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DIAGNOSTIC VALUE OF CORTISOL IDENTIFICATION IN BIOLOGICAL BODY FLUID IN CASE OF INFECTIOUS DISEASES (LITERATURE REVIEW)

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Disorders of control mechanisms caused by glucocorticoid hormones of adrenal cortex have a significant role in the pathogenesis of infectious diseases, first of all, due to cortisol, one of the key hormones with anti-inflammatory activity. Currently the conception about the mechanisms of cortisol influence, its functional abilities, connection with immune and nerve cells, involvement in cytokine regulation, features of free-radical oxidation has been extended. There has been identified the dependence of cortisol influence upon the isoform, amount and affinity of its receptors on target cells. The present review describes the study results concerning cortisol level in case of the most often occurring infectious diseases in children – acute respiratory and intestinal infections, infectious diseases of the central nervous system. There has been noticed a considerable data variability about cortisol level in normal state and in pathological one, however, the majority of articles have detected its connection with clinical manifestations and outcomes of the diseases. The study of cortisol level in cerebrospinal fluid is of a special interest in case of neuroinfections, specifying its direct connection with the disease severity and aetiology that gives new possibilities to develop effective diagnostic criteria. In general, the literature data specifies the advanced study of disorders of hypothalamus-hypophysial-adrenal gland functioning, receptor apparatus of target cells, as well as interrelations of cortisol with immune system in case of infectious diseases to reveal new criteria for diagnostics, course prediction and disease outcome, therapy correction.

Keywords: cortisol; respiratory infections; intestinal infections; hepatitis; neuroinfections; blood serum; cerebrospinal fluid.

ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ОПРЕДЕЛЕНИЯ КОРТИЗОЛА В БИОЛОГИЧЕСКИХ ЖИДКОСТЯХ ПРИ ИНФЕКЦИОННЫХ ЗАБОЛЕВАНИЯХ (ОБЗОР ЛИТЕРАТУРЫ)

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В патогенезе инфекционных заболеваний значимую роль играют нарушения регуляторных механизмов, оказываемых глюкокортикоидными гормонами коры надпочечников, в первую очередь кортизолом — одним из ключевых гормонов, обладающих противовоспалительной активностью. В настоящее время расширились представления о механизмах воздействия кортизола, его функциональных возможностях, связи с иммунными и нервными клетками, участии в цитокиновой регуляции, характеристиках свободно-радикального окисления. Установлена зависимость воздействия кортизола от изоформы, количества и аффинности его рецепторов на клетках-мишенях. В настоящем

обзоре представлены результаты исследования уровня кортизола при наиболее часто встречающихся инфекционных заболеваниях у детей – острых респираторных, кишечных и центральной нервной системы. Отмечен значительный разброс данных об уровне кортизола в норме и при патологии, однако в большинстве работ установлена его связь с клиническими проявлениями и исходами инфекционных заболеваний. Представляют интерес исследования уровня кортизола в цереброспинальной жидкости при нейроинфекциях, указывающие на его прямую связь с тяжестью и этиологией заболевания, что открывает новые возможности для разработки эффективных критериев диагностики. Данные литературы указывают на перспективность изучения нарушений функционирования гипоталамо-гипофизарно-надпочечниковой оси, рецепторного аппарата клеток-мишеней, а также взаимосвязей кортизола с иммунной системой при инфекционных заболеваниях с целью выявления новых критериев для диагностики, прогнозирования течения и исхода заболевания, коррекции терапии.

Ключевые слова: кортизол; респираторные инфекции; кишечные инфекции; гепатит; нейроинфекции; сыворотка крови; цереброспинальная жидкость.

INTRODUCTION

Glucocorticoid hormones of the adrenal cortex, primarily cortisol, have a pronounced regulatory and anti-inflammatory activity, which determines their role in the pathogenesis of infectious diseases. Cortisol is synthesized by the adrenal cortex under the influence of adrenocorticotrophic hormone (ACTH), and its secretion is regulated by the corticotropin-releasing hormone produced by the hypothalamus [3, 11, 22]. Cortisol secretion occurs according to the circadian rhythm, with a maximum level in the blood in the morning and a minimum level at night [6]. Under normal conditions, approximately 95% of cortisol levels in the blood are bound to carrier proteins, namely, plasma corticosteroid-binding globulin (transcortin) and albumin, while the free fraction of the hormone has bioactivity [25]. In the last two decades, other organs such as the thymus, intestine, and brain can also synthesize glucocorticoids, which is probably important for maintaining local homeostasis [39, 41, 42, 45]. The understanding of the mechanisms of the action of cortisol on various tissues and organs, its functionality, relationship with immune and nerve cells, interaction with cytokine regulation, and characteristics of free radical oxidation has significantly expanded [4, 17, 28, 49].

During the infectious process, the immune system is activated, pro-inflammatory cytokines, namely, interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), are released into the bloodstream, which contribute to the activation of the hypothalamic–pituitary–adrenal (HPA) axis and increased cortisol production [28]. As it enters the focus of inflammation, cortisol exerts an anti-inflammatory effect; reduces capillary permeability; reduces the expression of adhesion molecules on the membranes of endothelial cells; reduces the cytotoxic activity of cells, stabilizing the membranes of lysosomes and reducing the release of lysosomal enzymes; suppresses the expression of IL genes; inhibits the proliferation and migration of immunocompetent cells; induces apoptosis of lymphocytes and eosinophils; prevents the interaction of immunoglobulins (Ig) with mast cells and macrophages; reduces the formation and release of histamine from mast cells; and inhibits the expression of antigens on the surface of macrophages and production of IL-1 [3, 22, 28, 44]. Differences in the effect of cortisol on cells depend on its concentration. Low concentrations of endogenous cortisol increase the sensitivity of the immune system to a pathogen by activating cytokine receptors and complement factors, whereas high concentrations suppress immune responses [28]. A low level of glucocorticoids was found to enhance the production of IL-1 [11].

Cortisol influences cells as a result of the interaction with cytosolic and nuclear glucocorticoid receptors (GR), which have various isoforms (alpha, beta, P, etc.). This enables the hormone to interact with chromatin and influence gene expression, which leads to a decrease in the number of certain proteins in the cells [3]. GRs are expressed by nearly all cells in the body, and the effects differ depending on the cell type [14, 28]. The GH-alpha isoform represents a classical receptor that mediates the hormonal response. GR-beta is presumably an inhibitor of GR-alpha [30, 46]. The predominance of the expression of one or another receptor isoform determines the efficiency of the effect of cortisol on the target cell. Recent experimental studies, which aimed at examining the causes of cortisol resistance, have shown that pro-inflammatory cytokines (TNF-α and IL-1) increase the expression of both GR isoforms, but with a predominance of GR-beta [30, 46]. Patients with sepsis and septic shock were found to have a decrease in affinity for GR [40]. Experimental data show that a septic condition leads to a decrease in GR expression in the liver [33]. In the study of the receptor apparatus in children and adults with serious conditions, a decrease in GR expression on neutrophils, lymphocytes, and mono-

cytes was noted, which correlated with an adverse outcome of septic shock, especially in patients with high serum levels of cortisol [23, 33, 48]. The activation of the HPA axis during a critical condition may be accompanied by peripheral adaptation through the number of GRs and their affinity.

In clinical and laboratory practice, specialists are limited to determining the cortisol level in biological fluids without assessing the state of its intracellular receptors and level of binding proteins. Perhaps, this is one of the reasons, along with the difference in the methods of determination and test systems used, that cause a significant scatter of data on the cortisol level under normal conditions and infectious pathology in scientific literature. This review presents the results of a study of the cortisol levels in biological fluids (blood and cerebrospinal fluid [CSF]) of adults and children with common infectious diseases, which were published in Russian and international literature and available in the databases of PubMed and eLibrary.

INFECTIOUS DISEASES OF THE RESPIRATORY TRACT

Respiratory tract diseases rank one of the leading places among infectious diseases. In acute bronchopulmonary diseases in pediatric patients aged 1–6 months, the cortisol level increased in the blood serum of patients with bronchitis (281.82 ± 29.63 nmol/L) and pneumonia (320.78 ± 35.69 nmol/L) in relation to the comparison group (203.21 ± 28.39 nmol/L) [15]. Moreover, the maximum increase (420.62 ± 81.73 nmol/L) in cortisol levels was noted in patients with a rapidly arrested inflammatory process in the lungs. Patients with a longer duration of pneumonia had no significant change in cortisol levels. Hypocortisolemia below 100 nmol/L was associated with a severe disease with clinical manifestations of adrenal insufficiency in these patients [15]. A low cortisol level was noted in children aged 3–6 years in the acute period of recurrent obstructive bronchitis induced by acute respiratory viral infections (ARVI) compared with apparently healthy children, and its significant decrease after therapy. A correlation was found between the cortisol level and immune response, indicating its involvement in the regulation of the activity of immunocompetent cells [21].

Frequently ill (FIC) and episodically ill (EIC) children with ARVI, including those with lesions of the lower respiratory tract and pneumonia, were examined [5]. The cortisol levels in these pediatric patients were compared during the ARVI period and after recovery. As a result, in the acute period of ARVI in FIC, the cortisol level was significantly lower than that after recovery (297.17 ± 188.9 and 518.7 ± 125 nmol/L, respectively). A parallel decrease in IgA level in the presence of ARVI was also found in this group. In EIC, the cortisol level during these periods did not show significant differences (361.3 ± 151 and 434.03 ± 102.8 nmol/L) [5].

Different variants of the reaction of the adrenal glands to a viral infection in pediatric patients aged 1–10 years old, with ARVI of varying severities, were established [12]. A significant increase in cortisol levels in the blood serum in the acute period (>1600 nmol/L) indicated a moderate disease with short-term severe intoxication without complications. A moderate increase (800–1600 nmol/L in 37.1% of children) was noted in severe ARVI with prolonged severe intoxication and frequent bacterial complications. With serum cortisol levels of 300–800 nmol/L, ARVI proceeded with mild intoxication and without complications. Bacterial complications were also registered in cortisol levels <300 nmol/L (31.4%) [12]. A low cortisol level is an indicator of exhaustion in response to stress, which provokes the occurrence of complications. Other results were obtained when assessing the relationship between cortisol levels and outcomes of community-acquired pneumonia, and the cortisol level in the blood serum at admission was significantly higher in patients who died or were admitted to the intensive care unit than in patients who had recovered (360 μg/L versus 238 μg/L) [43]. Thus, an elevated cortisol level is a biomarker of predicting adverse outcomes in patients with community-acquired pneumonia.

The relationship between cortisol parameters in patients with community-acquired pneumonia (bacterial, viral, and mixed etiology) and the severity of the condition and mortality within 30 days was analyzed [35]. Serum cortisol levels in patients with critical illness were higher than those without critical illness (median (*Me*), 972 nmol/L versus 598 nmol/L) and increased with a worsening condition. Cortisol levels were also increased in non-survivors compared with survivors [*Me*, 870 nmol/L vs 602 nmol/L]. The threshold cortisol level in the blood serum (795 nmol/L) has been established, which enables the prediction of an unfavorable outcome of community-acquired pneumonia [35].

ACUTE INTESTINAL INFECTIONS (AII) AND HEPATITIS

In Russia, intestinal infections consistently rank second and third among all infectious diseases in pediatric patients, which leads to the search for new approaches to diagnosing and predicting the disease

course. Examination of children with AII (such as dysentery, salmonellosis, and mixed forms of AII) revealed an increase in cortisol levels in the blood serum in comparison with the control in the acute period in all examined pediatric patients (819.1 nmol/L, dysentery; 816 nmol/L, salmonellosis; 868 nmol/L, mixed form; 307.2 nmol/L, control group) [10]. With increasing disease severity, the cortisol level elevated in all groups, whereas in mixed infection, the increase in cortisol level was less significant (946.2 nmol/L) than that in dysentery (1159.1 nmol/L) and salmonellosis (1092.1 nmol/L) [10]. According to the authors, such a hormonal reaction indicates the depletion of the functional reserves of the adrenal glands and/or a decrease in sensitivity of hormone-synthesizing cells to ACTH because of severe endotoxinemia in patients with coinfection. In the study of pathomorphological changes in the intestinal mucosa in pediatric patients aged <1 year, who died from various AIIs, high levels of cortisol in the blood serum (5487.62 ± 34.5 nmol/L) and IgE were noted, whereas IgA and IgG levels did not increase and were lower in children aged 1–3 months compared with newborns [16].

Several studies have examined the cortisol level in the blood serum of patients with hepatitis of various etiologies and severity. In the acute period of mild hepatitis A and B in pediatric patients, the average cortisol levels in the blood serum were at maximum in hepatitis A (796.35 ng/mL at a rate of 617.96 ng/mL) and minimum in hepatitis B (604.38 ng/mL), accompanied by a significant increase in the IgE level (191.46 and 242.22 IU/mL, respectively) compared with the norm (39.47 IU/mL) [8].

Other data indicate different variants of hypercortisolemia in pediatric patients with viral hepatitis A, B, C, and D. An adequate response of stress systems in hepatitis A, B, C, and D is accompanied by a 3–4-fold increase in cortisol level in the acute period (911.39 ± 84.12 nmol/L in girls and 896.26 ± 96.26 nmol/L in boys) [2]. The ACTH level also rises to the same extent. A comprehensive examination of patients with hepatitis revealed three profiles of hypercortisolemia, which differ in the dynamics of cortisol levels, nature of the clinical course, and disease outcome, as well as changes in the subpopulation composition of blood lymphocytes, viral load, and biochemical criteria for damage to hepatocytes. Significant changes in the immune status (a total decrease in $CD3^+$ cells, hyperactivation of T-killers, and an increase in B-lymphocytes), i.e., a decrease in the cortisol level against the disease progression, indicate exhaustion in the early stages of the pituitary–adrenal system, which may be a prognostic sign of hepatic coma [2].

INFECTIOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM

Infectious diseases of the central nervous system (such as meningitis and encephalitis) are often associated with severe complications and high mortality. The inflammatory process in the central nervous system can contribute to the dysfunction of the HPA axis. High concentrations of cortisol and components of inflammation can adversely affect the brain tissues [7, 47]. On the contrary, with the generalization of the inflammatory process, the function of the adrenal glands can be impaired, which leads to an inadequate response to ACTH stimulation and disruption of cortisol production.

A study presented changes in the blood serum levels of cortisol and ACTH in meningitis in several groups with enteroviral meningitis, viral meningitis of unclear etiology, purulent meningitis of unclear etiology, and meningoencephalitis of unclear etiology [13]. In all groups, the cortisol levels were significantly increased in the acute period (from 761.1 ± 75.0 nmol/L in enteroviral meningitis to 1594.4 ± 183.9 nmol/L in purulent meningitis) compared with the control group (342.3 ± 13.6 nmol/L). Moreover, the ACTH level decreased, which was a consequence of the pathogen effect on the pituitary gland. The highest cortisol level was noted in bacterial purulent meningitis (BPM) compared with viral ones. In addition, cortisol levels in BPM were significantly higher in the severe form than in the moderate form. No significant differences were registered in the group with viral meningitis [13].

In patients with acute BPM of various etiologies, the cortisol levels in the blood serum of patients with pneumococcal meningitis were not different from those with meningococcal meningitis (377.4 and 326.5 nmol/L, respectively), exceeding those in the control group (162.9 nmol/L) [9]. A previous study revealed changes in the cortisol levels over time in pediatric patients with bacterial and viral neuroinfections [1]. The maximum cortisol level was detected in the acute period of BPM (2150.3 ± 191.2 nmol/L) compared with viral encephalitis (931.6 ± 225.8 nmol/L). Differences in cortisol levels in pediatric patients with emergency and critical conditions were noted depending on the nosological form and disease course [1]. The association of the HPA axis with inflammation markers and disease severity in pediatric patients with meningococcal infection was examined [47]. The results showed a difference in cortisol levels in severe and extremely severe generalized forms of meningococcal infection, as the cortisol level was the highest in meningococcal meningitis, associated

with septic shock, and it was lower in fulminant meningococcal sepsis [47]. Other authors did not reveal significant differences in the cortisol level in the blood serum in moderate and severe BPM (310.4 and 317.03 nmol/L, respectively) [7].

The levels of cortisol and ACTH, depending on the disease outcomes in pediatric patients in a septic state, were also examined [34]. In cases with a lethal outcome, cortisol levels were lower (0.62 μmol/L), and ACTH levels were higher (1234 ng/l). Survivors had higher cortisol values (0.89 μmol/L) and a moderately increased ACTH level (231 ng/L) [34]. Other authors have come to the same conclusions. Pediatric patients who died from fulminant meningococcemia had a lower cortisol/ACTH ratio than survivors [24]. This was also confirmed in the studies where the cortisol level in deceased pediatric patients was lower (*Me* 654 nmol/l) than in survivors (*Me* 2184 nmol/l) [29]. ACTH levels in deceased children were higher (*Me* 1271 ng/l) than in survivors (85 ng/l). The mean cortisol/ACTH ratio decreased depending on the disease severity. These results indicate impairment of the direct link and feedback in the functioning of the HPA axis with the progression of the infectious process [29]. At the initial stage of the meningococcal infection in children, the levels of ACTH and cortisol were increased and then decreased [27]. The authors suggested that the decrease in cortisol level during infection may be secondary, since high concentrations of pro-inflammatory cytokines (TNF-α and IL-1) can block the stimulatory effect of corticotropin-releasing hormone on the pituitary gland and, consequently, ACTH-induced cortisol release [27].

Several studies have analyzed the cortisol level in the CSF in neuroinfections. CSF is known to have limited contact with blood given the barrier structure of the central nervous system, which includes the blood–brain barrier [18]. Analysis of literature data showed the possibility of the transport of hormones of peripheral endocrine glands, including cortisol, into the CSF [31, 37]. CSF cortisol may suppress intrathecal inflammation, improving the outcome of bacterial meningitis, and long-term exposure to high levels of cortisol has a neurotoxic effect [19], which may affect the functioning of the HPA axis. Certain studies also determining cortisol levels in the CSF and studying its dynamics in neuroinfections.

Studies have revealed an increase in the CSF levels of ACTH and cortisol with BPM of varying severity [7]. In moderate BPM, the cortisol level in the CSF was 88.18 nmol/L; severe course, 104.1 nmol/L; and conditional control, 64.75 nmol/L. The dependence of the cortisol level in the CSF on both the severity of the condition and etiology of meningitis was noted [19]. The maximum levels of cortisol in the CSF were established in severe BPM with lethal outcomes (121.6 nmol/L in meningococcal meningitis and 118.7 nmol/L in pneumococcal meningitis). In the case of a viral infection, the cortisol level was lower (46.2 nmol/L with moderate enteroviral meningitis, 70.2 nmol/L with moderate herpesvirus meningitis, and 61.1 nmol/L with severe herpesvirus infection). A positive correlation of the cortisol level in the CSF and blood serum in BPM was established. The author proposed to use the cortisol level as a marker for differentiating bacterial and aseptic meningitis [19].

This is confirmed by data showing that cortisol levels in BPM are higher than in aseptic meningitis, while the CSF level of cortisol correlated with serum cortisol [38]. Studies have shown higher cortisol levels in the CSF in patients with pneumococcal meningitis than in those with meningococcal meningitis (318 and 171 nmol/L, respectively) [26]. In the blood serum, no such significant differences were noted (1145 and 1058 nmol/L in pneumococcal and meningococcal meningitis, respectively).

Serum cortisol and CSF levels were compared in adult patients with meningitis. The serum and CSF cortisol concentrations in patients with BPM correlated with each other and exceeded significantly those in patients with aseptic meningitis ($p < 0.001$) [32]. The cortisol level in the CSF of 46.1 nmol/L was suggested as the optimal threshold for the differential diagnostics of meningitis.

A comparative analysis of the CSF level of cortisol in adult patients with tuberculous and aseptic (viral) meningitis [36] revealed that cortisol levels in tuberculous meningitis are significantly higher than those in aseptic meningitis (8.82 ± 0.67 and 3.47 ± 0.96 μg/dL) and the control group (1.05 ± 0.36 μg/dL). According to the authors, cortisol can be used as a diagnostic marker in tuberculous meningitis.

CONCLUSION

The contemporary scientific literature indicates that the cortisol level in biological fluids in infectious diseases depends on many factors [27, 32, 37, 38, 47]. A significant variation is demonstrated in the blood serum level of cortisol; however, most studies have emphasized the relationship of its level with the clinical presentation and disease outcome. In neuroinfections, it is promising to study the cortisol level in the CSF, indicating its direct dependence on the severity of the condition and disease

etiology. Multiple correlations of cortisol with markers of blood–brain barrier damage, neurospecific proteins, expression of neuroprotective factors, and metabolic parameters have been established [20]. The literature emphasizes the prospects of studying dysfunctions of the HPA axis, receptor apparatus of target cells, and association of cortisol level with the immune system in infectious diseases to identify new criteria for diagnosing, predicting the disease course and outcomes, and correcting the therapy.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article, and they have read and approved the final version before its publication.

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