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Case Report

Cortisol, depression and reduced cortico-cortical cross-talk in Cushing's syndrome

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ABSTRACT: In the present report assumed relationships between hypercortisolism, depression and cortico-cortical cross-talk in Cushing's syndrome were investigated. Electroencephalographic (EEG) recordings and depression ratings from three patients diagnosed with mild, moderate and severe hypercortisolism were obtained. Reductions in cortico-cortical cross-talk as quantified by EEG coherence and increased depression were observed in the moderate and severe as compared to the mild hypercorticolism state. These findings provide preliminary evidence for the hypothesis that loss of cortico-cortical cross-talk might be linked to hypercortisolism and the severity of depressive symptoms. (J. Endocrinol. Invest. 27:683-686, 2004)

INTRODUCTION

Cushing's syndrome is a multi-system disorder characterized by the chronic excess of glucocorticoids (1). Apart from the well-known systemic effects of hypercortisolemia, such as weakness, proximal muscle atrophy, moon facies, centripetal obesity and osteoporosis, cognitive deficits and changes in mood have been reported. Cushing's syndrome often goes accompanied by depression. The depressive symptoms in Cushing's syndrome are undoubtedly at least partially mediated by hypercortisolemia (2). Support for this notion was provided by Nieman et al.(3), who were the first to show amelioration of suicide depression after the treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. Furthermore, cortisol also seems to reduce neural interactions between different areas of the brain. Using electroencephalogram (EEG) coherence analysis, an inverse relationship between basal cortisol levels and neural interaction between the frontal and parietal cortex has been demonstrated (4). EEG coherence can be considered to be an electrophysiological marker for information transfer between cortical brain areas, often designated as cortico-cortical cross-talk (5). Thus, EEG coherence can be viewed as an index for the functional integrity of cortical networks. Cerebral atrophy, for instance, goes accompanied by reductions in EEG coherence, hence indicative for loss of functional integrity and cross-talk within the cortex. Recently, Leuchter et al. (6) already showed evidence for relationships between lowered cortico-

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cortical cross-talk, reduced structural connectivity, that is white-matter lesions, and depression.

As noted above, high cortisol levels, as often observed in depression, are associated with reduced cortico-cortical cross-talk between frontal-parietal brain regions. Contrariwise, recently we established elevations of the frontal-parietal cortico-cortical coupling after a single administration of testosterone, a hormone with antidepressant properties (unpublished observation). The latter increases in cortico-cortical cross-talk were observed in the delta (1-3 Hz) frequency range. This is in particular interesting, because Roemer et al. (7) demonstrated that higher pre-treatment interhemispheric coherence in the delta frequency range predicts more positive therapeutical outcome in clinically depressed subjects.

Whereas testosterone in itself has antidepressant properties, cortisol-receptor antagonists have been reported to reduce negative effects of cortisol on mood. Van der Lely et al. (8), Murphy et al. (9) and more recently Belanoff et al. (10) demonstrated antidepressant efficacy of the antiglucocorticoid mifepristone in major depressive Cushing' syndrome patients. As noted, depression constitutes in part of the clinical symptomatology of Cushing's syndrome and has been associated with reductions in cortico-cortical cross-talk in different brain regions. It can thus be hypothesized that hypercortisolism goes accompanied by a breakdown of cortico-cortical cross-talk.

MATERIALS AND METHODS

In the present clinical report, three right-handed females from a random sample respectively diagnosed with mild, moderate and severe Cushing's disease were compared to investigate the above hypothesis. The diagnosis of Cushing's syndrome was established by the presence of an elevated 24 hour urine-free cortisol concentration, the absence of a diurnal rhythm of plasma cortisol and an insufficient 1 mg dexamethasone overnight suppression of cortisol. The diagnosis of Cushing's disease was confirmed by demonstrating an increase in plasma cortisol and adrenocorticotropin (ACTH) after corticotropin-releasing hormone (CRH) administration, and a decrease in plasma cortisol by at least 40% of the basal level at the end of a 7 hour infusion of 7 mg dexamethasone (1 mg/ hour). ACTH was measured using an immunometric technique on an Advantage Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, U.S.A.). The lower limit of detection was 1.0 pmol/ L and the inter-assay variation was 11.4, 10.7 and 6.8% at 11, 68 and 310 pmol/ L respectively (n=32). Normal values (8 a.m.) are between 20-70 pmol/ L.

Cortisol in serum was determined on the Advia Centaur Random Access Analyzer (Bayer, Tarrytown, U.S.A.). Inter-assay variability was 6-10%. Normal values (8 a.m.) range between 200-600 nmol / L. Cortisol in urine was measured after dichloromethane extraction using an immunometric technique on an Advantage Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, U.S.A.). Urine free cortisol diurnal concentrations normally range from 50-200 nmol/ L in healthy subjects. The length of disease was approximately 3 years. Clinical depression was rated according to the DSM-IV criteria. The diagnostic tests and the main characteristics for the three female patients with Cushing's disease are plotted in Table 1.

EEGs were recorded from the frontal (Fp1, Fp2, F3, F4, F7, F8, Fz), temporal (T3, T4, T5, T6) and parietal (P3, P4, Pz) electrode positions according to the International 10-20 EEG System, using an Electro-Cap with Ag/AgCl electrodes (Neurosoft, Inc.). EEG signals were referenced to the right mastoid. For the purpose of artefact reduction, vertical (VEOG) and horizontal (HEOG) electro-oculograms (EOG) were recorded during the actual acquisition phase. Ag/AgCL electrodes were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. Electro-Cap-International (ECI) EEG Gel was used for both EEG and EOG and all electrode impedances were less than 5,000 Ohms. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low-pass cut-off frequency 70 Hz and a time constant of 3 seconds). For the EEG recordings NeuroScan software (Neurosoft Inc, El Paso, Texas) was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the digitisation rate was 250 Hz. Subjects were comfortably seated in a dimly lit room and instructed to minimize head movements during the 8 minute EEG acquisition.

Table 1. *Diagnostic tests and main characteristics in the three female patients with Cushing's disease. Mih: mild hypercortisolism* ***(a)****; Moh: moderate hypercortisolism* ***(b)****; Seh: severe hypercortisolism* ***(c)****; iv: intravenously.*

		Mih (a)	Moh (b)	Seh (c)
Age (years)		48	59	53
Depression (DSM-IV)		Mild	Moderate	Severe
Urine free cortisol (nmol / 24 hours)		320	700	4000
CRH test (100 µg, iv) Cortisol responses (nmol / L)				
	Basal level	590	830	1630
	Peak level	990	1890	2240
ACTH response (pmol / L)	Basal level	59	117	120
	Peak level	257	194	212
Dexamethasone test (7 mg / 7 hours, iv) Cortisol response (nmol / L)				
	0 hours	570	760	1520
	7 hours	80	410	740

Offline, using Brain Vision (BrainProducts GmbH., Munich), the EEG signal was digitally low-pass filtered at 30Hz and corrected for vertical and horizontal eye movements using linear regression analysis. Signals containing residual muscular or other sources of artefact (± 50 µV) were rejected prior to further analysis. After segmentation, averaged artefact free EEG signal was extracted through a Hamming window (length 10%). Fast Fourier Transform method was used to derive estimates of spectral power (μV^2) in the 1 Hz frequency bins for each electrode site in the delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz) and beta (14-30 Hz) frequency bands respectively. Finally, coherence analysis was applied to compute cortico-cortical cross-talk in the different bandwidths between the different cortical brain areas.

RESULTS

As hypothesised, compared to the patient with mild hypercortisolism (case a), the patients with moderate (case b) and severe hypercortisolism (case c) clearly showed reductions in cortico-cortical cross-talk in practically every frequency bandwidth, as can be seen from Figure 1. The overall assessed cortico-cortical cross-talk in the 1-30 Hz frequency range was 0.33, 0.13 and 0.22 for mild, moderate and severe hypercortisolism respectively, indicating reductions in the functional integrity of cortico-cortical networks.

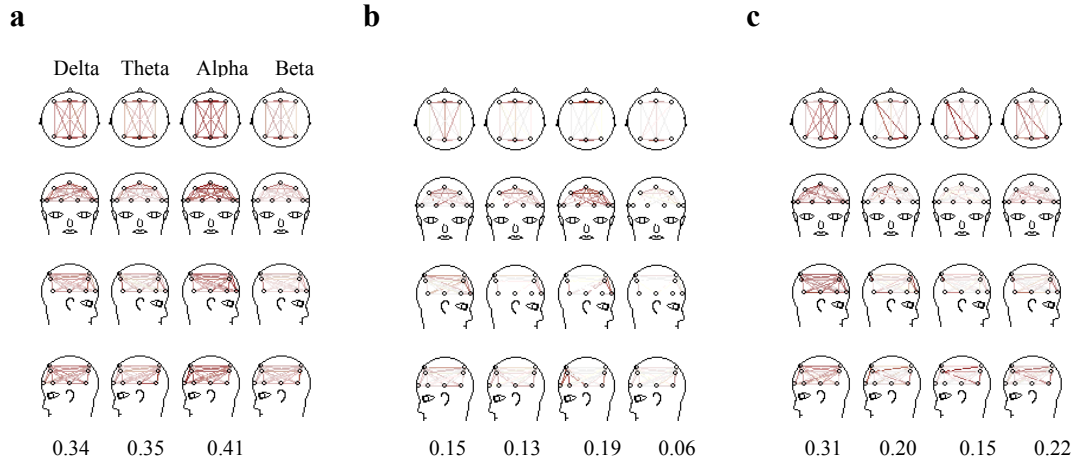

Figure 1. *Overall cortico-cortical cross-talk in the delta, theta, alpha, beta frequency range for the patient with mild* ***(a)****, moderate* ***(b)*** *and severe hypercortisolism* ***(c)****.*

DISCUSSION

As noted, hypercortisolism in general (11, 12) and Cushing's syndrome in specific (13) have been associated with cerebral atrophy. These reported volume reductions were explained in terms of catabolic effects on proteins and diminished glucose metabolism. Reductions in functional cortico-cortical cross-talk as observed here in the patients with moderate and severe hypercortisolism, have concordantly been associated with cortical atrophy (14). Nevertheless, evidence for at least partial reversibility of brain-volume loss following remission of hypercortisolism has recently been provided by Bourdeau et al. (15). Based on these latter findings and the current results, the reinstatement of the functional cortico-cortical connectivity after correcting for hypercortisolism would be in the line of expectations.

Furthermore, all three patients were diagnosed with a clinical depression according to the DSM-IV, and the intensity of which co-varied with the severity of hypercortisolism. This is in accordance to what is normally observed in Cushing's syndrome.

The involvement of reduced information transfer between different brain regions in depression was recently put forward by Schutter et al. (16). These authors argued that the antidepressant effects of clinical studies in depressive patients utilizing fast repetitive transcranial magnetic stimulation over the frontal cortex, commonly argued to be due to enhancement of neuronal activity (17,18), do more likely result from enhanced cortico-cortical cross-talk (16,19). This suggestion finds strong support in the recent observation of increased cross-talk between the frontal and parietal regions after repetitive transcranial magnetic stimulation over the frontal cortex in healthy volunteers (20). Presently, an overall reduction in cross-talk was observed. In further research it would be interesting to investigate whether mood deterioration in hypercortisolism is partially related to reductions in fronto-parietal interactions.

It should furthermore be noted that age could be a confounding factor in the issue of cortico-cortical cross-talk, and there is indeed evidence for a relationship between aging, heightened cortisol levels (21) and reductions in interhemispheric cortico-cortical cross-talk (22). However, several reports indicate that is unlikely that age influences basal cortisol levels (23-25). The latter reports concur with the present observation, since there was no linear increase between age and basal cortisol levels (see Table 1). However, as can be seen from Figure 1 cortisol levels did not seem to influence cortico-cortical cross-talk in a linear fashion also. The largest reduction in cross-talk was found in the oldest patient with moderate hypercortisolism. Thus out data not only suggest that cortisol does not increase with age in a linear fashion, but also that the elderly are more vulnerable to the negative influences of pathological cortisol levels on the brain, as has been observed in the area of cognitive functioning (23).

In conclusion, the postulated hypothesis that high levels of cortisol are associated with loss of cortico-cortical cross-talk and severity of depressive symptoms has presently found provisional support. However since, for instance, Dorn et al. (26) have demonstrated that depressive symptomatology can persevere up to a year after correction of hypercortisolism, hence indicative for a complex dissociation between cortisol and depression, more systematically controlled and longitudinal studies are required to scrutinize the here-observed relationships. For example, within-subject studies comparing depression and cortico-cortical cross-talk in the pre- to the post-treatment period of Cushing's disease, when cortisol levels have returned to normal values, might yield a more definite answer to the hypothesized relations between cortisol, depression and cortico-cortical cross-talk in Cushing's disease.

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