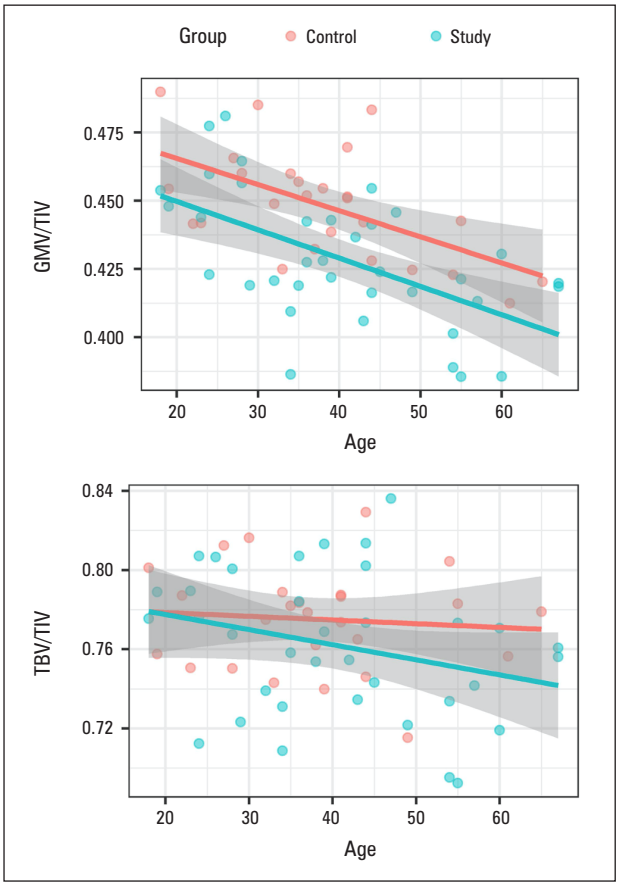

Figure 2. *Total intracranial volume (TIV) adjusted grey matter volume (GMV) and total brain volume (TBV) as a function of patient's age. Single point is one participant (red — control group; blue — study group). Best fitting linear model (red and blue line) with 95% confidence interval is shown (shaded area)*

campal volume did not differ significantly compared to the control group.

A statistically significant reduction in the volume of grey matter was demonstrated in the study group as compared to the control group ($p < 0.001$), with no significant differences in the volume of the whole brain. However, there is a strong positive correlation between grey matter volume and brain volume ($r = 0.75$, $p < 0.001$), independent of the study group.

Limitations

Although the study group consisting of 36 patients with active CD is representative and the most numerous among the studies available in the literature assessing the effect of GC on hippocampus volume, the size of the group prevents comprehensive statistical analyses and makes it difficult to demonstrate significant differences between the groups.

Hormonal tests were not performed in the control group. However, the history taken before the study and the questionnaires completed by the patients allowed the exclusion of symptoms of hypercortisolaemia, current or previous steroid treatment, and diagnosed diabetes.

Interpretation

Volume of the hippocampus

The results of the studies conducted so far, regarding morphological and functional changes in the hippocampus in the course of hypercortisolaemia, are not unequivocal. Most of the research on volumetry in CD or Cushing's syndrome (CS) is based on subjective manual methods of volume measurement. Only in recent years have the methods of automatic segmentation of the CNS become popular.

One of the first studies to show a reduction in hippocampal volume as a result of chronic GCs treatment conducted by Brown et al. dates back to 2004 [15]. The study group consisted of 17 patients receiving long-term GC therapy. Compared to the control group consisting of 15 healthy subjects, the patients demonstrated impaired declarative memory and symptoms of depression, a smaller volume of hippocampus in MRI scans, and a lower concentration of N-acetylasparagine (NAA) in the MRS examination.

Table 4. *Results of multivariate linear regression with grey matter volume (GMV) adjusted to total intracranial volume (TIV) as dependent variable*

	β	SE	LI	UI	t	p
Intercept	0.06	0.17	–0.28	0.39	0.34	0.732
Sex	0.00	0.33	–0.67	0.67	–0.01	0.994
Age	–0.53	0.10	–0.73	–0.33	–5.31	< 0.001
Group	0.70	0.20	0.30	1.10	3.53	0.001
Model fit	σ	R^2	F	df num.	df den.	p
	0.77	0.41	14.89	3	58	< 0.001

β — standardized regression weight; SE — standard error; LI and UI — lower and upper intervals of the 95% interval of β; t and p — test statistic and corresponding significance of the β coefficient; σ — residual standard deviation; R2 — adjusted R-squared; F, df num. and df den., and p — test statistics, numerator and denominator degrees of freedom, and significance level of the ANOVA test for the linear model fit

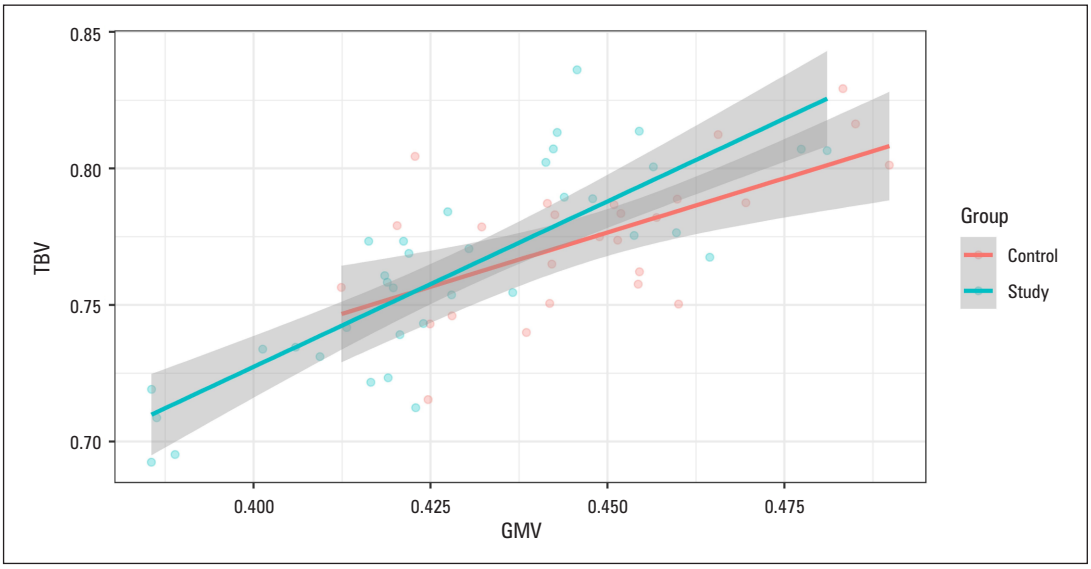

Figure 3. *Relationship between grey matter volume (GMV) and total brain volume (TBV). Single point is one participant. Blue line is best fit linear model and shaded area is 95% confidence interval*

In the study group, the volume of the left hippocampus was 8% lower than in the control group. In the case of the right hippocampus, the difference was 9%. These results failed to achieve statistical significance ($p = 0.034$). The results of Brown et al. [15] are comparable to those obtained in studies of patients diagnosed with depression [9, 16, 17].

There are two case-control studies available in the literature using the 3T MRI system and automatic volume measurement methods. Burkhardt et al. [18] demonstrated a significant reduction in the hippocampal volume and cerebellum in a group of 19 patients with active CD (mean age of 46 years and mean disease duration of 2 years), compared to a control group consisting of 40 subjects. On the other hand, Resmini et al. [19] analysed 33 patients with CD (including 11 with active disease and 22 cured patients; mean age of 45 years and mean disease duration of 5.5 years) and 34 healthy controls. Hippocampal volumes did not differ significantly between the groups. There were essential differences in the inclusion and exclusion criteria in the above studies, regarding both the study group and the control group.

According to a meta-analysis [20] based on above studies [18, 19], there is no strong evidence of a lower hippocampus volume in patients with CD. The analysis of the hippocampus included 30 patients. It was shown that the volume of the right hippocampus was smaller in the study group. However, in the pre- and postoperative analysis of the volume of the right hippocampus, no increase in its volume was found after surgery. There were also no significant differences in the volume of the left hippocampus and the total volume of both hippocampi.

Studies on the atrophy and biochemical composition of the hippocampus with the use of MRS and studies on the potential for the reversal of changes in the hippocampus after normalization of GCs levels brought interesting results [21, 22]. The work of Resmini et al. [23] compares a group of 18 patients cured of CS with matched healthy controls. In the study group, the average period from the normalization of cortisol levels was 8.5 years (± 3.2). The volume measurements made with the FreeSurfer software showed no difference in the hippocampal volume between the groups. On the other hand, MRS showed a reduced NAA peak and an increased glutamine and glutamate peak in the hippocampi of the study group. These changes suggest a reduction in the number of neurons and the proliferation of glial tissue as a consequence of the repair processes. MRS appears to be more sensitive in detecting damage to the hippocampus caused by chronic hypercortisolaemia. Disturbances detected in MRS may precede macroscopic changes in the form of atrophy.

Scientific reports link hypercortisolaemia with dysfunction and atrophy of the hippocampus. The hippocampal volume decreases with age, even in healthy subjects [24]. In our study, no statistically significant differences were found in the hippocampal volume in the group of patients with CD compared to the control group. These results, obtained on the largest group of patients with active CD available in the literature, constitute another important contribution to the ongoing discussion on this topic.

Brain volume

Increased cortisol concentration is considered to be one of the factors that reduce the volume of the whole brain. Such an effect of hypercortisolaemia in the course of CS and CD has been demonstrated in studies performed both in adults and in children [25–28]. Bourdeau et al. [26] found that in a group of 38 patients, cerebral atrophy affected 86% of patients with CD and 100% of patients with CS caused by adrenal gland tumour. A meta-analysis by Andel et al. [28] involving 19 studies with a total of 339 patients with CS showed reduced brain volume and dilated ventricular system in patients with hypercortisolaemia. After recovery, an incomplete remission of these changes was observed.

Over a period of 25 years, Gnjidić et al. [29] assessed the brain volume of 60 patients with ACTH-secreting pituitary adenoma. Neuroradiological studies showed brain atrophy due to CD compared to the control group ($p < 0.001$). The degree of atrophy correlated with the duration of CD and decreased after adenoma surgery and normalization of cortisol levels.

Imaging studies also showed an association between GC treatment and brain volume. As early as in 1978, CT scans performed by Bentson et al. [30] revealed various degrees of brain atrophy in 15 patients aged 8 to 40 years, undergoing long-term treatment with GCs, in most cases due to immunological diseases. There was also a correlation between the degree of atrophy and the dose of GCs.

The short-term effect of intravenous methylprednisolone treatment on brain volume in patients with exacerbation of multiple sclerosis was assessed by Chapman et al. [31]. In a prospective study, a group of 10 patients underwent an MRI examination before drug administration, after receiving the first dose, and then 4 and 8 weeks later. A significant reduction in brain volume was observed over the 8-week observation period.

Elevated cortisol concentrations and stress may also result in changes in the volume of the cerebellum, which contains numerous GC receptors. In the works of Santos et al. [32] and Burkhardt et al. [18], the volume of the cerebellum was reduced in patients with CD. On the other hand, Andela et al. [33] demonstrated an increase in the volume of the cerebellum 6 months after the CD had been cured.

Our results indicate a significant reduction in the volume of the grey matter in the study group compared to the control group ($p < 0.001$). The volume of the whole brain was lower in the group of patients with CD, but the results were not statistically significant. These results indicate cortical brain atrophy in the study group, which is the first stage in the process of whole brain atrophy. The age distribution in the study group and short duration of disease could have resulted in the lack of a significant reduction in the volume of the whole brain. The obtained results are consistent with previous reports and confirm the occurrence of brain atrophy during hypercortisolaemia.

The differences in brain volume between the study group and the control group became more pronounced with age. This trend indicates a greater intensity of unfavourable brain processes under the influence of hypercortisolaemia in elderly people. The existence of protective factors or more efficient repair mechanisms in young people cannot be ruled out either.

Conclusions

Hypercortisolaemia causes grey matter atrophy.

There were no statistically significant differences in the volume of the hippocampus or for the whole brain in patients with Cushing's disease compared to the control group.

Hypercortisolaemia should be considered in the differential diagnosis of patients with atrophy of the brain that is atypical for the patient's age.

In clinical trials incorporating brain atrophy as an endpoint, the effect of steroids should be considered.

Conflict of interest

The authors have no conflict of interest to declare.

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