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Effects of chronic prednisone therapy on mood and memory

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Abstract

Background—In animals, stress and corticosteroids can be associated with both reversible and irreversible changes in the hippocampus. Changes in memory and hippocampal structure, perhaps in part due to cortisol elevations, are reported in some patients with mood disorders. Minimal data are available on the effects of long term exposure to corticosteroids on the human hippocampus. We previously reported greater depressive symptom severity, poorer memory and smaller hippocampal volumes in patients with asthma or rheumatic diseases receiving long-term prednisone therapy than in controls.

Methods—In this report, patients and controls were assessed a mean of 4 years after the first assessment to determine if depressive and manic symptoms and cognition remained stable, improved or worsened. Seven prednisone-treated patients and six controls were identified and agreed to reassessment with psychiatric symptom and neurocognitive measures. Follow-up MRIs for hippocampal volume analysis were available for two prednisone-treated participants.

Results—With the exception of an increase in depressive symptoms in those receiving prednisone, participants and controls did not show significant change in mood or cognition from the initial assessment. One participant discontinued prednisone and showed improvement in psychiatric symptoms and cognition. Hippocampal volumes were available in two prednisone-treated participants and showed inconsistent findings.

Limitations—A limitation is the small sample size.

Conclusions—Our findings, although preliminary in nature, suggest that long-term prednisone therapy is associated with initial changes in mood, memory and hippocampal volume that appear to stabilize over time.

Keywords

hippocampus; corticosteroids; memory; prednisone; depression

INTRODUCTION

In animal models, stress and corticosteroids are associated with memory impairment and reversible and irreversible hippocampal changes (McEwen, 2000). Humans exposed to an excess of cortisol or exogenous corticosteroids also show hippocampal changes and cognitive impairment (Brown et al., 2004; Starkman et al., 1992). Changes in mood (Brown et al.,

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2002; Naber et al., 1996) and declarative memory (Brown et al., 2006; Brunner et al., 2005; Newcomer et al., 1999) are reported even during brief exposure to exogenous corticosteroids.

A prior report compared a group of 17 corticosteroid-dependent patients (mean dose 15.6 mg/day of prednisone, mean duration 92.0 months) with asthma or rheumatic illnesses with 15 controls with similar demographic characteristics and medical histories but with minimal lifetime corticosteroid use (Brown et al., 2004). Compared to controls, the corticosteroid-treated group had poorer performance on the Rey Auditory Verbal Learning Test (RAVLT), a measure of declarative memory (hippocampal) performance, the Stroop Color Word Test, a measure of working memory (prefrontal cortex) performance, smaller hippocampal volumes, lower levels of N-acetyl aspartate, a putative marker of neuronal viability in the temporal lobe region, and greater depressive symptom severity.

These findings may be applicable to patients with major depressive disorder. A subset of depressed patients has elevated cortisol or a frequently associated finding of non-suppression on the dexamethasone test (Arana et al., 1985). In addition, some studies of patients with major depressive disorder report hippocampal atrophy compared to controls (Sheline et al., 1996).

In this report we conducted a follow-up study of corticosteroid-dependent patients and controls from two previous studies who received mood, cognitive and, in some cases, structural MRI assessments at baseline (Brown et al., 2003; Brown et al., 2004). We re-examined mood and cognition and, in two cases, hippocampal volume at follow-up to determine if mood, cognition and hippocampal volume remained stable over time.

METHODS

Methods of the original studies, including neuroimaging techniques, are described in detail in Brown et al. (2003; 2004). To summarize, in one study (Brown et al., 2004) 17 adult outpatients with asthma or rheumatologic diseases who were receiving chronic prednisone therapy and 15 controls with similar medical histories but with minimal lifetime corticosteroid exposure were enrolled. Exclusion criteria included lifetime posttraumatic stress disorder, schizophrenia, major depressive disorder or bipolar disorder, substance abuse/dependence, illnesses with significant neurological manifestations and contraindications to MRI. Participants were assessed with the Structured Clinical Interview for DSM-IV (First et al., 1995), Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), Young Mania Rating Scale (YMRS) (Young et al., 1978), Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), neurocognitive tests that included the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) and Stroop Color Word Test-Victoria version (Spreen and Strauss, 1998), and structural MRI and ^{1}H magnetic resonance spectroscopy of the brain.

In a separate study, a similar baseline assessment, except without imaging, was performed in 10 corticosteroid-dependent patients who were enrolled in a 12-week trial of lamotrigine (Brown et al., 2003). Inclusion criteria were virtually identical to the study described above (Brown et al., 2004). Four of the participants also participated in the imaging study described above (Brown et al., 2004) leaving six additional participants. For the present analysis, assessment scores for these participants were combined with those from the study described above to increase the sample of prednisone-treated patients for follow-up analysis.

IRB approval was obtained to contact the former participants from both studies for a follow-up assessment. Written informed consent was obtained. The total number of potential participants was 23 on corticosteroid therapy and 15 controls. Of these 38, 13 participated in the re-assessment, 17 could not be reached or had moved out of the area, 1 was deceased and 7 declined to participate. Of the 7 who declined to participate, 4 stated work schedule conflicts

or transportation difficulties as the reason, while the remainder did not give a reason for the decision.

In the 13 follow-up participants, the HRSD, YMRS, BPRS, RAVLT, and Stroop Color Word Task were administered. In addition, as part of a baseline assessment for another study, we were able to obtain follow-up MRIs on two of the participants. Mood and cognitive assessments were performed by a research assistant who was blinded to participant treatment status. Hippocampal volumes were measured by the same blinded rater (DJW) as in the original study.

Statistical Analysis

Independent t-tests for continuous measures or Chi Square tests for discrete measures were used to examine participant characteristics. Psychiatric symptoms and cognition were assessed between groups using independent 2-sided t-tests and within groups using paired t-tests. Significance was set at $p \leq 0.05$ for all analyses. Cognitive data are reported as normative values (*t*-scores) that control for age. Statistical analyses were performed using SPSS Version 13.0.

RESULTS

Demographic characteristics of the patients and controls are given in Table 1. The group receiving prednisone and controls only differed significantly on education, although a substantial, but not statistically significant, difference in age was observed. Participants in both groups were on multiple other medications. The number and types of other medications were similar at initial and follow-up assessments.

Of the 13 participants, 6 were on long-term prednisone therapy at baseline and remained on prednisone at follow-up, with two at the same dose, three at a reduced dose and one at a higher dose. One participant on prednisone at baseline had discontinued prednisone 12 months prior to the follow-up assessment. Six participants were controls who were not on prednisone at baseline or follow-up.

Our primary goal was to examine changes using a within-group analysis (Table 2). However, we also explored between-group differences. In the prednisone-treated group (N=6) a within-group analysis revealed that the HRSD increased significantly from baseline to follow-up. In controls, the YMRS decreased significantly from baseline to follow-up. No other statistically significant changes from baseline to follow-up were found in either group. A between-group analysis showed that at baseline, the corticosteroid-treated group had significantly lower scores on the YMRS, RAVLT total, RAVLT delayed and Stroop than controls. At follow-up patients on prednisone had significantly lower scores on RAVLT total words recalled, higher scores on the BPRS, HRSD, and YMRS, and a trend for lower scores on the Stroop, but no significant difference on RAVLT delayed. The participant who discontinued prednisone showed decreases from initial assessment to follow-up on the BPRS (33 to 31), HRSD (19 to 12), and YMRS (5 to 1), improvement on the Stroop (39 to 54) and RAVLT delay (39 to 49) but not on RAVLT total words recalled (46 at both assessments).

We had follow-up MRIs of two participants. Both were receiving a prednisone dose of 10 mg/day at baseline and follow-up assessments. One of these participants, a 49 year old woman at the time of the follow-up assessment later had a right hippocampal volume of 2037.6 mm^3 at the initial assessment and 1864.9 mm^3 at the follow-up assessment 65 months (change of −8.5%) and a left hippocampal volume of 1882.1 mm^3 at the initial assessment and 2110.5 mm^3 at the follow-up assessment (change of +12.1%). The other participant, a 48 year old man at follow-up initially had a right hippocampal volume of 2077.8 mm^3 and a volume of 1790.8 mm^3 at follow-up (change of −13.8%) 66 months later, and a left volume of 2066.9 mm^3 which changed to 1995.2 mm^3 at reassessment (change of −3.5%). This equals a mean decrease, from

initial assessment to follow-up, of 11% on the right and an increase of 4% on the left in the two participants.

DISCUSSION

A long-term follow-up assessment of mood, cognition, and in two cases, structural MRI in a group of patients on long-term prednisone therapy and controls was conducted. The main finding was that cognition was relatively stable over time in both groups, and that the prednisone-treated group tended to continue to have higher scores on psychiatric symptom scales and poorer performance on the RAVLT than controls.

The findings of our original study suggested higher levels of depression and poorer performance on the RAVLT and Stroop in patients who had received prednisone therapy at a mean dose of approximately 16 mg/day for a mean duration of 92 months than in controls. The present study suggests that these differences in mood and cognition, with the exception of the HRSD, had not increased substantially over time. Prednisone may initially induce changes in memory over a period of time. However, these changes then appear to remain stable over time. Cognition did not improve but neither did it worsen compared to the controls suggesting that an ongoing neurodegenerative process is not occurring.

Even brief exposure to exogenous corticosteroids is associated with a decline in declarative memory performance (Brown et al., 2006; Brunner et al., 2005; Newcomer et al., 1999). However, changes in hippocampal volume may take much longer to emerge. Hajek et al. (2006) reported a decline in declarative memory performance but no change in hippocampal volume after a mean of 73 and 173 days of prescription corticosteroid therapy. In our earlier report we found poorer performance on a declarative memory task and smaller hippocampal volumes in patients receiving a mean of 92 months of prednisone therapy as compared to controls. Our present findings suggest that declarative memory changed little over time. Thus, the effects of corticosteroids on memory appear to be an acute effect that does not increase over time.

Scores on the HRSD increased from baseline to follow-up in the corticosteroid treated group. Whether this increase is secondary to life events, life with a chronic illness, the cumulative effects of prednisone or other factors cannot be determined. The reason for the decline in YMRS scores in the control group is unclear. However, neither the baseline nor follow-up values suggest clinically significant manic symptomatology.

The one participant who completely discontinued prednisone therapy between the initial and follow-up assessments showed substantial improvement in psychiatric symptoms and some cognitive measures. These findings are potentially consistent with improvement in mood and cognition in patients who discontinue long-term prednisone therapy. Unfortunately, we were not able to find more participants who discontinued prednisone therapy.

As repeat hippocampal volumes were only available for two participants, the findings must be interpreted with great caution. Changes in volume did not show a consistent pattern and the overall change was small. Raz et al. (2004) reported healthy adult controls showed a decrease in hippocampal volume of 0.86%/year over a 5 year follow-up period. In contrast, Hashimoto et al. (2005) reported a mean decrease in hippocampal volume of 5.04% after 1 year in placebo-treated patients with Alzheimer's disease. As with the cognitive data, the imaging data in these patients do not clearly suggest a neurodegenerative process of the magnitude seen in Alzheimer's disease.

The study has limitations. First, the two groups showed differences in education and age. The differences were not found in the original sample (Brown et al., 2004). However, the controls

who were identified and agreed to participate in the follow-up study were 11 years older than the prednisone-treated patients. However, the use of normative scores for the cognitive measures adjusts for age. Additionally, our primary aim was to examine within-group changes over time not between-group differences. Second, our sample size was small. The original study did not have a planned long-term follow-up assessment. Thus, we did not remain in contact with former study participants over the years limiting ability to enroll them in the follow-up study. The strength of this study is that it is the first, to our knowledge, to longitudinally examine the effects of long-term corticosteroid therapy on mood and memory.

In conclusion, at reassessment, a mean of 4 years after the original assessment, corticosteroid-treated patients and controls showed little change in declarative memory performance. The results suggest that long-term corticosteroid-therapy is associated with initial deficits in declarative memory that remains relatively stable over time. One participant discontinued corticosteroid therapy between the assessments and showed improvement on some memory measures. Additional research is needed to confirm these preliminary observations and determine if memory changes associated with long-term corticosteroid therapy are reversible with corticosteroid discontinuation.

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Table 1

Demographic characteristics of corticosteroid-treated patients and controls

Characteristic	Corticosteroid-treated patients (N=6)	Controls (N=6)
Age, mean ± SD[b]	48.3 ± 11.1	59.5 ± 6.2
Gender, N (%)		
Male	1 (17)	0 (0)
Female	5 (83)	6(100)
Years of education, mean ± SD[a]	12.7 ± 0.8	15.2 ± 1.6
Medical illness, N (%)		
Asthma	0	1
Rheumatic Diseases	6	3
Asthma and Rheumatic Diseases	0	2

[a] between-group difference $p \leq 0.05$,

[b] between-group difference $p \leq 0.1$

Table 2

Data at original assessment and follow-up

	Corticosteroid-treated patients (N=6)		Controls (N=6)	
Assessment	**Original**	**Follow-up**	**Original**	**Follow-up**
HRSD	7.6±6.6	14.0±9.2,[ab]	4.6±1.8	5.3±1.5
YMRS	3.6±1.2[b]	5.7±2.3[b]	5.6±1.6	2.0±2.6[a]
BPRS	23.5±4.4	28.8±7.6[b]	23.0±3.4	21.0±2.0
RAVLT total	46.9±8.2[b]	47.4±9.9[b]	64.1±6.6	59.4±7.2
RAVLT delay	51.4±9.7[b]	49.7±11.2	61.5±5.0	58.6±7.9
Stroop Color Word	44.5±8.2[b]	43.1±6.8[c]	54.3±5.7	52.6±9.7
Mean corticosteroid dose	10.7±2.5	8.3±4.0	N/A	N/A
Mean time on corticosteroids (months)	96.0±104.4	149.4±116.3	N/A	N/A

[a] within-group change from original to follow-up assessment $p \leq 0.05$,

[b] between-group difference $p \leq 0.05$,

[c] between-group difference $p \leq 0.1$

HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; BPRS = Brief Psychiatric Rating Scale; RAVLT = Rey Auditory Verbal Learning Test