Memory impairment in Cushing's disease

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In the present study the cognitive performance of 25 patients with Cushing's disease (CD) was extensively evaluated in comparison with normal control subjects, matched one by one. The results indicate a selective impairment of memory functions: the number of patients showing a significantly impaired mnesic performance increases with age. Moreover, the neuropsychological impairment tends to recover in those cases who underwent further controls after surgical treatment. The neuropsychological data are discussed in the light of recent evidence in the literature concerning the effects of adrenal steroids on the brain.

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Several lines of evidence can be found in the literature about the close relationship existing between corticosteroids and neurobehavioral disorders (1). In fact, patients with Cushing's Disease (CD), as well as subjects treated with exogenous corticosteroids are known to frequently develop various degrees of cognitive disturbances (2–4). However, several studies have found that depressed patients with hypercortisolemia or hypercorticoluria and those who fail to suppress cortisol when given dexamethasone show more severe memory disturbances in respect to the depressed patients who normally suppress (5, 6). Recovery of intellectual deficits has also been reported both in subjects with CD (7) and in patients receiving steroid medication after the discontinuance or reduction of the therapy (4). Furthermore, cases of endogenous depression associated with hyperadrenocorticism are reported, in which the correction of endocrine imbalance improved the affective state (7).

CD may be considered as a clinically available model to study the interactions between cognition and chronic exposure to high corticosteroids levels. Moreover, cognitive studies on CD subjects carried out using extensive neuropsychological batteries and appropriate control groups are lacking in the literature.

On these grounds, in the present study we evaluated the mental status, memory and attention in particular, in a selected group of CD patients.

Patients and methods

Twenty-five subjects (17 females and 8 males) were selected from a larger population of CD patients who had been referred to the Department of Endocrinology of the Niguarda Hospital, Milan, during the period from September 1989 to October 1991. The mean age was 35.7 ± 14.3 yrs (range 16–58), the mean educational level 8.7 ± 3.5 yrs (range 5–17). All the patients presented ACTH dependent CD with high levels of ACTH and cortisol; the diagnosis was made on the basis of the usual criteria (clinical, hormonal and neuroradiological). The neurological examination did not show any pathological findings. In particular, neither hemianopsia nor papilledema was present. No signs of increased intracranial pressure were detectable. In all cases brain CT scan showed intrasellar lesions. The other neuroradiological findings, in particular the hippocampal regions studied by Nuclear Magnetic Resonance (NMR), were within the normal range in relation to the age of subjects. The mean illness duration (time ranging from the symptom onset to the diagnosis) was 19 ± 12 months (range 6–40). All the patients were right-handed.

Subjects with psychosis and/or severe affective disorders (both depressive and hypomanic) were excluded from the study on the basis of the administration of a psychiatric interview and specific psychological tests (Minnesota Multiphasic Personality Inventory, Zung's rating scales for anxiety and depression: SAS index < 60). Patients with previous neurological and/or psychiatric disorders, with history of drug abuse, and previous head trauma were also excluded.

The Intelligence Quotient (IQ) evaluated by the Wechsler Adult Intelligence Scale (WAIS) (8) was within the normal range (85–122); in 4 subjects the IQ was between 80–89, in 16 between 90–109, in 4 between 110–119, and 1 patient obtained more than 120.

All the subjects were fully oriented in space and time. About a half of them reported a mild impairment of memory and attention in every-day life tasks. None of the patients met the criteria for dementia according to DSM III; the Mini Mental State (9) score was higher than 24 ($M \pm SD = 28.9 \pm 1.2$).

Plasma ACTH levels ranged from 80 to 200 pg/mg (normal values range 10–80 pg/mg); the Urine Free Cortisol (UFC) ranged from 160 to 5000 μg/24 h (normal values range 20–90 μg/24 h). The mean of 3 determinations for both plasma ACTH and UFC was calculated for each patient; the hormonal determinations were performed in the same month as the neuropsychological tests (see methods below).

Eight (4 women and 4 men) of 23 subjects who presented pituitary tumor were evaluated again 6 months after the surgical ablation of the neoplasia (transsphenoidal microsurgery). The mean age of this group was 31.1 ± 11.7 yrs (range 16–47), and the mean educational level 9.7 ± 2.1 yrs (range 8–13). The mean illness duration was 15 ± 6 months (range 6–24).

Sixty normal subjects (15 subjects for each decade), whose age ranged from 16 to 60 yrs, were recruited from inpatients hospitalized at the Department of Neurology of the University of Pavia for neurological disorders not involving CNS (i.e. peripheral nerve entrapment, lumbosacral pain or sciatalgia). None of them had a history of head trauma, alcohol or drug use, nor suffered from endocrinological disorders. From this population 25 subjects were matched "one by one" with the CD patients for age, sex and educational level and selected as the control group for administration of the neuropsychological tests after informed consent.

CD patients and all the control subjects (60 cases) were administered the following neuropsychological tests:

- Logic memory, immediate and delayed recall (after 30 min), which assesses verbal short- and long-term memory (10).
- Serial learning test, which assesses verbal memory, both short- and long-term (11). Ten lists, each containing 12 unrelated disyllabic words, are presented to the subject. Primacy and recency scores (number of items correctly recalled, after each list presentation, from the first and the last two of each the list, respectively) are considered.
- Digit span, forward and backward, a subtest of the WAIS, which evaluates short-term verbal memory and brief attentional skills (8).
- Corsi's test, which assesses short-term spatial memory (11).
- Visual Reproduction, immediate and delayed recall (after 30 min), a subitem of the Wechsler Memory Scale, which assesses visuo-spatial memory functions (12).
- Raven's Coloured Progressive Matrices 47, which evaluate non-verbal intelligence and visuo-spatial abilities (13).
- Digit Symbol Substitution Test (DSST), a subtest of the WAIS. This task is a sensitive measure of psychomotor speed and sustained attention (8).
- Similarities, a subtest of the WAIS. This task is an excellent measure of general intellectual ability (8).
- Cancellation task, which assesses selective attention (11).
- Trail Making test (parts A and B). This test measures divided attention and psychomotor functioning (14).
- Word fluency; this test requires the subject to produce as many words as he can belonging to four semantic categories (fruits, colours, animals and towns); two minutes are allowed for each category (11).
- Street's Completion test, which assesses visuo-perceptive functions (11).

At the control after therapy the tests were administered in a different equivalent form (except for Street's test and Raven's Matrices).

The neuropsychological tests were administered during the patients' hospitalization, when the diagnosis was being defined, or at subsequent controls as inpatients after surgical treatment.

The analysis of the results was carried out using ANOVA 1W, t test for paired data and linear regression test.

Results

CD patients showed, in respect to normal controls a significant impairment at logic memory test, both learning ($p < 0.01$) and retrieval ($p < 0.001$), at primacy score ($p < 0.01$), at digit span backward ($p < 0.01$), at visual reproduction, both learning ($p < 0.05$) and retrieval ($p < 0.001$), and at DSST ($p < 0.01$). The other neuropsychological tests were within the normal range (Table 1).

We then subdivided our patients into 4 groups according to age (16–29; 30–39; 40–49; 50–59 yrs) and calculated the percentage of subjects per group who at each neuropsychological test scored 2 SD below the mean value of the correspondent control group (15 normal subjects for each decade). The percentage of patients with abnormal scores at Logic Memory, Visual Reproduction and Digit Symbol increased with age (Fig. 1).

A consistent trend was also detectable between lowered memory performance (z scores obtained from the mean values of each correspondent decade) and symptom duration, although the statistical significance was not reached ($r = -0.35$).

No significant correlation was found between cog-

Table 1. Neuropsychological evaluation (M±SD): CD patients vs controls (ANOVA 1W)

	CD patients (25 cases)	Controls (25 cases)	F	p
Logic memory				
Learning	6.3±2.2	8.2±2.4	8.6	<0.01
Retrieval	7.1±3.1	10.0±2.5	13.1	<0.001
Serial learning test				
Primacy	4.4±1.5	5.5±1.4	7.2	<0.01
Recency	14.3±3.7	15.1±3.5	0.6	n.s.
Digit span forward	5.6±1.0	5.5±1.2	0.1	n.s.
Digit span backward	3.5±0.8	4.1±0.8	7.5	<0.01
Corsi's test	5.5±1.0	5.7±0.9	0.5	n.s.
Visual reproduction				
Learning	8.8±3.7	10.9±2.2	5.7	<0.05
Retrieval	6.8±3.9	10.0±2.2	12.5	<0.001
Raven's Matrices 47	26.2±4.4	26.9±3.8	0.4	n.s.
DSST	36.8±14.1	47.3±11.2	8.4	<0.01
Similarities	13.4±2.6	14.0±3.3	0.6	n.s.
Cancellation test	53.8±6.0	54.2±4.6	0.1	n.s.
Trail Making Test A	45.4±7.9	42.3±8.0	1.9	n.s.
Trail Making Test B	75.8±13.7	69.9±11.4	2.7	n.s.
Word fluency	18.9±5.1	20.4±4.2	1.4	n.s.
Street's test	7.4±2.0	7.8±1.2	0.7	n.s.

Table 2. Neuropsychological evaluation (M±SD) after surgical ablation in 8 CD patients with pituitary adenoma (t test for paired data)

	Before	After	t	p
Logic memory				
Learning	6.0±1.3	9.4±2.3	−4.2	<0.01
Retrieval	7.7±2.0	10.7±2.5	−4.6	<0.01
Serial learning test				
Primacy	4.9±1.0	5.0±0.9	−1.0	n.s.
Recency	14.2±1.9	14.6±1.9	−1.6	n.s.
Digit span foward	5.6±0.9	6.2±1.0	−2.4	<0.05
Digit span backward	3.4±0.7	3.7±0.5	−1.1	n.s.
Corsi's test	5.7±0.7	5.9±0.6	−1.0	n.s.
Visual reproduction				
Learning	11.2±2.1	10.8±2.9	1.2	n.s.
Retrieval	8.5±3.1	8.9±2.5	−0.5	n.s.
Raven's Matrices 47	28.1±3.3	29.0±4.0	−1.7	n.s.
DSST	39.2±14.8	46.7±17.3	−4.3	<0.01
Similarities	14.1±1.9	14.6±2.2	−1.9	n.s.
Cancellation test	55.9±3.7	56.4±2.2	−0.4	n.s.
Trail Making Test A	43.5±8.5	42.1±8.6	0.9	n.s.
Trail Making Test B	65.6±10.8	64.5±11.0	0.8	n.s.
Word fluency	19.6±5.5	19.9±5.3	−1.2	n.s.
Street's test	8.1±1.4	8.2±1.3	−1.0	n.s.

nitive variables (z scores) and plasma ACTH and UFC levels ($r = -0.20$).

The neuropsychological tests did not correlate with Zung's scale scores (anxiety and depression).

The patients (8 cases) who were re-tested after 6 months from the surgical ablation of the neoplasia, showed a significant improvement at logic memory test, both learning and retrieval ($p < 0.01$), at digit span forward ($p < 0.05$), and at DSST ($p < 0.01$) (Table 2). The demographic characteristics of these subjects did not differ from those of the entire population. UFC levels were within the normal range.

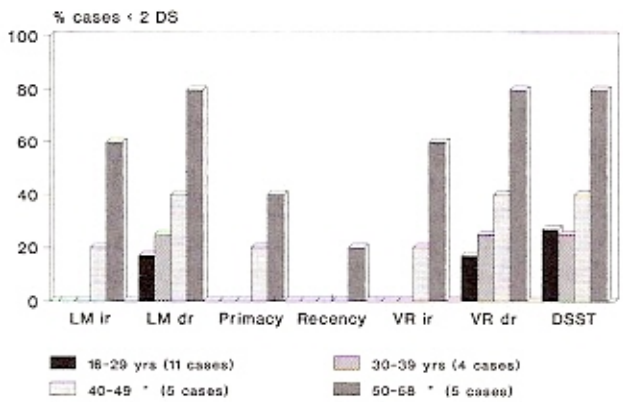

Fig. 1. Percentages of CD patients scoring 2 SD below the mean values of the correspondent control group subdivided by decades. LM ir = Logic Memory immediate recall; LM dr = Logic Memory delayed recall; VR ir = Visual Reproduction immediate recall; VR dr = Visual Reproduction delayed recall; DSST = Digit Symbol Substitution Test.

Conclusions

The results of this study point to a mnesic impairment of moderate degree of CD patients in respect to normal controls matched one by one. Due to the selection criteria we used, neither steroid psychosis nor depression was present, so that memory impairment cannot be related to concomitant psychiatric disorders. Therefore, our patients represent a highly-selected group. The low performance obtained by our subjects at Digit Symbol test may indicate an impairment of attentive and visuo-motor functions. However, the high sensitivity to even minimal brain damage and the relatively scarce specificity of this test should be stressed. On the other hand, the performance at the other tests exploring attentive abilities fell within the normal range. No deficits in other cognitive functions could be detected.

Whelan et al. (2) found global cognitive dysfunctions in about two thirds of their CD population, suggesting that the pattern of deficits is similar to that of patients with other types of diffuse bilateral neuropathological processes, such as toxicity, anoxia, infectious cerebral disorders and even Alzheimer's disease. However, the lack of a control group in this study makes the evaluation of the results difficult.

No correlation between ACTH and UFC, and memory impairment was found, perhaps because random basal cortisol measurements are typically variable (1). However, when both ACTH and UFC levels and HPA axis dysfunction returned to normal, after surgical treatment, we observed a significant amelioration of memory deficits, at least in the small group of patients we studied.

Investigations conducted in recent years have stressed the numerous effects of adrenal steroids on the brain and neuronal activity as well as on its structure and chemistry (15). Hippocampus in particular is considered the crucial point in these studies, as this brain area is the richest in glucocorticoid-binding receptors and controls the negative feedback of Hypathalamus-Pituitary-Adrenal (HPA) axis. In recent years, Sapolsky and coworkers (16) have formulated the "glucocorticoid cascade hypothesis", based on experimental evidence that chronic exposure to high doses of endogenous corticosteroids damage the hippocampal structures, by decreasing the number of corticosteroid-receptor-bearing neurons. As hippocampus is involved in learning and memory processes, it can be hypothesized that such changes might lead to long-lasting cognitive alterations.

Some aspects of the memory impairment we found in CD subjects might refer to an involvement of bilateral hippocampal structures: indeed only secondary episodic memory was damaged, an impairment of storage ability being hypothesizable. On the other hand, involvement of hippocampal regions has already been found in CD; signs of limbic atrophy, in fact, have been described at autopsy in CD patients (17), these data being later confirmed in vivo by other authors (18). By contrast, neuroradiological findings of the hippocampus in our subjects were within the normal range. Moreover, it should be stressed that the hippocampus is not uniform in its sensitivity to glucocorticoid-induced damage (15). Sapolsky's hypothesis undoubtedly represents an interesting experimental model, but at the present time the clinical correlates are far from being clear. Changes in hippocampal activity "per se" cannot explain the steroid-related cognitive impairment, also because of the differential CNS binding pattern of endogenous and exogenous corticosteroids (15). Furthermore, memory is a very complex function in terms of both anatomical structure and physiopathological functioning. For these reasons, memory disturbances frequently occur in the presence of diffuse neuropathological processes, such as CD. Corticosteroids association with cognitive performance is therefore quite complex and may vary with both age and diagnosis of the subjects under investigation (1). Adrenal steroids have at least two types of effects (15); some of them are relatively rapid and involve membrane receptor sites, with a consequent alteration of neuronal electrical activity, others are long-lasting and involve changes in gene expression that can alter the regulation of enzymes and neurotransmitter receptors. These latter effects could explain both the presence of cognitive dysfunctions in CD subjects and the reversibility of the intellective impairment when the hormonal imbalance returns to normal. In this perspective, it can be hypothesized that older individuals, because of a loss of neuroplasticity and ability to compensate the neural damage may show a greater susceptibility to the effects of glucocorticoids on the brain.

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