



PERGAMON

Psychoneuroendocrinology 27 (2002) 367–383

www.elsevier.com/locate/psyneuen

PNEC

Persistent cognitive impairment following surgical treatment of Cushing's syndrome

Hélène Forget ^{a,*}, André Lacroix ^b, Henri Cohen ^c

^a *Département de psychoéducation et de psychologie, Université du Québec à Hull, Pavillon Alexandre-Taché, 283, boulevard Alexandre-Taché, Case postale 1250, succursale B, Hull, Québec, Canada, J8X 3X7*

^b *Service d'endocrinologie, Hôtel-Dieu du Centre hospitalier de l'Université de Montréal (CHUM), Montréal, Canada*

^c *Centre de neuroscience de la cognition, Université du Québec à Montréal, Montréal, Canada*

Received 7 September 2000; received in revised form 15 June 2001; accepted 22 June 2001

Abstract

Chronic exposure to elevated glucocorticoid (GC) levels in Cushing's syndrome (CS) is associated with deficits in cognitive function. It has already been shown that CS patients scored significantly lower than controls on several aspects of cognitive function (*J. Int. Neuropsychol. Soc.* 6 (2000) 20). In the present study, 13 subjects who presented with CS were investigated one year after surgical treatment to determine the extent to which the effects of hypercortisolism on cognitive function are reversible. Subjects were evaluated with a battery of tasks, similar to the original battery of a year earlier and including tests of attention, visuospatial processing, memory, reasoning and verbal fluency. Except for one task of visual organization, the results showed little change in performance, suggesting that prolonged exposure to high levels of GC can cause long-lasting deleterious effects on cognitive function. The data suggest that correction of hypercortisolism is not necessarily correlated with short-term improvement in cognitive function. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Hypercortisolism; Cushing's syndrome; Neuropsychological functions

* Corresponding author. Tel.: +1-819-595-3900x1-2261; fax: +1-819-595-2384.
E-mail address: helene_forget@uqah.quebec.ca (H. Forget).

1. Introduction

It is now well established that the brain is an important target of circulating adrenal cortical hormones (McEwen, 1988). The steroid hormones secreted by the adrenal cortex — principally the glucocorticoids (GC) — have morphological and functional repercussions on the central nervous system. For example, it is known both from clinical experience and controlled studies that cognitive and mood symptoms can be observed in patients suffering from hypercortisolism. Studies have also shown site- and function-preferential effects of GC on hippocampal cells (McEwen, 1997; McEwen and Magarinos, 1997). In fact, chronic exposure to high GC levels — such as those seen in recurrent depressive disorder, prolonged physical and psychological stress, normal aging and dementia — can modify the morphology and cognitive functioning of the hippocampus (Uno et al., 1990; Starkman et al., 1992; De Leon et al., 1993; Sheline et al., 1996; Lupien et al., 1998).

Patients with Cushing's syndrome (CS), a disease characterized by chronic exposure to elevated endogenous adrenocortical hormones, principally cortisol, provides a natural model to study the interactions between hypercortisolism and brain morphology and functioning in humans. Using structural neuroimaging (standard MRI) of the brain, Starkman et al. (1992) reported selective atrophy of the hippocampus in individuals who were estimated to have suffered from CS from one to four years. These authors found a significant correlation between the severity of the hypercortisolism and the extent of hippocampal formation atrophy as well as with the severity of the accompanying learning and memory deficits. Their results suggest there exists an association between reduced hippocampal formation, memory dysfunction and elevated cortisol in patients with CS. The results of Mauri et al. (1993) also point to a mnemonic impairment of moderate degree in CS patients relative to matched normal controls.

The wide distribution of GC receptors in the cerebral cortex, however, suggests that extrahippocampic sites can also be the target of adrenal hormones. Indeed, it is likely that multiple regions of the brain are affected to some degree by hypercortisolism. Bentson et al. (1978), with computerized tomography (CT) scans, described cerebral atrophy in 15 patients on long-term GC therapy. Oberfield et al. (1994) observed increased cortisol secretion in 15 HIV infected children, eight of which showed CT scan evidence of hippocampal atrophy. A link has also been shown between hypercortisolism and cerebral atrophy in the context of depressive disorders (Rothschild et al., 1989). Kellner et al. (1983) obtained a significant correlation between ventricular dilation (as measured by CT scan) and urinary free cortisol. Similarly, Schlegel et al. (1989) found that mean plasma cortisol was positively related to elevated ventricular/brain ratio. In addition, Schmidt et al. (1999) found that healthy human adults treated with prednisone exhibit a right frontal EEG alpha activity during treatment. Although limited in number, the reported pathological data suggest that cerebral atrophy is present in CS. A pneumoencephalography study of 31 patients with CS revealed a high degree of cortical atrophy of the cerebral and cerebellar hemispheres (Momose et al., 1971). More recently, Leclerc et al. (1996) and Bourdeau et al. (1999) have shown that third ventricular width and bicaudate

diameter were much larger in their CS patients when compared to controls. Also, subjective ratings of atrophy performed by blind raters showed that the patients with CS had significantly higher cerebral atrophy grades relative to control data (Leclerc et al., 1996; Bourdeau et al., 1999; Simmons et al., 2000). Finally, Negro et al. (2000) showed a total brain volume reduction in CS patients with volumetric decrements specifically observed in the frontal lobes and cerebellum.

Several cognitive functions other than the commonly reported effects on memory and learning can also be affected by the dysregulation of adrenal steroidogenesis. In a recent study (Forget et al., 2000), we found that untreated CS patients scored significantly lower than controls on general intellectual performance (IQ scores) and in tests of treatment of visual and spatial information, attention, reasoning and verbal fluency. Differences were also observed in verbal and nonverbal aspects of memory. Starkman et al. (1981) reported that 83% of their Cushing's patients had impaired memory and 66% had impaired concentration. Finally, Whelan et al. (1980) had previously suggested that the pattern of neuropsychological deficits in CS patients were comparable to those seen in patients with other types of diffuse bilateral neuropathological processes.

It is unclear at this time whether these changes in structure and cognitive function in subjects with CS are reversible after successful treatment. Heinz et al. (1977) demonstrated a reversible cerebral atrophy in one patient with CS after adrenalectomy. More recently, Starkman et al. (1999) measured the hippocampal volume prior and after surgical treatment in 22 patients with Cushing's disease. Their study showed that the hippocampal formation volume can increase following sustained reduction of previously elevated cortisol concentrations. These results suggest that morphologic changes in hippocampal formation volume are reversible with treatment. Bourdeau et al. (1999) also confirmed that the cerebral atrophy in CS can be partially reversed after correction of hypercortisolism. With respect to cognitive functioning, the results of the only study which investigated recovery of neuropsychological deficits showed a significant amelioration in verbal memory performance 6 months after the surgical treatment (Mauri et al., 1993). Using a more qualitative approach, Gotch (1994) showed that 66% of treated patients with CS reported that the disease still had a negative influence on several dimensions of their lives such as physical, cognitive and affective capacities.

In this context, the focus of the present study was to evaluate whether the detrimental effects of an excess of GC hormones on cognitive performance can be reversed one year after corrective surgery in a group of CS patients. The choice of tasks allowed us to explore specific dimensions of information processing such as perceptual and constructional aspects of visual information processing, concept formation and reasoning, attention and language as well as verbal and nonverbal memory.

2. Methods

2.1. Patients

Eleven women and two men ($n=13$) with ACTH-dependent Cushing's Disease ($n=9$) or ACTH-independent CS due to adrenal disease ($n=4$) participated in this

study. All patients had also participated in a previous study where pretreatment of cognitive decline was reported (original cohort of 19 participants; Forget et al., 2000). They were investigated a second time, 12 months after surgical treatment. Six of the patients in the Forget et al. (2000) study were not re-investigated because they had not attained eucortisolemia status one year after surgical treatment. No significant differences regarding demographic data and initial symptoms were found between participating and nonparticipating subjects. Mean age at time of testing was 47.36 ± 13.02 years and the mean educational level was 12.09 ± 3.89 years. Mean duration of disease (from estimated symptom onset to diagnosis confirmation) was 33.82 ± 14.70 months (range: 15–60 months). Patients were admitted to the Division of Endocrinology of the Hôtel-Dieu, Notre-Dame and St-Luc Hospitals of the Centre Hospitalier de l'Université de Montréal (CHUM) for diagnostic studies and were tested at the same facility following clinical and biochemical remission. All subjects verbally demonstrated an adequate understanding of the study, and written informed consent was obtained prior to inclusion into the study.

Etiology of CS had been established by the usual clinical criteria, including a disease-compatible history and physical findings (e.g., truncal obesity, skin and muscle atrophy, moon facies) and biochemical criteria including lack of normal cortisol circadian rhythm, excessive cortisol secretion as indicated by high urinary-free cortisol concentrations, as well as failure to suppress cortisol normally after dexamethasone administration. Prior to treatment, urinary free cortisol concentrations ranged from 198 to 11510 nmol/24 h (normal range is 55–195 nmol/24 h); range of AM plasma cortisol levels was 279–3153 nmol/l and range of PM plasma cortisol levels was 354–3858 nmol/l (normal range is 165–695 nmol/l). Plasma ACTH levels ranged from zero to 24 pmol/l (normal values are 4–16 pmol/l). Following diagnosis, patients underwent pituitary or adrenal surgical treatment. Post-operatively, patients experienced secondary adrenal insufficiency because of suppression of the hypothalamic–pituitary–adrenal axis. Until recovery of hypothalamic–pituitary–adrenal function had occurred, the patients required maintenance replacement with physiological doses of cortisol (20–30 mg hydrocortisone daily) over a few months period. One year later, the absence of relapse of CS was confirmed for all patients and they were then reassessed with a battery of tasks. At that time, CS patients were found to be eucortisolemic.

2.2. Tests and procedure

A battery of tasks including tests to assess attention (Visual target detection, Stroop Test, Digit Symbol Substitution Test, Trail-making Test), visuospatial processing of information (Judgment of Line Orientation, Bells Test, Hooper Visual Organization, Gollin Figures, Block Design, Object Assembly, Visual Reproduction-Copy), memory performance (California-Verbal Learning Test, Logical Memory, Digit Span, Visual Memory, Benton Visual Retention Test), reasoning and concept formation (Comprehension, Picture Completion, Picture Arrangement, Arithmetic, Similarities, Raven's Standard Matrices) and verbal fluency (Vocabulary, Letter and Category Fluency).

Visual Target Detection was tested via a letter-cancellation task adapted from the *d2* cancellation test (Richer et al., 1993). The selective attention task includes three conditions gradually increasing in difficulty: detecting occurrences of a target letter randomly interspersed among *ds*, detecting occurrences of a target letter among other distractor letters; detecting occurrences of three different target letters among distractors. The Stroop task (Stroop, 1935) measures intentional attention, the inhibition of a response to the salient detail and attention to the less salient detail. The test includes reading words (color names), color naming of colored patches, and color naming of the ink in which words representing incompatible color names are typed. Number of items completed in 45 s and errors in each of the three conditions were recorded. The Digit Symbol Substitution (DSS) test, a subtest of the WAIS-R, is a test of incidental learning, ability to learn new material, rapid and systematic visual scanning, memory, response speed, visuomotor coordination and selective attention. Participants are asked to fill, as quickly as possible, rows of small blank spaces with the number that is paired with the symbol above the blank space. Finally, the Trail-Making Test measures visual scanning, mental tracking, and the ability to keep track of two simple concepts (Lezak, 1995). The participant must first draw lines to connect consecutively numbered circles (Trail A) and then connect the same number of consecutively numbered and lettered circles by alternating between the two sequences (Trail B). Judgment of Line Orientation (Benton et al., 1978) examined the ability to estimate angular relationships between line segments by visually matching angled line pairs to a number of radii forming a semicircle. The test consists of 30 items, each showing a different pair of angled lines to be matched to the display cards. The Bells Test (Gauthier et al., 1989) is sensitive to visual inattention, visual exploration and detection of salient stimuli. It consists of 315 silhouetted objects distributed in a pseudorandom manner on a sheet of paper with 35 bells scattered among them. Participants were asked to circle bells as fast and as accurately as possible. In the Hooper Visual Organization Test (Hooper, 1983), the participant's task was to name each of 30 more or less readily recognizable cut-up objects. The test is designed to measure the ability to organize and integrate visual stimuli. The Gollin Figures Test (Gollin, 1960) evaluates the ability to extract meaning from incomplete visual information. The test consists of 18 picture series of five line drawings of common objects ranging in completeness from a barely suggestive sketch to a complete drawing of the figure. Block Design, a subtest of the WAIS-R (Wechsler, 1981) is a construction test where the subject uses white and red blocks to construct replicas. The test evaluates abilities in perception, at the conceptual level and in constructive execution. It also evaluates visuospatial organization, rapid detection of the underlying principles of organization and the ability to translate that detection into a replica. Object Assembly, also a subtest of the WAIS-R, contains four cut-up cardboard figures of common objects given in order of increasing difficulty. This is a test of visuospatial manipulation with great importance accorded to perceptual-conceptual and constructional abilities. Visual Reproduction (copy administration) test, a subtest of Wechsler Memory Scale (WMS) (Wechsler, 1974), is a drawing task. This test investigates both perceptual organization and construction

skills. The test material consists of a reproduction of three figures and the participant is instructed to copy the figures.

The California Verbal Learning Test (CVLT; Delis et al., 1987) assesses various aspects of verbal learning and memory and includes three lists of words. The first list consists of five presentations with recall of 16 items from four semantic categories; the second has the same structure, with only two semantic categories being the same as in first list and one presentation; the third, a recognition list, includes 16 target items from the first list, plus distractors that share or do not share semantic or phonological membership with items in that list. Administration and scoring were conducted according to the instruction manual. Digit Span, forward and backward, a subtest of the WAIS, evaluates short-term verbal memory or working memory and brief attentional skills. Logical Memory, a subtest of WMS, is a story task; two stories are read to the participants and there are immediate and delayed free recalls. Visual Memory, also a subtest of WMS, is a visual memory task includes both immediate and delay recall. It consists of four items composed with more or less simple geometric designs. The Benton Visual Retention test evaluates short-term (15 s) visual memory for three geometric designs varying in size form, and details of spatial location relative to each other.

Comprehension, a subtest of the WAIS-R, evaluates verbal reasoning. The test includes open-ended questions which tap common-sense judgment and practical reasoning. Picture Completion, another subtest of the WAIS-R, consists of 20 incomplete pictures arranged in order of difficulty with instructions to tell what important part is missing. This test measures visual recognition, remote memory, logical reasoning and judgment about visually presented material with a social content. Picture Arrangement, a subtest of the WAIS-R, consists of 10 sets of cartoon pictures that make up stories. Each set is presented in scrambled order with instructions to rearrange the pictures to make the most sensible story. This test also evaluates concept formation, judgment and reasoning concerning visually presented material with a social content. Arithmetic, a subtest of the WAIS-R, is composed of 14 arithmetic reasoning problems. These problems evaluate logical mathematic abilities and resistance to distraction. Similarities, also a subtest of the WAIS-R, is a test of verbal concept formation. Participants are asked to explain in what ways the two words in a pair are alike. The word pairs range in difficulty from the simplest to the most difficult. Raven's Standard Matrices (Raven et al., 1976) consist of a series of visual pattern matching and analogy problems pictured in nonrepresentational designs. The test requires subjects to conceptualize spatial, design and numerical relationships ranging from the very obvious and concrete to the very complex and abstract. Vocabulary, a subtest of the WAIS-R, is made up of 35 words arranged in order of difficulty. The score reflects both extent of recall vocabulary and the precision of speaking vocabulary. Letter and Category Fluency requires the subjects to produce within a 2 min period as many words as possible belonging to a specific category and words with a specific initial letter. Verbal and Performance IQ scores were also obtained with the WAIS-R.

The Beck Depression Inventory (Beck, 1987) was also used for the evaluation of

depression. The standard Beck score was modified by omitting items 18, 19 and 20 which are not appropriate for CS patients (e.g., weight loss).

2.3. Statistical methods

The question of interest was whether the return to a more normal level of hormonal functioning following surgical treatment was also marked by a significant improvement in the neuropsychological performance of CS patients. *t*-test statistics for paired measures were applied to evaluate mean performance differences (pre- and post-surgical treatment) for this sample of CS patients. Bonferroni corrections were applied to protect against Type I error when performing multiple comparisons. Prior to application of *t*-test, multivariate analyses of variance (MANOVAs) were conducted to compare the overall performance profile between CS patients and controls, matched for age, education and sex, in general intellectual functioning, attention, visuospatial processing of information, memory performance, reasoning and concept formation, and verbal functions.

3. Results

3.1. General description

The demographic characteristics of reassessed subjects did not differ from those of the original sample. The mean age of the reassessed participants was 47.36 ± 13.02 years, and that of the original group was 46.79 ± 10.97 years ($t_{(1,12)} = 0.97$, $P > 0.05$). The mean educational level of the reevaluated subjects and of the original group were 12.09 ± 3.89 and 12.16 ± 4.06 , respectively ($t_{(1,12)} = 0.89$, $P > 0.05$). In addition, duration of disease of reassessed participants and original population were similar (mean duration: 43.82 ± 14.70 and 42.7 ± 26.9 , respectively; $t_{(1,12)} = 1.37$, $P > 0.05$). Finally, a significant improvement in Beck Depression Inventory scores was noted for those reassessed subjects ($t_{(1,12)} = 5.13$, $P < 0.05$), showing the beneficial effect of adrenal steroids suppression on depressive disorder symptoms.

3.2. Neuropsychological testing

The following tables summarize the results of the control group and CS subjects before and one year after the corrective surgery on general intellectual functioning (Table 1), attention (Table 2), visuospatial processing (Table 3), memory (Table 4), concept formation (Table 5) and verbal function and language skills (Table 6). MANOVAs were conducted to compare the cognitive performance of these 13 CS subjects to that of a group of age- and sex-matched controls. As in the assessment of a year earlier, the performance of CS subjects was significantly lower on verbal and performance IQ scores (P 's < 0.01). Moreover, in tests of attention, treatment of visual and spatial information, verbal and nonverbal aspects of memory, reasoning

Table 1
Comparison of IQ scores (mean±SD)

	Control (n=13)	CS subjects (n=13)			CS subjects (n=13)		
		Before surgery	<i>F</i>	<i>P</i> ^a	After surgery	<i>t</i>	<i>P</i>
Verbal IQ	101.6±9.9	91.3±10.2	9.43	0.006	89.9±7.8	−0.12	0.911
Performance IQ	106.1±12.2	92.9±11.7	8.98	0.007	93.0±7.7	−1.81	0.100
Full scale IQ	103.7±11.6	91.2±11.0	11.02	0.003	90.2±6.9	−1.22	0.252

^a All significant differences are between CS patients (before surgical treatment) and controls.

Table 2
Comparison of speed^a in attentional tasks (mean±SD)

	Control (n=13)	CS subjects (n=13)			CS subjects (n=13)		
		Before surgery	<i>F</i>	<i>P</i> ^b	After surgery	<i>t</i>	<i>P</i>
Target Detection Task							
Visual Detection	4.4±1.2	3.9±0.6	0.99	0.330	3.9±1.0	0.02	0.986
Baseline (Condition A)							
Single-target detection	2.3±0.5	1.9±0.4	2.60	0.122	2.5±2.1	−1.08	0.306
(Condition B)							
Three-target detection	1.6±0.3	1.1±0.4	5.30	0.037	1.2±0.5	0.87	0.404
(Condition C)							
Trail-Making Test							
Trail A	0.9±0.3	0.7±0.2	3.07	0.095	0.8±0.2	−1.20	0.259
Trail B	0.5±0.2	0.31±0.1	5.11	0.035	0.34±0.1	−0.80	0.442
Stroop Task							
Word reading (W)	2.3±0.4	2.1±0.2	1.75	0.201	2.2±0.3	−1.02	0.332
Color naming (C)	1.7±0.4	1.61±0.2	0.44	0.511	1.62±0.2	0.18	0.862
Color naming with	0.9±0.2	0.7±0.2	6.29	0.021	0.8±0.2	−0.53	0.610
interference (CW)							
DSS test	0.6±0.2	0.5±0.09	4.04	0.069	0.5±0.1	−1.18	0.264

^a Speed=items/s

^b All significant differences are between CS patients (before surgical treatment) and control subjects.

and language skills, results revealed a number of significant differences between CS patients and control subjects.

t-tests¹ for paired measures (with Bonferroni correction) were conducted to compare the neuropsychological performance of the CS patients prior to, and after correc-

¹ To estimate the statistical power of the tests, we used the ratio of the mean difference over the standard deviation on present data set. With α set at 0.05 and a sample size of 13 subjects, the statistical power is 0.44.

Table 3
Comparison of performance scores in visuospatial tasks (mean±SD)

	Control (<i>n</i> =13)	CS subjects (<i>n</i> =13)			CS subjects (<i>n</i> =13)		
		Before surgery	<i>F</i>	<i>P</i> ^b	After surgery	<i>t</i>	<i>P</i>
Simple perceptual recognition							
Judgment of Line							
Orientation	21.6±5.4	18.4±4.6	2.20	0.153	18.6±4.4	−0.12	0.904
Perceptual inattention							
Bells Test ^a	13.4±1.6	4.1±1.2	1.18	0.289	4.0±1.9	−1.53	0.157
Perceptual organization							
Hooper Visual							
Organization	26.7±1.5	24.0±1.9	12.93	0.002	26.0±2.1	−6.03	0.011
Construction Tasks							
Block Design	9.7±2.4	7.6±1.9	4.87	0.039	8.3±2.5	−0.97	0.356
Object Assembly	9.8±1.3	8.1±2.2	4.98	0.035	8.2±3.1	−0.13	0.902
Visual reproduction	14.6±0.6	13.0±1.5	9.86	0.005	13.1±0.9	−0.28	0.787

^a Scores on this test are negatively correlated with performance.

^b All significant differences are between CS patients (before surgical treatment) and control subjects.

Table 4
Comparison of verbal and nonverbal memory performance scores (mean±SD)

	Control (<i>n</i> =13)	CS subjects (<i>n</i> =13)			CS subjects (<i>n</i> =13)		
		Before surgery	<i>F</i>	<i>P</i> ^a	After surgery	<i>t</i>	<i>P</i>
CVLT							
First five trials	55.8±8.7	54.9±14.0	0.03	0.858	55.0±13.0	−0.08	0.940
Tuesday list	7.6±2.4	5.3±2.0	5.85	0.025	5.8±2.3	−0.58	0.572
SFR ^b	11.9±2.3	12.2±3.3	0.09	0.768	11.3±3.0	0.95	0.365
LFR ^c	12.8±2.1	12.6±2.9	0.03	0.867	12.6±2.5	−0.98	0.395
Recognition	14.7±1.2	14.7±1.8	0.49	0.486	15.3±0.6	−1.05	0.319
Logical memory							
Immediate recall	9.3±1.9	7.9±3.2	1.30	0.267	8.7±4.3	−0.66	0.523
Long-term recall	7.5±1.8	7.1±2.9	0.11	0.745	7.5±3.4	−0.38	0.712
Digit Span							
Forward	7.6±2.8	5.3±1.0	6.00	0.024	5.8±1.7	−1.10	0.296
Backward	6.2±2.2	5.7±1.6	0.29	0.590	5.4±2.1	0.54	0.602
Visual memory							
Immediate recall	13.9±0.9	11.5±2.7	7.30	0.014	11.2±2.5	0.33	0.748
Long-term recall	11.4±2.6	9.4±4.7	1.49	0.236	9.3±3.2	0.13	0.902

^a All significant differences are between CS patients (before surgical treatment) and control subjects.

^b SFR: short-term free recall

^c LFR: long-term free recall

Table 5

Comparison of concept formation and reasoning performance scores (mean±SD)

	Control (n=13)	CS subjects (n=13)			CS subjects (n=13)		
		Before surgery	F	P ^a	After surgery	t	P
Concept formation							
Similarities	10.4±1.1	8.8±2.0	4.67	0.043	8.8±2.2	0.09	0.982
Raven's	55.8±11.2	41.8±8.2	7.98	0.011	41.7±9.4	0.04	0.971
Reasoning							
Comprehension	11.8±2.4	9.0±2.6	6.84	0.017	9.0±2.1	−1.48	0.982
Picture Completion	10.7±1.9	8.7±1.9	5.91	0.025	9.6±2.5	−1.34	0.993
Picture Arrangement	8.2±3.5	6.9±2.7	0.91	0.350	7.0±2.5	−0.23	0.821
Arithmetic	9.4±2.3	7.8±2.4	2.66	0.118	8.2±1.9	−0.79	0.450

^a All significant differences are between CS patients (before surgical treatment) and control subjects.

Table 6

Comparison of verbal functions and language skills performance scores (mean±SD)

	Control (n=13)	CS subjects (n=13)			CS subjects (n=13)		
		Before surgery	F	P ^a	After surgery	t	P
Vocabulary	10.9±2.9	8.3±2.0	5.50	0.029	10.8±4.8	−1.81	0.101
Letter fluency	40.6±9.7	28.5±7.1	11.09	0.003	35.0±10.8	−2.55	0.029
Category fluency	42.0±9.1	37.5±8.2	1.44	0.243	39.1±9.0	−0.66	0.525

^a All significant differences are between CS patients (before surgical treatment) and control subjects.

tive surgery. The results showed that there were no changes in any performance domain (all P 's > 0.05), except for one task, the Hooper test ($t_{(1,12)}=6.03$, $P=0.011$), suggesting that prolonged exposure to high levels of GC can cause long-lasting negative effects on cognitive function, at least in the small group of patients studied here.

4. Discussion

In a previous study of 19 patients with untreated CS, Forget et al. (2000) showed that several domains of cognitive function were negatively affected by hypercortisolism. Although the present follow-up study was conducted six months after urinary free cortisol levels had returned to normal (at least one year after successful surgical treatment), there were no noticeable improvement in cognitive performance in this group of CS patients. These results suggest that excess cortisol production has a long-lasting negative impact on several aspects of cerebral function. Our observations do not agree with the data from the Mauri et al. (1993) study where partially revers-

ible functional changes in brain function, following correction of GC overproduction, were reported. Reasons for such discrepant results may be due to the small number of patients used in these studies (8 in Mauri et al., 13 in the present study) and to the difference in mean age of the two samples of patients (31.3 years in Mauri et al., 47.3 years in the present study). Also, the mean illness duration for our sample of subjects was approximatively twice that reported for the Mauri et al. sample (33 months vs. 15 months). Finally, our study included patients with ACTH-dependent Cushing's Disease and ACTH-independent CS due to adrenal disease, whereas Mauri et al. (1993) restricted their study to ACTH-dependent Cushing's Disease only. Thus, the plasma ACTH levels of our patients are lower by comparison to those reported by Mauri et al. (0–106 pg/mg vs. 80–200 pg/mg), while urinary free cortisol concentrations remain comparable.

The patients with remission of hypercortisolism showed, however, a significant improvement in depressed mood. These results support the observations from previous studies of patients with CS, which had also revealed a decrease in the frequency and duration of depressive episodes after successful treatment (Starkman et al., 1986). A more recent study showed that the incidence of atypical depression progressively decreased after correction of hypercortisolism — this disorder, however, continued to be the prevailing psychiatric diagnosis after the successful cure of CS (Dorn et al., 1997). It is likely that the psychopathology symptoms still seen after the correction of CS may be related to the as yet unexplored interaction between endocrine and psychosocial factors. Indeed, strong associations are found between higher levels of urinary and plasma cortisol and poorer social and occupational functioning in depressed patients, one year after adequate treatment for depression (Rothschild et al., 1993).

Although the present results imply that persistent cognitive impairment may be a hallmark of chronic exposure to high levels of GC secretion, the relatively good performance on the Hooper Visual Organization test — and, to some extent, in the Verbal Fluency task — also suggests that these impairments may be reversible. This resolution of cognitive diminution, as shown by the improved test scores, may signal the emergence of a more general process of remission.

The cognitive decline and deficits reported in a number of studies with CS patients may be a consequence of the structural and morphological changes associated with the syndrome. For example, cerebral atrophy has been reported to be a feature of CS (Momose et al., 1971; Heinz et al., 1977; Leclerc et al., 1996; Starkman et al., 1999; Cohen et al., 2001) and it is probable that the often-seen cognitive impairment is a result of the morphological changes in the hippocampus and in other brain regions. If it is confirmed that normalization of cortisol levels is associated with reversal of hippocampal atrophy, there are several possible explanations for the absence of reversibility of cognitive deficits following successful treatment of CS. A first hypothesis involves adaptation of plasticity of neural systems other than the hippocampal formation. As noted previously, this is a very dynamic structure, capable of changes in neuronal morphology such as reversible synaptogenesis (McEwen et al., 1995a) and reversible atrophy of dendrites regulated by GC (McEwen et al., 1995b; Magarinos et al., 1996). In patients with hypercortisolism, changes in the

hippocampal formation volume are associated with circulating adrenal steroids acting through GC receptors (Starkman et al. 1992, 1999; Bremner et al., 1995; Sheline et al., 1996). However, the reversibility of extrahippocampic atrophy, as with the head of the caudate nucleus, is not clear and not significantly correlated with the degree of urinary free cortisol decrease after treatment (Starkman et al., 1999). In addition, the hippocampus is apparently unique within the brain for its capacity to regenerate neurons (Gould et al., 1998). These latter effects suggest that, in CS patients, the long-term exposure to GC may produce long lasting damage in the extrahippocampic sites as well as impairment in cognitive function — at least until 12 months after surgical treatment.

It is also possible that the reversibility of the hippocampal formation volume atrophy associated with a decrease in urinary free cortisol is partial or incomplete. Boudreau et al. (1999) have observed a partial reduction of cerebral atrophy after surgical treatment of CS. Starkman et al. (1999) have also observed an increase of 10% in hippocampal formation volume following treatment of CS patients. This increase is consistent with the magnitude of changes reported in other studies of the human hippocampus (e.g., Bremner et al., 1995; Sheline et al., 1996). These observations suggest that the chronic exposure to GC produces partial or incomplete reversibility of hippocampal atrophy and may still be associated with sustained cognitive decline one year after surgical treatment.

Also, it seems likely that the endangering actions of GC on nerve cells become more pronounced with aging, and may be accompanied by a significant decrease of plasticity in hippocampal pyramidal neurons. In this regard, Landfield et al. (1981a,b) examined the morphological parameters associated with hippocampal aging in intact young, mid-aged and aged rats. They found that aged rats displayed a significant decrease in CA3 and CA1 pyramidal cell density, relative to young and mid-aged rats. These same investigators had previously proposed that GC may accelerate some aspects of brain aging (Landfield et al., 1978). In the normal elderly human, the frequency of occurrence of hippocampal formation atrophy is strongly related to age (De Leon et al., 1997). In animals, Kerr et al. (1992) showed that GC affected the rate of age-dependent hippocampal neuronal loss. Finally, Starkman et al. (1999) reported that older age was associated with a smaller increase in hippocampal formation volume after cortisol reduction. Collectively, these findings show the vulnerability of the hippocampus to neuronal loss, particularly in older brains. Interestingly, in the present study CS patients were, on average, 10 years older than those in Starkman et al. (1999) and in Mauri et al. (1993). In this perspective, the persistent cognitive impairment of our CS patients may be a deleterious consequence of either the increased vulnerability of the hippocampal formation to high levels of GC or a diminished capacity for reversibility of cellular atrophy after cortisol reduction.

Although there are indications that the hippocampal atrophy in CS is partially reversible (Starkman et al., 1999), current evidence does not allow us to exclude permanent neuronal loss as a later stage of chronic exposure to elevated GC levels in CS. After all, there is no evidence that MRI-determined volumes are correlated with the number of hippocampal neurons. Furthermore, anatomical evidence suggests that there may be irreversible loss of hippocampal neurons in recurrent depressive

illness — a condition often associated with elevated cortisol levels (Sheline et al., 1996). Also, in a series of studies with rats and primates, it has been shown that exposure to certain levels of GC can cause reversible changes in the morphology of hippocampal cells as atrophy of apical dendrites of CA3 pyramidal neurons (Luine et al., 1994). However, with longer periods of exposure to GC levels — such as those seen in prolonged physical and psychological stress and aging — overt loss of such neurons occurs, probably causing irreversible damage in the hippocampus and permanently impairing cognitive function (Sapolsky et al., 1985; Mizoguchi et al., 1992; Sapolsky, 1994; McEwen and Sapolsky, 1995). Therefore, it is unclear at this time whether reductions of hippocampal volume in CS may represent a form of reversible atrophy or a permanent loss of neurons. Several mechanisms may underlie the reversibility of hippocampal formation atrophy following a decrease in urinary free cortisol in CS. These mechanisms are apparently still at work when there is neuron loss. For example, glial hypertrophy can be observed in response to normalization of cortisol levels (McEwen and Sapolsky, 1995).

Finally, the persistent cognitive deficit seen in CS subjects, despite the remission of hypercortisolism, is broadly in agreement with the findings of long-term intellectual impairment after successful treatment of another endocrine disorder, hyperthyroidism. Bommer et al. (1990) showed significant differences in ability between remitted hyperthyroid patients and controls on several neuropsychological tests including Digit Symbol Substitution, word fluency, memory, and time estimation. In an earlier study, Perrild et al. (1986) had found EEG-abnormalities 10 years after treatment in 68% of former hyperthyroid patients (vs. 41% among controls). Impairment was also observed in seven out of 11 tests concerning attention, memory and abstraction. More recently, Fahrenfort et al. (2000) showed long-term psychopathological sequelae as well as mental disturbances despite the remission of hyperthyroidism.

It is clear that a number of methodological concerns may constrain the impact of the present study as the relatively small sample size did not allow for comparative statistical treatment of ACTH-dependent Cushing's Disease and ACTH-independent CS due to adrenal disease. Although both etiologies of CS exhibit elevated levels of cortisol, they nonetheless differ in potentially confounding variables such as in the suppression of pituitary ACTH. Also, there is the possibility of a Type II error, given the statistical power of the tests. Finally, control subjects were not re-evaluated one year later and the practice effect inherent in some neuropsychological tests was not assessed here. Nevertheless, the near total absence of improvement in the neuropsychological performance of CS patients, at least one year after surgery, argues for the long term deleterious effects of GC hypersecretion. It should be noted that 12 months is an adequate interval between successive administrations of the same test (see Lezak, 1995). At any rate, the results of this study must be interpreted with caution and there is a need for follow-up studies to determine whether the observed cognitive decline in patients with remitted CS is indeed reversible.

5. Conclusion

This is the second study to investigate the recovery of cognitive decline in CS. In contrast to the first study, the data showed that a return to normal levels of cortisol following surgical treatment was not accompanied, 12 months later, with improvement in cognitive performance. However, it is important to realize that there may be a delay of several months to years from the correction of elevated cortisol levels to remission of cognitive deficits — as is sometimes the case for psychiatric symptoms (Haskett, 1985). It is therefore necessary to follow for longer periods of time CS patients who have undergone corrective surgery, before concluding whether the sustained cognitive impairments observed here reflect a permanent influence of abnormally high levels of GC secretion. The potential for reversibility of GC-induced alterations of cognitive performance has important theoretical and clinical implications, and more work is needed to comprehensively examine the relationship between adrenocortical hormones, cognitive function and brain morphology and metabolism.

Acknowledgements

The contribution of the various members of the Division of endocrinology of the CHUM in referring CS patients is greatly appreciated. This research was aided by grants from Fonds de la Recherche en Santé du Québec and Programme de coopération Québec/Nouveau-Brunswick (H.F.).

References

- Beck, A.T., 1987. Beck Depression Inventory. The Psychological Corporation, San Antonio, TX.
- Benton, A.L., Varney, N.R., Hamsher, K., 1978. Visuospatial judgment: a clinical test. *Archives of Neurology* 35, 364–367.
- Bentson, J., Reza, M., Winter, J., Wilson, G., 1978. Steroids and apparent cerebral atrophy on computed tomography scans. *Journal of Computer Assisted Tomography* 2, 16–23.
- Bommer, M., Eversman, T., Pickardt, R., Leonard, A., Naber, D., 1990. Psychological and neuropsychological symptoms in patients with subclinical and remitted hyperthyroidism. *Klin. Wochenschr.* 68, 552–558.
- Bourdeau, I., Bard, C., Leclerc, L., Lesage, J., Lacroix, A., 1999. Cerebral atrophy in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. In: 81st Annual Meeting of The Endocrine Society, San Diego, CA, June 13, 1999. OR 21–6: p. 91 (abstract).
- Bremner, J.D., Randall, P., Scott, T.M., Bronen, R.A., Seibyl, J.P., Southwick, S.M., 1995. MRI-based measurement of hippocampal volume in patients with combat-related post-traumatic stress disorder. *American Journal of Psychiatry* 151, 973–981.
- Cohen, H., Landry, P., Bard, C., Boulanger, Y., Forget, H., Lacroix, A., 2001. Cognitive and metabolic alterations in Cushing's syndrome. International Neuropsychological Society, Brasilia, Brazil.
- De Leon, M.J., Golomb, J., George, A.E., Convit, A., Tarshish, C.Y., McRae, T., De Santi, S., Smith, G., Ferris, S.H., Noz, M., Rusinek, H., 1993. The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. *American Journal of Neuroradiology* 14, 897–906.
- De Leon, M.J., George, A.E., Golomb, J., Tarshish, C., Convit, A., Kluger, A., 1997. Frequency of

- hippocampal formation atrophy in normal aging and Alzheimer's disease. *Neurobiological Aging* 18, 1–11.
- Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test: Adult Version. The Psychological Corporation, San Antonio, TX.
- Dorn, L.D., Burgess, E.S., Friedman, T.C., Dubbert, B., Gold, P.W., Chrousos, G.P., 1997. The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *Journal of Clinical Endocrinology and Metabolism* 82, 912–919.
- Fahrenfort, J.J., Wilterdink, A.M.L., van der Veen, E.A., 2000. Long-term residual complaints and psychosocial sequelae after remission of hyperthyroidism. *Psychoneuroendocrinology* 25, 201–211.
- Forget, H., Lacroix, A., Somma, A., Cohen, H., 2000. Cognitive decline in patients with Cushing's syndrome. *Journal of the International Neuropsychology Society* 6, 20–29.
- Gauthier, L., Dehaut, F., Joanette, Y., 1989. The Bells test: a quantitative and qualitative test for visual neglect. *International Journal of Clinical neuropsychology* 11, 49–54.
- Gollin, E.S., 1960. Developmental studies of visual recognition of incomplete objects. *Perceptual and Motor Skills* 11, 289–298.
- Gotch, P.M., 1994. Cushing's syndrome from the patient's perspective. *Endocrinology and Metabolism Clinics of North America* 23, 607–617.
- Gould, E., Tanapat, P., McEwen, B.S., Flugge, G., Fuchs, E., 1998. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc. Natl. Acad. Sci. USA* 95, 3168–3171.
- Haskett, R.F., 1985. Diagnostic categorization of psychiatric disturbance in Cushing's syndrome. *American Journal of Psychiatry* 142, 911–916.
- Heinz, E.R., Martinez, J., Haengeli, A., 1977. Reversibility of cerebral atrophy in anorexia nervosa and Cushing's syndrome. *Journal of Computer Assisted Tomography* 1, 415–418.
- Hooper, H.E., 1983. Hooper Visual Organization (VOT) Manual. Western Psychological Services, Los Angeles.
- Kellner, C.H., Rubinow, D.R., Gold, P.W., Post, R.M., 1983. Relationship of cortisol hypersecretion to brain CT scan alterations in depressed patients. *Psychiatric Research* 8, 191–197.
- Kerr, D.S., Campbell, L.W., Thibault, O., Landfield, P.W., 1992. Hippocampal glucocorticoid receptor activation enhances voltage-dependent Ca^{2+} conductances: relevance to brain aging. *Proc. Natl. Acad. Sci. USA* 89, 8527–8531.
- Landfield, P., Waymire, J., Lynch, G., 1978. Hippocampal aging and adrenocorticoids: quantitative correlations. *Science* 202, 581–584.
- Landfield, P.W., Baskin, R.K., Pitler, T.A., 1981a. Brain aging correlates: retardation by hormonal–pharmacological treatments. *Science* 214, 581–584.
- Landfield, P.W., Braum, L.D., Pitler, T.A., Lindsey, J.D., Lynch, G., 1981b. Hippocampal aging in rats: a morphometric study of multiple variables in semithin sections. *Neurobiological Aging* 2, 265–275.
- Leclerc, I., Noel, B., Bard, C., Cordeau, M.P., Lacroix, A., 1996. Cerebral atrophy in Cushing's disease. 10th International Congress of Endocrinology, San Francisco, CA, June 15, 1996. OR–36–3: p. 113 (abstract).
- Lezak, M.D., 1995. *Neuropsychological Assessment*, 3rd ed. Oxford University Press, New-York.
- Luine, V., Villegas, M., Martinez, C., McEwen, B.S., 1994. Repeated stress causes reversible impairments of spatial memory performance. *Brain Research* 639, 167–170.
- Lupien, S.J., DeLeon, M., DeSanti, S., Convit, A., Tarshish, C., Nair, N., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat. Neuroscience* 1, 69–73.
- Magarinos, A.M., McEwen, B.S., Flugge, G., Fuchs, E., 1996. Chronic psychological stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *Journal of Neuroscience* 16, 3534–3540.
- Mauri, M., Sinforiani, E., Bono, G., Vignati, F., Berselli, M.E., Attanasio, R., Nappi, G., 1993. Memory impairment in Cushing's disease. *Acta Neurologica Scandinavica* 87, 52–55.
- McEwen, B.S., 1988. Glucocorticoid receptors in the brain. *Hospital Practice* 15, 107–121.
- McEwen, B.S., 1997. Possible mechanisms for atrophy of the human hippocampus. *Molecular Psychiatry* 2, 255–262.

- McEwen, B.S., Sapolsky, R.M., 1995. Stress and cognitive function. *Current Opinion in Neurobiology* 5, 205–216.
- McEwen, B.S., Magarinos, M., 1997. Stress effects on morphology and function of the hippocampus. *Annals New York Academy of Science* 821, 271–284.
- McEwen, B.S., Gould, E., Orchinik, M., Weiland, N.G., Woolley, C.S., 1995a. Oestrogens and the structural plasticity of neurons: Implications for memory, ageing and neurodegenerative processes. In: Goode, J. (Ed.), *Ciba Foundation Symposium No. 191. The Non-productive Actions of Sex Steroids*. CIBA Foundation, London, pp. 52–73.
- McEwen, B.S., Albeck, D., Cameron, H., Chao, H.M., Gould, E., Hastings, N., Kuroda, Y., Luine, V., Magaarinos, A.M., McKittrick, C.R., Orchinik, M., Pavlides, C., Vaher, P., Watanabe, Y., Weiland, N., 1995b. Stress and the brain: a paradoxical role for adrenal steroids. In: Litwack, G.D. (Ed.), *Vitamins and Hormones*. Academic Press, San Diego, pp. 371–402.
- Mizoguchi, K., Kunishita, T., Chui, D., Tabira, T., 1992. Stress induces neuronal death in the hippocampus of castrated rats. *Neuroscience Letter* 138, 157–164.
- Momose, K.J., Kjellberg, R.N., Kliman, B., 1971. High incidence of cortical atrophy of the cerebral and cerebellar hemispheres in Cushing's disease. *Radiology* 99, 341–348.
- Negro, P.J., Bertolino, A., Rosenstein, D., Orban, Z., Grant, S., Rakow, R., Weinberger, D., Rubinow, D.R., Nieman, L., Chrousos, G.P., Gold, P.W., Contoreggi, C., 2000. Generalized brain volumetric reductions in Cushing's disease. In: 82nd Annual Meeting of The Endocrine Society, Toronto, Canada, June 21–24, 2000. p. 466 (abstract 1931).
- Oberfield, S.E., Cowan, L., Levine, L.S., 1994. Altered cortisol response and hippocampal atrophy in pediatric HIV disease. *Journal of Acquired Immune Deficit Syndrome* 7, 57–62.
- Perrild, H., Hansen, J.M., Arnung, K., Olsen, P.Z., Danielsen, U., 1986. Intellectual impairment after hyperthyroidism. *Acta Endocrinol.* 112, 185–191.
- Raven, J.C., Court, J.H., Raven, J., 1976. *Manual for Raven's Progressive Matrices*. H.K. Lewis, London.
- Richer, F., Décary, A., Lapierre, M.-F., Rouleau, I., Bouvier, G., Saint-Hilaire, J.-M., 1993. Target detection deficits in frontal lobectomy. *Brain and Cognition* 21, 203–211.
- Rothschild, A.J., Benes, F., Hebben, N., Woods, B., Luciana, M., Bakanas, E., Samson, J.A., Schatzberg, A.F., 1989. Relationships between brain CT scan findings and cortisol in psychotic and nonpsychotic depressed patients. *Biological Psychiatry* 26, 565–575.
- Rothschild, A.J., Samson, J.A., Bond, T.C., Luciana, M.M., Schildkraut, J.J., Schatzberg, A.F., 1993. Hypothalamic–pituitary–adrenal axis activity and 1-year outcome in depression. *Biological Psychiatry* 34, 392–400.
- Sapolsky, R., 1994. Glucocorticoids, stress and exacerbation of excitotoxic neuron death. *Seminars in Neuroscience* 6, 323–331.
- Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1985. Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging. *Journal of Neuroscience* 5, 1222–1227.
- Schlegel, S., von Bardeleben, U., Wiedemann, K., Frommberger, U., Holsboer, F., 1989. Computerized brain tomography measures compared with spontaneous and suppressed plasma cortisol levels in major depression. *Psychoneuroendocrinology* 14, 209–216.
- Schmidt, L.A., Fox, N.A., Goldberg, M.C., Smith, C.C., Schulkin, J., 1999. Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. *Psychoneuroendocrinology* 24, 461–483.
- Sheline, Y.I., Wang, P.W., Gado, M.H., Csernansky, J.C., Vannier, M.W., 1996. Hippocampal atrophy in recurrent major depression. *Processing National Academy of Science USA* 93, 3908–3913.
- Simmons, N.E., Do, H.M., Lipper, M.H., Laws, E.R., 2000. Cerebral atrophy in Cushing's disease. *Surg. Neurol.* 53, 72–76.
- Starkman, M.N., Scheingart, D.E., Schork, M.A., 1981. Depressed mood and other psychiatric manifestations of Cushing's syndrome: relationship to hormone levels. *Psychosomatic Medicine* 43, 3–18.
- Starkman, M.N., Scheingart, D.E., Schork, M.A., 1986. Cushing's syndrome after treatment: Changes in cortisol and ACTH levels, and amelioration of depressive syndrome. *Psychiatry Research* 19, 177–188.
- Starkman, M.N., Gebarski, S.S., Berent, S., Scheingart, D.E., 1992. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biological Psychiatry* 32, 756–765.

- Starkman, M.N., Giordani, B., Gebarski, S.S., Berent, S., Schork, M.A., Schteingart, D.E., 1999. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biological Psychiatry* 46, 1595–1602.
- Stroop, J.R., 1935. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18, 643–662.
- Uno, H., Ross, T., Else, J., Suleman, M., Sapolsky, R., 1990. Hippocampal damage associated with prolonged and fatal stress in primates. *Journal of Neuroscience* 9, 1705–1711.
- Wechsler, D., 1974. Wechsler Memory Scale Manual. The Psychological Corporation, San Antonio, TX.
- Wechsler, D., 1981. WAIS-R Manual. The Psychological Corporation, New York.
- Whelan, T.B., Schteingart, D.E., Starkman, M.N., Smith, A., 1980. Neuropsychological deficits in Cushing's syndrome. *The Journal of the Nervous and Mental disease* 12, 753–757.