

Role Of Increasing Levels Of The Hormone Cortisol In Cognitive Impairment In Parkinson's Disease: Vascular Parkinsonism

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Abstract

This article is based on a review of the literature and recent clinical studies on changes in plasma cortisol hormone concentrations in cognitive impairment in Parkinson's disease. The article presents the reasons for the relationship between cognitive impairment in Parkinson's disease, in particular vascular Parkinsonism and neurodegenerative diseases, as well as the results of neuropsychological tests.

Methods: We studied the level of morning plasma cortisol in 68 patients with Vascular Parkinsonism (VP) who were hospitalized in 1st neurology department of TMA in the period from 2015 to the present. The relationship between increased morning plasma cortisol and cognitive impairment was determined. The results of the study were statistically analyzed. Cortisol was determined in all blood samples of patients of the Main and Control groups. The control group consisted of 47 volunteers.

Results: Normal levels of cortisol were observed in 20 patients (29%) with vascular parkinsonism,, moderate increases in cortisol were observed in 37 patients (54.4%), and elevations in cortisol were observed in 11 patients (16.1%). Was determined the relationship between the value of cortisol and the assessment of cognitive impairment. In the main group, a statistically significant moderate inverse correlation was determined between plasma cortisol level and cognitive impairment in VP. When studying cortisol levels in VP, its significant increase is noted than in the control ($p < 0.05$).

Conclusion: Increased levels of the hormone cortisol in Parkinson's disease play an important role in cognitive impairment and during the course of the disease and affect the effectiveness of VP therapy.

Key words: Parkinson's disease, Vascular Parkinsonism, cortisol hormone, cognitive disorders, circadian rhythm, hippocampal mineralocorticoid receptors, depression, stress, subthalamic nucleus, deep brain stimulation.

1. INTRODUCTION

Elevated levels of cortisol are found in many diseases, including infectious diseases associated with aging, depression and depression-related conditions; even in some without any known origin and without known therapy. Recent studies indicate that the insular cortex and the hormone cortisol show signs of parkinsonism. Dopaminergic changes at the level of the island may be associated with changes in personality (i.e. Search for novelty) and symptoms of hemispheric neglect [1].

Endocrine disorders of the hypothalamic-pituitary-adrenal system in patients with Alzheimer's disease (AD) and Parkinson's disease (PD) have been described repeatedly. However, there is no data on the daily secretory structure of cortisol for these major neurodegenerative diseases [1].

Thus, Hartman and colleagues reviewed the 24-hour pulsating secretion of cortisol in 12 patients with BA and 12 patients with PD compared to 10 normal volunteers, comparable in age and age. Twenty-four hours' blood samples were taken from 1800 hours to 1800 hours at 15-minute intervals. Cortisol half-life, cortisol secretory bursts/24 hours, pulse interval, mass of secreted cortisol per explosion, amplitude of cortisol secretory bursts, pulsating cortisol production, 24-hour mean and integral cortisol concentrations were calculated using deconvolution analysis. In addition, relative daily fluctuations and a rest period were determined. It was found that patients with Alzheimer's disease (AD) and Parkinson's disease (PD) had significantly higher total plasma cortisol concentrations (24-hour pulsating cortisol production: AD + 56%; PD + 52% / 24-hour integrated cortisol: AD + 37%; PD + 29%) compared. This sustained hypercortisolism is due to a higher mass of cortisol released per flash (BA + 62%; BP + 79%), but not an increase in the half-life of cortisol, the frequency or amplitude of the secretory pulse. Despite this similarity between patients with BA and PD, the relative daily variation of cortisol secretion was significantly reduced in patients with PD (-22%). Based on these results and recently published data on animals, scientists hypothesized that a decrease in the expression of the mineralocorticoid receptor (MR) of the hippocampus may be the cause of a flattened secretory curve of daily cortisol observed in patients with PD, whereas the intact daily profile in patients with BA may be due to the relative increase in MR compensating for the loss of hippocampal neurons, usually occurring in this disorder.

K. Phillips P. Salmon and co-workers at the University of Louisville, USA studied as Parkinson's disease progressed in patients with increased stress factors that often had an impact on psychological and physical health. Attentive stress reduction programs. However, as expected, patients with PD had a significant decrease in nocturnal cortisol ($p = 0.021$) and a significant decrease in IL-1 β ($p = 0.004$), which indicates an improvement in the functioning of HPA and inflammatory stress markers, respectively [2].

David Sancho Cantus, Natalia SantiestebanLópez and co-authors analysed a systematic review of studies published in various databases on stress and cortisol concentrations. We analysed 17 analytical studies: quasi-experimental and control. The population was approximately 20 to 80 years old, and the distribution between the sexes was fairly fair.

The results obtained from the point of view of biomarkers differed from those expected; theoretically, this is associated more with cortisol as a stressful biomarker. It is a less studied biomarker, but an excellent candidate for future research. In addition, it has been shown that stress contributes to neurodegeneration, and the dopaminergic system is particularly sensitive. According to the literature, cortisol is a valid biomarker for measuring stress in patients with PD [3].

Hemraj B. Dodiya, Christopher B. Forsyth et al. Caused stress in rodents with rotenone for 12 weeks. For the first six weeks, restraining stress caused a significantly higher level of cortisol in the urine [4].

On the other hand, dysfunction of the central serotonergic system was associated with depression in Parkinson's disease. In order to assess central serotonergic function in Parkinson's disease due to depression, Vladimir S. Kostić, Dusica Lečić (1996, Yugoslavia) investigated cortisol responses to a single dose with fenfluramine (60 mg orally), a serotonin releasing / absorbing agent, within 5 hours in 11 patients with Parkinson's disease associated with major depression (SADS-RDC), 22 incapacitated parkinsonism and 20 healthy people,

matched by age and sex. There was no difference in cortisol responses between groups. [5]. Endogenous circadian rhythms are best characterized by analysis of circadian markers.

Circadian profiles of melatonin, cortisol and clock genes in a group of 30 patients with early PD and 15 selected controls (Breen et al., 2014) [14]. Patients with PD had elevated cortisol levels and decreased melatonin levels. Part of the value of all these studies is that they use rigorous circadian experimental constructs that control exogenous signals well, which are known to affect the endogenous circadian system, such as light exposure, food patterns, ambient temperature, and physical activity. The cortisol rhythm is also disrupted by PD. While patients with PD have a constant cortisol circadian rhythm, the amount of cortisol secreted increases with early PD [14]. However, somatotrophic, thyrotrophic and lactotrophic axes, apparently, are not damaged at the early stage of PD [15], [16].

Depression of late age is a risk factor for dementia. This may increase the risk of reliably reducing cognitive function in the short term, and the associated risk factors remain unclear. Cortisol levels may be one of the important predictors. On this issue, Xiaomei Zhong and his co-authors assessed whether patients with late depression are at an increased risk of significant global decline in cognitive abilities after 1 year, and studied risk factors associated with them that predict cognitive decline. According to the results during the 1-year follow-up period, 19 patients with late depression (28.4%) demonstrated a significant global decline in cognitive abilities, whose risk was 6.4 times (95% CI = 1.3–31.1, $p = 0.021$) higher than normal elderly people. Elevated serum levels of cortisol and old age were associated with a risk of cognitive decline, which was 1.6 and 1.2 times higher (95% CI = 1.07–2.5, $p = 0.02$ and 95% CI = 1.04–1.4, $p = 0.01$, respectively). Cortisol is one of the hormones involved in the stress response, and serum cortisol concentration increases after stress. Studies have shown that the reaction to the effects of stressor activates the hypothalamus-pituitary-urethra axis in fish, which leads to the release of cortisol into the bloodstream [8].

Exposure to stressors can lead to a significant increase in serum cortisol concentrations [11] in fish [8]. Serum cortisol concentration measurement is commonly used to evaluate the effects of stress with and without anaesthetics.

Some other studies have reported that cortisol is an indicator of stress, and Hsp90 is a downstream product of cortisol [9]. Robert H. and his co-authors proved a link between plasma cortisol levels and cognitive decline in 416 cognitively normal elderly people. In cognitively healthy older people, $A\beta +$ is associated with a more significant decrease in cognitive functions, and high plasma cortisol levels can accelerate the effect of $A\beta +$ on reducing general cognition, episodic memory and executive function. These results suggest that treatment methods aimed at reducing plasma cortisol and $A\beta$ levels may be useful in reducing cognitive decline in the preclinical phase of AD. [10]

Considering the functional organization of the subthalamic nucleus (STN), Philip Ruzhik and his co-authors suggested that subthalamic deep brain stimulation (STN-DBS) in Parkinson's disease can have a differential effect on the hypothalamic-pituitary-adrenal axis in relation to the STN. In addition, we looked for any morning changes in plasma cortisol levels associated with STF-GSM, due to postoperative anxiety and weight gain. In addition, lower cortisol levels were closely associated with increased anxiety and weight gain. These changes mimic the effects of chronic stress and suggest the disturbing effect of STF-GSM on the limbic and motivational systems. Patients with at least one contact located in the middle part of the STN experienced a significantly greater decrease in cortisol levels than patients with one or both active contacts more laterally. In addition, lower cortisol levels were closely associated with increased anxiety and weight gain. These changes imitate the effects of chronic stress and suggest the disturbing effect of STF-fuel and lubricants on the limbic and motivational systems [11].

2. OBJECTIVE

Elevated cortisol levels are found in many diseases, including infectious, related to aging, depression, and associated with a depressive status.

3. MATERIAL AND METHODS

We studied the level of morning plasma cortisol in 68 patients with Vascular Parkinsonism (VP) who were hospitalized in 1st neurology department of TMA in the period from 2015 to the present. The relationship between increased morning plasma cortisol and cognitive impairment was determined. The results of the study were statistically analyzed. Cortisol was determined in all blood samples of patients of the Main and Control groups. The control group consisted of 47 volunteers.

The concentration of cortisol was studied by enzyme immunoassay on an automatic analyzer EL 808 Ultra Microplate Rider (BIO-TEC Instruments, Inc) using standard sets of reagents "Steroid IFA-cortisol-01" series No. 061P and "Non-extraction IGF-1 ELISA DSL-10-2800". The reference values of the norm of cortisol were 50 - 250 mg / ml. To assess cognitive status, we evaluated on the MMSE scale, MOCA test.

The data obtained in the study were subjected to statistical processing on a personal computer Mac using the software package MicrosoftOffice Excel-16.13.1, including using built-in functions

Statistical processing. The methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (σ), standard error of the mean (m), relative values (frequency,%). For sophisticated mathematical analysis, we used GraphPadPrism 7 for Mac. For the analysis of normally distributed quantitative features when comparing two independent samples, the Student's test was used; linear regression was used to determine the relationship between cortisol and other patient indicators.

For all types of statistical analysis, the differences were calculated statistically significant at the achieved level of significance $p < 0.05$

4. RESULTS

Table 1. Vascular Parkinsonism disease duration in main group patients.

	1-5 year	5-10 year	More than 10 years
Men n=39	13(19.1%)	18(26.4%)	8(11.8%)
Women n=29	14(20.5%)	8(11.8%)	7(10.3%)

Normal levels of cortisol were observed in 20 patients (29%) with vascular parkinsonism,, moderate increases in cortisol were observed in 37 patients (54.4%), and elevations in cortisol were observed in 11 patients (16.1%).

Table 2. Cortisol hormone levels in the patients morning blood serum in the immunofluorescent method.

Groups	50 – 250mg / ml	250 – 500mg / ml	500 - 900mg / ml
Main group n=68	20 (29.4%)	37(54.4%)	11(16.1%)
Control group n=47	32(68%)	9(19.1%)	3(6%)

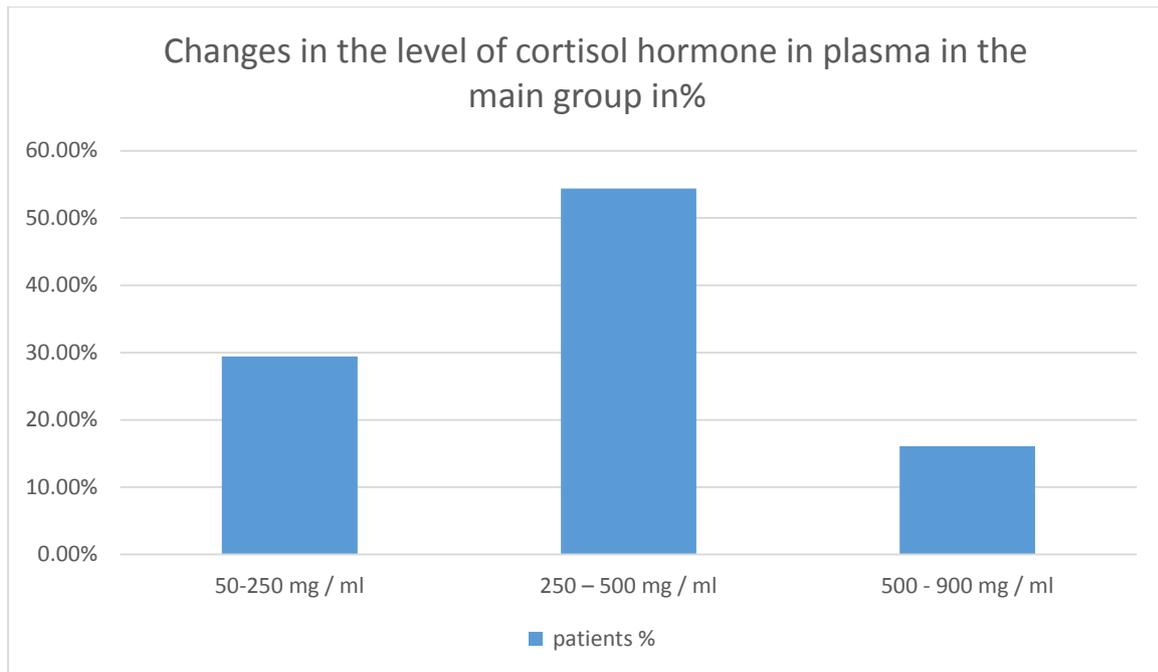


Table 3. The main and control groups scored differently on the Mini Mental State Examination (MMSE) scale.

	Below than 10	Between 11-19 points	Between 20-23 points	24-27 balls	Between points 28- 30
Main group	6 patients 8.2 ±2.1	19 patients 17.64±4.3	16 patients 22.34±2.1	18 patients 26.±2.4	9 patients 28.67±4.3
%	8.9%	27.94%	23.5%	26.47%	13.23%
Control group	Not observed	12 patients 18±2.1	22 patients 22.71±5.1	6 patients 26.4±1.1	18 patients 29±1.1
%	0%	25%	45.83%	12.5%	37.5%

Table 4. Cognitive impairment in patients with cortisol hormone levels greater than 250 mg / mL

Indices	Men			Women		
	R	CI	P	R	CI	P
Age	-	-0.160-0.190	0.8	-	-0.2358-1233	0.72
Phase on the Hoehn and Yahr scales	0.05	0.111-0.222	0.6	0.01	0.234-0.5678	0.5
MMSE	-0.45	-0.08-0.290	0.3	-0.2	-0.1244-0.3445	0.3
Disease duration	0.03	-0.107-0.225	0.5	0.4	-0.67-0.974	0.4
Cortisol level in plasma mg / ml	0.35	-2.645-0+2230	0.02*	0.25	-0.08-0.290	0.03*

Note: * - validity of data between male and female genders (P<0,05)

Table 5. Spearman's rank correlation coefficient. The relationship of cortisol levels and indicators of cognitive impairment.

Groups	MMSE	MOCA test
Main group n=68	r=-0.45 p=0.03	r=-0.13 p≥0.05
Control group n=47	r=0.77 p=0.02	r=0.74 p=0.04

Was determined the relationship between the value of cortisol and the assessment of cognitive impairment. In the main group, a statistically significant moderate inverse correlation was determined between plasma cortisol level and cognitive impairment in VP. When studying cortisol levels in VP, its significant increase is noted than in the control (p <0.05).

5. DISCUSSION

In this clinical trial, we examined the effect of increased serum cortisol levels on cognitive performance in vascular parkinsonism. Although our clinical trial supports the findings of the clinical trials cited in the literature review above, our study showed changes in serum cortisol levels only once, increased salivary cortisol levels and increased circadian rhythm in participants can lead to cognitive impairment. In our study, we used only brief neuropsychological questionnaires to assess cognitive performance, but the results of comprehensive surveys may alter clinical trial results.

The results obtained from the point of view of biomarkers differed from those expected; theoretically, this is associated more with cortisol as a stressful biomarker. It is a less studied biomarker, but an excellent candidate for future research. In addition, it has been shown that stress contributes to neurodegeneration, and the dopaminergic system is particularly sensitive. According to the literature, cortisol is a valid biomarker for measuring stress in patients with PD [3].

In addition to VP, in some cases there is also an increase in the hormone cortisol in PD, but in many cases cognitive dysfunction may not be observed. Based on these results, late-age depression was associated with a significantly increased risk of significant cognitive decline in the short term. Dysregulation of cortisol may contribute to the pathology of cognitive impairment. [7]

6. CONCLUSION

Increased levels of the hormone cortisol in Parkinson's disease play an important role in cognitive impairment and during the course of the disease and affect the effectiveness of VP therapy. The cortisol rhythm is also disrupted by PD. While patients with PD have a constant cortisol circadian rhythm, the amount of cortisol secreted increases with early PD.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

FINANCIAL SUPPORT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGMENTS

All authors participated in the research process and data collection.

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