ORIGINAL ARTICLE

HOMEOSTATIC ROLE OF GLUCOCORTICOIDS IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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ABSTRACT

The aim: To establish the clinical and pathogenetic role of glucocorticoid imbalance as an important link of impairment of the adaptive system homeostasis and to determine ways of its correction as a way to increase the effectiveness of the pulmonary tuberculosis treatment.

Materials and methods: The effectiveness of glucocorticoids in the pulmonary tuberculosis treatment was studied in 304 patients, of which 134 patients (group 1) received only antibacterial therapy, 67 patients (group 2) were supplemented with glucocorticoids (20-30 mg of prednisolone, daily, in 3 doses, with their cessation by gradual reduction of dose). 103 patients (group 3) also received antibacterial therapy in combination with glucocorticoids (20-30 mg of prednisolone, in the morning, in a daily dose every other day, cessation was carried out simultaneously without reducing the dose).

Results: The study found that the level of cortisol in patients with pulmonary tuberculosis was significantly higher than normal, did not have age and gender dependence, but showed a connection with the severity of clinical forms of tuberculosis, the duration of disease development and the presence of intoxication. It was established that the daily fluctuations of cortisol persist in tuberculosis patients, but its level significantly exceeds the norm, which indicates the functional stressing of the adaptive system.

Conclusions: The article substantiates the homeostatic role of glucocorticoids in the complex treatment of tuberculosis patients when administered in a double physiological dose every other day, taking into account the daily biorhythm of the hypothalamic-pituitary-adrenal axis function.

KEY WORDS: tuberculosis, pathogenetic therapy, cortisol

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INTRODUCTION

Our studies have shown that the main condition for the development of tuberculosis in individuals infected with mycobacteria of tuberculosis is the formation of cellular immunodeficiency, which is characterized by a correlation with impaired glucocorticoid function of the adrenal cortex [1], reflecting their pathogenetic role in the development of this disease. These results became the basis for a study in patients with disorders of the level of cortisol in the blood plasma, as the final link in the neuroendocrine regulation of adaptive processes carried out by the hypothalamic-pituitary-adrenal system, which can be of an important pathogenetic importance in the development of tuberculosis and can be an objective justification for the use of glucocorticoids in the treatment of patients with tuberculosis. The necessity for such a justification follows from the fact that modern literary sources indicate that the main arguments for the use of glucocorticoid drugs in the treatment of tuberculosis are clinical manifestations in the form of pronounced exudation in pleurisy [2, 3]. Scientists at Harvard Medical School, by administering dexamethasone every 6 hours in the tuberculosis treatment, believe that glucocorticoids are not dangerous for patients with active tuberculosis [4]. Critchley J.A., Orton L.C. and Pearson F. believe that there is no sufficient data to confirm or refute the use of glucocorticoids as a supplement to anti-tuberculosis drugs [5]. Obviously, the reasoning of the authors of the publications is based on the anti-inflammatory and desensitizing effect of glucocorticoid drugs. At the same time, we must not forget that glucocorticoids are the final link of the complex hypothalamic-pituitary-adrenal adaptation system, the functional activity of which has a clearly expressed daily biorhythm, in the regulation of which glucocorticoids are involved according to the principle of feedback, the use of which in the treatment of patients without taking into account the daily biorhythm of the hypothalamic-pituitary-adrenal system can be accompanied by a negative impact on the adaptation system and the entire body. This issue is not covered in modern literature.

To create an optimal mode of etiopathogenetic therapy for patients with pulmonary tuberculosis, we studied the pathogenetic role of endogenous cortisol and developed ways to correct hormonal homeostasis disorders in tuberculosis.

THE AIM

The aim was to establish the clinical and pathogenetic role of glucocorticoid imbalance as an important link in

the disorder of the homeostasis of the adaptive system in patients with pulmonary tuberculosis and to determine ways of its correction as a way to increase the effectiveness of their treatment.

MATERIALS AND METHODS

The effectiveness of treatment of 304 patients with pulmonary tuberculosis treated with protocol antibacterial therapy was studied. Of these, 134 patients (group 1) received only anti-tuberculosis drugs. 67 patients (group 2) received anti-tuberculosis drugs and glucocorticoids daily, in three doses with a gradual dose reduction before decline. 103 patients (group 3) received antibacterial therapy and glucocorticoids in the morning, once, in a daily dose, every other day, with simultaneous declining without dose reduction. Glucocorticoid drugs were prescribed at a dose adequate for 20-30 mg of prednisolone. The duration of hormone therapy in both groups was 2-3 months, during the period of intensive chemotherapy.

The role of the adaptive system in the pathogenesis of tuberculosis was determined by the functional state of the adrenal cortex, which was estimated by the amount of cortisol in the blood plasma of 76 patients aged 20-59 years (average age was 33,1±1,1 years). There were 61 men (80,3%) and 15 women (19,7%). Disseminated pulmonary tuberculosis was in 28 (36,8%) patients, focal - in 8 (10,5%), infiltrative - in 32 (42,2%) and fibro-cavernous - in 8 (10,5%). The destructive process with bacterial excretion was observed in 70 (82,1%) patients, in 6 patients, tuberculosis was in the infiltration phase, which made it possible to assess the state of the adaptive system in the early period of tuberculosis development and during its progression. The control was the results of a survey of 12 healthy volunteers aged 21-50 years (average age was 27,6±1,5 years). The amount of blood plasma cortisol in the control group was 121,0±5,0 μg/l.

Blood plasma cortisol was determined in 26 (34,2%) patients from group 1, 19 (25,1%) patients from group 2, and 31 (40,7%) patients from group 3. To determine the level of daily fluctuations in cortisol in 18 patients and 12 healthy volunteers, cortisol was determined in the morning (8-9 hours) and in the evening (20-21 hours). Determination of cortisol in the patients' blood plasma was carried out by radioimmunoassay using standard kits from CJS (France) and by the method of enzyme immunoassay using a standard set DRG® Cortisol ELISA (EIA 1887) (DRG International Inc., USA).

The study was conducted in accordance with the ethical standards set out in the Declaration of the Helsinki Medical Assembly. All patients gave their informed consent to the study, approved by the Bioethics Commission of Poltava State Medical University.

Statistical analysis of the results was carried out using Microsoft Excel, the difference in indicators was considered statistically significant at $p<0,05$.

RESULTS

The study found that in patients with pulmonary tuberculosis, the plasma cortisol level averaged 146,5±8,0 μg/l, which significantly exceeded this indicator in healthy people (121,0±5,0 μg/l, $p<0,05$). There weren't detected any age and gender differences in the amount of cortisol in the blood plasma of patients, but dependence on clinical forms of tuberculosis was observed. In patients with focal pulmonary tuberculosis, this indicator was 133,1±9,0 μg/l, which, compared to the norm, showed an increasing tendency, but did not differ statistically (121,0±5,0 μg/l, $p>0,05$). In patients with infiltrative tuberculosis, the level of cortisol increased to 159,6±6,5 μg/l ($p<0,01$), and in patients with disseminated tuberculosis, its level reached 176,8±8,2 μg/l ($p<0,01$) and only in patients with fibrous-cavernous pulmonary tuberculosis, its number was slightly lower than the norm and amounted to 116,3±8,2 μg/l ($p>0,05$).

The duration of the tuberculosis development affected the amount of cortisol, which remained at an increased level, but was characterized by a tendency to decrease as the duration of the disease increased from the onset of the first symptoms to hospitalization. The highest level of cortisol was observed in patients identified in the first month of the disease and was 167,7±12,8 μg/l, after 2-3 months – 162,6±5,9 μg/l, after 4-6 months - 159,2±4,8 μg/l, 7-9 months – 149,1±2,2 μg/l and more than 9 months – 148,7±14,5 μg/l. Although the difference in indicators in the middle of the group did not differ significantly, the correlation coefficient revealed a dependence of indicators on the duration of the disease development and was, respectively, r_{1-2}-0,437, r_{1-3}-0,443, r_{1-4}-0,657 and r_{1-5}-0,707, which indicates a dependence of the decrease in the functional ability of the adrenal cortex on the duration of the tuberculosis development.

Depending on the phase changes of tuberculosis, it was established that during the initial phase of infiltration, the level of cortisol in the blood plasma of patients was 136,5±4,6 μg/l, while the further progression of the disease with the development of the destruction phase was accompanied by a significant growth, and reached 160,3±5,2 μg/l ($p<0,02$).

The level of cortisol in the blood of patients reveals dependence on the clinical manifestations of intoxication. In patients with symptoms of intoxication, the level of cortisol in the blood reached 161,5±6,1 μg/l, while in its absence, this indicator was 139,9±9,0 μg/l ($p<0,02$).

The determination of fluctuations in the level of the blood plasma cortisol in 18 patients in the morning and evening showed that this indicator was, respectively, 146,0±6,8 μg/l and 84,2±5,1 μg/l ($p<0,001$), while in 12 healthy volunteers, these indicators were significantly lower and, respectively, were 121,0±5,0 μg/l ($p<0,05$) and 47,7±4,9 ($p<0,05$) μg/l. The study showed that the amount of cortisol, in both healthy and sick people, was characterized by daily fluctuations with a maximum level in the morning and a significant decrease in the evening. But in tuberculosis patients, the level of cortisol both in the morning and in the evening was significantly higher than normal, which reflected the functional stress of the adaptation system.

Therefore, the determination of the amount of cortisol in the blood plasma of tuberculosis patients is characterized by a regular increase as the disease progresses and a

longer and more severe course of various clinical forms of pulmonary tuberculosis is formed; reflects the natural stress of the activity of the hypothalamic-pituitary-adrenal system, as a system of adaptation of the body under stress, is accompanied by a significant increase in cortisol in the blood and a violation of its daily fluctuations. In the context of the development of the chronic course of tuberculosis, the functional state of the body's adaptive capacity is significantly reduced, which reflects a decrease in the level of cortisol in patients with chronic fibrous-cavernous pulmonary tuberculosis.

The study of the level of cortisol in the blood plasma at the end of the course of hormone therapy established that the mode of administration of glucocorticoid drugs has a significant effect on adrenal function. In patients treated with glucocorticoids daily, the level of cortisol was 86,1±3,8 μg/l, which was significantly lower than normal (121,0±5,0 μg /l, $p<0,05$) and indicated a deep inhibition of adrenal cortex in patients of this group. At the same time, the level of cortisol in patients treated with glucocorticoids every other day was 131,7±1,4 μg/l, which significantly exceeded the the group with daily intake of the drug ($p<0,001$, r-0,761) and indicated the absence of a suppressive effect glucocorticoid on the function of the hypothalamic-pituitary-adrenal system when administered in accordance with its functional activity. The daily biorhythm of cortisol level in patients of this group was also characterized by normalization and was, compared to the control in the morning, 128,0±3,0 μg/l (norm 121,0±5,0 μg/l, $p<0,05$), in the evening – 49,5±2,7 μg/l (norm 47,7±4,9 μg/l, $p>0,05$), which fully corresponded to the control indicators.

Correction of pathogenetic disorders of hormonal homeostasis had a positive effect on the treatment results. In the first weeks of hormone therapy, patients noted a clinical improvement in their well-being, more easily tolerated intoxication and chemotherapeutic stress. Objective measures of treatment effectiveness in hormone therapy groups were the best. So, at the end of inpatient treatment, the frequency of cessation of bacterial excretion in the groups was at the same level and, accordingly, was: in group 1 – 93,7%, in group 2 – 96,1% and in group 3 – 97,9%. Closure of decay cavities was characterized by a significant difference in indicators and was in group 1 - in 69,4% (78 out of 134) patients, in group 2 - in 71,5% (48 out of 76) patients and in group 3 - in 91,3% (94 of 103) patients, $p<0,001$. The use of hormone therapy in accordance with the physiological biorhythm of the hypothalamic-pituitary-adrenal system contributed to a reduction in the duration of hospital stay. For patients in group 3, this indicator was 192,4±1,6 ($p<0,001$) days, while in group 1 it was 232,2±1,9 days, and in group 2 – 231,0±1,5 ($p<0,001$) days.

The results of treatment differed in groups and in residual changes in the lungs after tuberculosis. Large residual changes in the form of foci and pneumofibrosis, tuberculomas, residual cavities with pneumofibrosis in group 1 were 62,7%, with daily administration of glucocorticoids – 40,4% ($p<0,01$) and with intermittent hormone therapy - 21,2% ($p<0,001$).

DISCUSSION

The results of the study showed that in patients with pulmonary tuberculosis, a natural disturbance of the homeostatic balance of the hormonal balance is determined with a significant increase in cortisol in the blood plasma, the level of which increases as the severity of clinical forms of tuberculosis increases, phases of its development, intoxication, which reflects the functional tension of the hypothalamic-pituitary adrenal system, as an adaptive system of the body, the resource of which is characterized by a tendency to a gradual decrease depending on the duration of the disease development. The activity of the adaptive system and the results of determining the daily fluctuations of cortisol in the blood of patients, the level of which, though is different in the morning and evening hours, is confirmed, but in patients these indicators significantly exceed the physiological level, which is an important pathogenetic link for the violation of neuro-hormonal homeostasis, affects the formation of immunodeficiency and the progressive development of the tuberculous process (Yareshko, Kulish, 2020).

Glucocorticosteroid drugs, the effects of which were studied with daily and intermittent administration, were used to correct the identified pathogenetic neuro-humoral disorders. The results obtained after 2-3 months of treatment showed that glucocorticoids actively affect the functional state of the adrenal cortex. With daily administration of glucocorticoids, the level of cortisol in the blood of patients was significantly reduced compared to the norm, which indicated the suppressive effect of glucocorticoids on the function of the hypothalamic-pituitary-adrenal system, which regulates the biosynthesis of cortisol by the adrenal cortex, forming its functional insufficiency. This explains the need to gradually reduce the pharmacotherapeutic dose before canceling hormone therapy in order to avoid withdrawal syndrome.

A different picture was obtained using glucocorticoids synchronized with the daily activity of the hypothalamic-pituitary-adrenal system function. In patients treated with glucocorticoids once, in the morning, in a daily dose every other day, the level of cortisol after completion of the course of hormone therapy decreased to the upper limit of the norm, which indicated the normalization of adrenal function and the absence of a negative effect of the intermittent regime on the functional state of the hypothalamic-pituitary-adrenal system. Stabilization of the biorhythm of the activity of the hypothalamic-pituitary-adrenal system makes it possible to carry out the entire course of hormone therapy with a pharmacotherapeutic dose, to cancel the drug simultaneously, without reducing the dose, regardless of the duration of the course of hormone therapy. That gives reasons to consider glucocorticoids as a factor regulating disorders of neuro-endocrine homeostasis and increasing the effectiveness of treatment of pulmonary tuberculosis when administered synchronously with the physiological biorhythm of the hypothalamic-pituitary- adrenal system.

The results of this work give reason to believe that the goal of the study has been achieved, its originality is con-

firmed by the fact that we did not find similar studies in the available literature, and given that in practical medicine all over the world glucocorticoids are used in the daily administration regime, forming additional complications for a sick person, it is difficult to overestimate the practical significance of the work.

CONCLUSIONS

1. Pulmonary tuberculosis is characterized by a violation of hormonal homeostasis with a regular increase in blood plasma cortisol, shows dependence on the severity of clinical forms of tuberculosis, the phase of the process and intoxication. Disruption of the daily biorhythm of the level of cortisol in tuberculosis patients is manifested by a significantly higher level both in the morning and in the evening. In chronic fibro-cavernous tuberculosis, plasma cortisol levels are below normal.
2. The mode of administration of glucocorticoids in a dose of 20-30 mg for prednisolone at the end of a 2-3 month of hormone therapy significantly affects the level of cortisol in the blood plasma of patients. Daily administration of glucocorticoids reduces the blood plasma cortisol levels, suggesting a suppressive effect of exogenous glucocorticoids on the biosynthesis of endogenous cortisol of the adrenal cortex. The use of glucocorticoid drugs taking into account the daily biorhythm of the functional activity of the hypothalamic-pituitary-adrenal system does not show a negative effect on the level of cortisol in blood plasma, determines the normalization of its level in blood plasma and the daily biorhythm of its fluctuations upon completion of hormone therapy, which indicates the stabilization of the daily biorhythm of functional activity of the hypothalamic-pituitary-adrenal system.
3. Clinical results of glucocorticoid drugs regimens in tuberculosis protocol chemotherapy show mixed influence on the results of treatment effectiveness of patients. Hormone therapy improves the well-being of patients, facilitates the tolerance of the chemotherapeutic load, increases the frequency of closure of cavities, reduces the severity of residual changes, but does not affect the results of cessation of Mycobacterium tuberculosis excretion. The effectiveness of treatment is higher in the intermittent regimen of glucocorticoids using.
4. The use of glucocorticoid drugs in a double physiological dose in accordance with the physiological biorhythm of the daily activity of the hypothalamic-pituitary-adrenal system has no negative effect on the function of the adrenal cortex and on the whole body, does not give complications (cushingoid, adrenal atrophy), normalizes hormonal homeostasis and daily biorhythm of the cortisol level in the blood of patients, ensures the use of a pharmacotherapeutic dose of glucocorticoids throughout the course of treatment, does not require dose reduction before cancellation, which provides a positive clinical effect of glucocorticoid therapy of pulmonary tuberculosis.

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Conflict of interest:
The Authors declare no conflict of interest.

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