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Original article

Prospective study of hippocampal volume and function in human subjects treated with corticosteroids

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Abstract

***Purpose.* –** Decreased hippocampal volume reported in neuropsychiatric and endocrine disorders is considered a result of putative neuronal damage mediated by corticosteroids. This is the first prospective study of hippocampal volume and function in patients treated with corticosteroids.

***Methods.* –** 14 subjects treated systemically with prednisone or betamethasone for dermatological or rheumatic disorders underwent prospective neurocognitive testing (Auditory Verbal Learning Test—AVLT, Trail Making Test—TMT, Digit Span—DS) and nine of them also repeated magnetic resonance volumetry.

***Results.* –** The mean duration of treatment between the first and the second assessment was 73 ± 38 days with mean daily dose of 37 ± 17 mg prednisone and 193 ± 29 days, with mean daily dose of 24 ± 15 mg prednisone between the first and the third assessment. There was a trend towards decreases in total AVLT scores and an improvement in the TMT and DS, but no significant changes in the volumes of the right or the left hippocampi between the assessments. Prednisone dose did not correlate with the hippocampal volume change.

***Conclusion.* –** We observed a trend for decline in verbal memory despite improvement in psychomotor speed, attention/working memory and no macroscopic hippocampal volume changes during 36–238 days of treatment with therapeutic doses of corticosteroids.

Keywords: Hippocampus; Corticosteroids; Magnetic resonance imaging; Memory

1. Introduction

Decreased hippocampal volume reported in certain neuropsychiatric and endocrine disorders is considered to be a result of putative neuronal damage mediated by corticosteroids [29]. Neurotoxicity of corticosteroids has been studied in rats and primates. Evidence for similar effects of corticosteroids in human include the negative correlation between the levels of corticosteroids and hippocampal volume in patients with Cushing's syndrome [31] the correlation between hippocampal volume increase and therapeutic reduction of corticosteroids in Cushing's disease [32] and decreased hippocampal volume in subjects treated with corticosteroids [6]. The retrospective nature of most of these studies [6,31] makes the causality of changes difficult to interpret.

If corticosteroids are indeed a sufficient cause of hippocampal damage, then their administration should lead to decline in hippocampal function and structure. This is the first prospective study of hippocampal volume and function in patients treated with corticosteroids.

2. Subjects and methods

Patients treated with corticosteroids for pemphigus vulgaris ($N = 2$), bulous pemphigoid ($N = 9$), lichen planum ($N = 1$), or systemic lupus ($N = 2$) recruited between 2001 and 2003 participated in the study. The exclusion criteria were history of mood disorders, Alzheimer's disease, vascular dementia, posttraumatic stress disorder, Cushing's syn-

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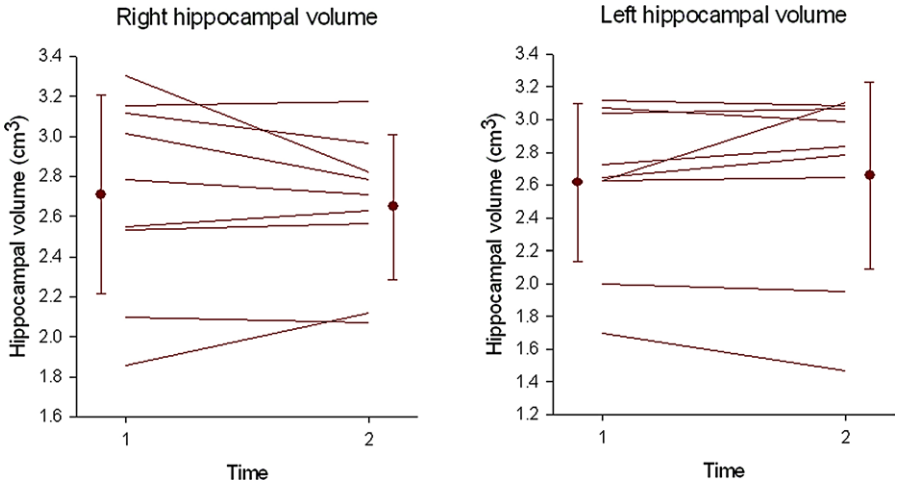

Fig. 1. Left and right hippocampal volume at time 1 and time 2.

drome, substance abuse and presence of metal implants. Out of 23-screened subjects, 15 met the inclusion criteria. One patient discontinued the corticosteroid treatment. Two subjects received corticosteroid treatment intermittently in the past.

Fourteen remaining subjects (12 women, 2 men) underwent two and in six cases three prospective neurocognitive testings. One subject did not finish the second Digit Span (DS) test. MRI volumetry was performed twice within 3 months in nine subjects and within 5–8 months in six subjects. Twelve patients were treated with prednisone, two with betamethasone. The information about exact dose of corticosteroids was unavailable for one subject participating only in the neurocognitive testing. One of the patients was treated with piracetam (2400 mg/day), two occasionally used benzodiazepine hypnotics (flunitrazepam). None of the patients was treated with antidepressants or antipsychotics. As for potentially neuroprotective drugs, one of the patients who underwent MRI assessment was treated with diltiazem and one participating only on neurocognitive testing with nifedipine. All subjects signed the informed consent. The Research Ethics Committee of the Prague Psychiatric Center approved the study.

2.1. Magnetic resonance imaging

We acquired 124 coronal slices of the whole brain by 3D Spoiled Gradient Recalled Acquisition (slice thickness 1.5 mm, TR = 35 ms, TE = 5 ms, flip angle = 45, matrix size 256 × 256, NEX = 1) on 1.5T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI). The intensity values for gray and white matter were obtained from a histogram, as per method previously reported [10] by Image J software. Anatomical measurements were conducted using the Scion Image Beta-3b software for Windows (Scion Corporation, Inc., Frederick, MD), in a single batch, according to a well-established procedure [4], blindly by trained evaluator (TH). The intra-class correlation coefficients established by tracing 10 training scans were $R = 0.94$ for right hippocampus and $R = 0.93$ for left hippocampus (inter-rater reliability). Intra-class correlation coefficient for 10 randomly selected hippocampi of the study subjects measured twice by the same rater was $R = 0.92$, $P < 0.0001$ (intra-rater reliability). Average difference between two measurements of the same scan was 0.04 ± 0.09 cm^3 (range –0.06–0.25).

2.2. Hippocampal volume measurement

Manual tracing of hippocampus started from the slice in which the superior colliculus completely connected with the thalamus bilaterally and ended one slice posterior to the slice in which the mamillary body became visible. The superior border for tracing consisted of the corona radiata, and the ambient cistern, the inferior border was defined by the white matter and lateral border by the inferior horn of the lateral ventricle [4] (Fig. 1).

2.3. Neurocognitive testing

Standard versions of Auditory Verbal Learning test (AVLT), Trail Making Test (TMT) A and B and DS, all fully converted into Czech language were used [24,25,28]. The actual measures were the total score (sum of correctly recalled words in trials I–V) and the number of words correctly recalled in trial VI (post-distractor trial) for AVLT, time to completion of each trail in seconds for the TMT and sum of raw scores from Digits Forward and Digits Backward subtests for the DS. Parallel versions of AVLT were used for repeated tests.

2.4. Statistical analyses

The data were analyzed using two-tailed Wilcoxon test for matched pairs and Spearman rank correlation coefficient.

3. Results

The average age of patients was 59 ± 20 years (range 24–83). Mean interval between the onset of corticosteroids

treatment and the first assessment was 6 days (range 0–19). The average interval between the first and the second assessment was 73 ± 38 days (range 15–168) for 12 subjects who participated on neurocognitive testing and 64 ± 15 (range 36–78) for nine subjects who participated on neurocognitive plus MRI assessments. The average interval between the first and the third assessment was 193 ± 29 days (range 161–238). The mean daily dose per patient expressed in prednisone equivalents (1 mg betamethasone = 8.5 mg prednisone) was 37.1 ± 17.2 mg (range 15.8–61.6) between the first and the second assessment for 12 subjects who underwent neurocognitive testing and 32.0 ± 14.4 mg (range 15.8–55.8) for nine subjects who participated on neurocognitive plus MRI assessments. The average daily dose between the first and the third assessment was 24.2 ± 15.39 mg (range 10.1–49.9). Daily doses ranged from 7.5–90 mg prednisone per day.

There was a trend towards a decrease in the total AVLT score (46.5 ± 10.6 vs. 41.9 ± 8.7; $N = 14$, Wilcoxon test $Z = 1.76$, $P = 0.08$) from the first to the second assessment and a non-significant decrease in the number of words correctly recalled in trial VI (9.5 ± 2.6 vs. 8.6 ± 2.8; $N = 14$, $Z = 0.97$, $P = 0.33$). The decrease in AVLT performance between time one and time three was not significant (51.5 ± 9.2 vs. 48.2 ± 5.1; $N = 6$, $Z = 1.15$; $P = 0.25$ for the total score and 10.7 ± 1.8 vs. 9.0 ± 0.9; $N = 6$, $Z = 1.62$; $P = 0.11$ for the number of words correctly recalled in trial VI).

There was a trend towards improvement in DS from time one to time two (10.5 ± 3.8 vs. 11.9 ± 3.8; $N = 13$, $Z = 1.72$; $P = 0.09$) and a significant improvement from time one to time three (10.0 ± 4.0 vs.13.0 ± 3.7; $N = 6$, $Z = 2.20$; $P = 0.03$).

Patients significantly improved in TMT A from time one to time two (62.4 ± 27.5 vs. 46.2 ± 16.9 s; $N = 14$, $Z = 2.79$; $P < 0.01$), with a trend towards improvement also in TMT B (130.2 ± 83.2 vs. 97.5 ± 49.9 s; $N = 14$, $Z = 1.64$; $P = 0.1$). There was a significant improvement in TMT A between the first and the third measurement (61.8 ± 20.3 vs. 35.2 ± 9.8 s; $N = 6$, $Z = 2.20$; $P = 0.03$), with a non-significant difference in TMT B (99.9 ± 32.4 vs. 122.2 ± 69.8 s; $N = 6$, $Z = 0.73$; $P = 0.46$).

There were no significant changes in the volume of the right (2.7 ± 0.5 vs. 2.6 ± 0.4 cm^3; $N = 9$, $Z = 0.65$, $P = 0.51$; mean difference = –0.06, range = –0.48–0.26; 95% confidence interval = –0.22–0.1), or the left (2.6 ± 0.5 vs. 2.7 ± 0.6 cm^3; $N = 9$, $Z = 0.3$, $P = 0.77$; mean difference = 0.04, range = –0.23–0.47; 95% confidence interval = –0.11–0.19) hippocampus between the first and the second measurement (see Fig. 1) or between the first and the third measurements (2.7 ± 0.6 vs. 2.6 ± 0.7 cm^3; $N = 6$, $Z = 1.15$, $P = 0.25$; mean difference = –0.1, range = –0.32–0.21; 95% confidence interval = –0.31–0.11; 2.7 ± 0.5 vs. 2.7 ± 0.7 cm^3; $N = 6$, $Z = 0.94$, $P = 0.35$; mean difference = 0.07, range = –0.41–0.11; 95% confidence interval = –0.25–0.12 for the right and the left hippocampus, respectively).

There was no correlation between the number of days on corticosteroids before MRI and the volume of the right or the left hippocampus measured at time 1 ($N = 10$, Spearman rank $R = 0.49$, $P = 0.15$; $N = 10$, Spearman rank $R = 0.34$, $P = 0.34$, respectively). Mean daily dose of corticosteroids between the first and the second evaluation did not correlate with the right ($N = 9$, Spearman rank $R = –0.52$, $P = 0.15$) or the left hippocampal volume change ($N = 9$, Spearman rank $R = 0.38$, $P = 0.31$). The subject with the greatest exposure to corticosteroids had the greatest volume increase from time one to time two. The subject with the greatest hippocampal volume decrease was exposed to median levels of 27 mg prednisone.

4. Discussion

We did not observe any changes in hippocampal volume after an average of 64 days of treatment with a mean dose of 32 mg of prednisone per day, nor after average of 193 days with mean dose of 24 mg of prednisone per day. The lack of changes could be a type II error due to small statistical power. We would need 15 subjects to obtain 80% statistical power to detect an average effect size of 0.7, acquired in previous retrospective volumetric studies using similar methods in populations of similar age [5,33–35]. With nine subjects we have 60% power to detect differences similar to those reported in the above-mentioned studies. Since the observed average volume change (–2.2%; 95% confidence interval –8–3% and 2%; 95% confidence interval –4–7% for the right and left hippocampus, respectively) was lower than the previously reported mean volumetric decreases (8–19%) and there was not even a trend towards hippocampal volume shrinkage, increasing the sample size would be unlikely to change the results. Furthermore the MRI method is sensitive enough to detect volume changes in the previously reported range (8–19%) as the measurement error was only 1.5%.

The lack of changes in this study is in disagreement with majority of animal studies reporting histopathological abnormalities of hippocampus in rodents and non-human primates exposed to corticosteroids from weeks to months [19]. Interspecies differences as well as other factors can play a role. Animal studies typically use natural corticosteroids, which differ from synthetic preparations in penetration through blood brain barrier and affinity for corticosteroid receptors. Furthermore the doses of corticosteroids in animal experiments usually exceed therapeutic doses in humans. Different route of corticosteroid administration, with frequent parenteral or intracerebral application in animal studies, or too short time interval in our study could also contribute to this discrepancy. Hippocampal pathology in animal studies is usually assessed by histopathological techniques. Microscopic changes (decreased dendritic sprouting, neuronal shrinkage, neuronal loss [20,30,36]) do not necessarily have to translate to volume changes detectable by MRI, at least not in the early stages of the damage. Studies comparing MRI and histopathological techniques in assessing hippocampal damage are scarce. In patients with temporal lobe epilepsy hippocampal volume was the largest among those with mild histopatho-

logical hippocampal damage and the smallest among patients with severe gliosis and neuronal loss [12]. It is thus possible that only severe impairment with neuronal loss will lead to volume decrease measurable by MRI. However, no major cell loss was apparent in human post-mortem brain tissue of depressed patients or subjects exposed to exogeneous corticosteroids [14,21].

At the same time early microscopic changes could already compromise hippocampal function. Indeed, we observed a trend towards worsening of verbal memory, which is consistent with prior investigations of corticosteroid exposure [1,6]. Impaired performance in neurocognitive tests in the absence of structural changes is in agreement with several other studies. Patients with first episode of depression relative to healthy controls had impaired recollection memory without changes in hippocampal volume. On the other hand patients with multiple episodes of depression relative to first episode patients had smaller hippocampal volume but similar impairment in cognitive functions [16]. Similarly medication-free nonelderly depressed outpatients had declarative memory deficits despite normal hippocampal volume [37]. Impaired memory function in the absence of structural hippocampal damage was confirmed also in rats exposed to stress levels of corticosteroids for 3 months [2]. Tree shrews exposed to 4 weeks of psychosocial stress or cortisol treatment showed decline in hippocampus-mediated memory and only a trend for decrease in hippocampal volume measured by MRI volumetry [22].

The verbal memory decline appeared despite an improvement in psychomotor speed and attention/working memory as measured by the TMT and DS. This improvement could be due to resolution of somatic symptoms with treatment, or alternatively due to practice effect. Practice effect is of consideration in Trail A, less so in Trail B and it is negligible in DS [13]. The improvement in DS does not support emerging data suggesting impairment of frontal lobe functions (working memory) by corticosteroid treatment [15].

Neurocognitive deficits in the absence of structural changes can be also due to effects of corticosteroids on other receptors for neurotransmitters. In men, cognitive impairment is evident already after a single dose of 1 mg of dexamethasone or 10 mg of cortisol [11,38]. This effect is most likely not due to neurodegeneration but seems to be mediated by the agonistic action of corticosteroids and their metabolites on $GABA_A$ receptors [26].

The absence of structural hippocampal changes is in agreement with post-mortem data from patients treated with corticosteroids for short periods of time (days to months) [21] but in contrast with results from patients with mood disorders [29] and recent findings of 8–9% hippocampal volume decrease in corticosteroid treated patients [6]. However, the average duration of corticosteroid exposure in the study by Brown et al. [6] was 92 months as opposed to up to 8 months in the reported study. The similar profile of neurocognitive deficits in both studies again suggests the possibility of microscopic changes manifesting as functional impairment. Longer duration of exposure might be necessary for any gross volumetric changes detectable by MRI to occur. Prospective studies in human subjects exposed to psychological trauma (automobile accident, maltreatment leading to pediatric posttraumatic stress disorder) failed to observe volumetric changes of hippocampus after 6 months or more than 2 years [3,8]. Similarly no change in hippocampal volume was observed after 1 year in patients with major depressive disorder [9]. On the other hand studies in laboratory animals find first histopathological abnormalities already after 3 weeks of intense stress in rats [17] and after 4 weeks of psychosocial stress in tree shrews [18]. Marked neuropathological changes in CA2 and CA3 cell fields were seen 1 year after the implantation of cortisol pellets into hippocampi of vervet monkeys [30].

Alternatively corticosteroids alone may not be sufficient to cause hippocampal damage. Administration of exogenous corticosteroids inhibits the release of corticoliberin (CRH) and adrenocorticotropic hormone (ACTH), it does not mimic stress related activation of sympatoadrenal system and changes in glutamatergic and monoaminergic systems. These can directly contribute to excitotoxicity especially in neurons with increased vulnerability and decreased regenerative capacity mediated by higher levels of corticosteroids. For example corticoliberin, independent of glucocorticoids, has neurotoxic effects on hippocampal neurons [7]. It is possible that for neuronal damage to occur, interplay between more stress related hormones, releasing factors or neurotransmitters is necessary; for review see [19]. Glucocorticoid resistance mediated by alterations in genetic structure of glucocorticoid receptor or downstream ligand-independent pathways can also play an important role [23]. Some authors suggest that cell damage in CNS is associated with insufficient glucocorticoid signaling leading to unrestrained inflammation and release of inflammatory cytokines [27].

Main limitations of this study are small sample size, discussed above, relatively low doses of corticosteroids, and short duration of treatment. The dosage of corticosteroids in human subjects has to follow therapeutic guidelines. Data from human subjects treated with supratherapeutic doses of corticosteroids for extended periods of time thus cannot be obtained. As for the duration of corticosteroids exposure, first structural changes in rodents appeared already after 3 weeks of intense stress [17]. Longer-term follow up is warranted, but this would be complicated due to limited treatment duration in some patients, increased risk of drop-outs and demographic changes. In some patients treatment with corticosteroids was initiated already before MRI scanning (mean 6 days, range 0–19 days). Based on the above-mentioned prospective studies in men, this time gap is unlikely to have biased the volumetric results. Indeed there was no correlation between the number of days on corticosteroids before MRI and the volume of the right or the left hippocampus measured at time 1. We evaluated the inter- and intra-rater reliabilities. However, technical aspects of MRI acquisition (same placement of patients, movement etc.) during repeated scanning may somewhat increase the error of measurement.

In summary, we observed a trend for decline in verbal memory despite improvement in psychomotor speed and attention/working memory and no macroscopic hippocampal volume changes during 36–238 days of treatment with corticosteroids in therapeutic doses. This negative finding is of clinical significance. Administration of corticosteroids in therapeutic doses for up to 7 months seems to be safe with regard to macroscopic hippocampal volume changes. Microscopic impairment, below the resolution of current MRI, leading to memory decline, however, cannot be ruled out.

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