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Реферати

ОЦІНКА ФУНКЦІОНАЛЬНОГО СТАНУ ДИХАЛЬНОЇ СИСТЕМИ У ДІТЕЙ З БРОНХІАЛЬНОЮ АСТМОЮ ТА АЛЕРГІЧНИМ РИНІТОМ

Шумна Т.Є., Федосєєва О. С., Зінченко Т. П.

Дослідження функції зовнішнього дихання методом спірометрії проводилося у 138 дітей від 7 до 17 років, з них, І групу спостереження склало 78 дітей з бронхіальною астмою; ІІ групу - 40 дітей з алергічним ринітом; ІІІ групу - 20 практично здорових дітей. Встановлено, що у дітей з бронхіальною астмою, вентиляційна функція легенів за обструктивного типу була порушена в 67,95% випадків, за рестриктивного - в 16,67% і за мішаного - у 2,56% пацієнтів. У дітей з алергічним ринітом обструктивні вентиляційні порушення в 32,5% випадків були обумовлені наявністю поєднаної ортодонтичної патології, а саме, дистальним прикусом і в 12,5% - наявністю хронічного алергійного запалення респіраторного тракту без зубо-щелепних аномалій, що вимагало індивідуального підходу у виборі лікування і профілактики. Спірометрію необхідно проводити всім дітям з клінічними симптомами респіраторної алергії, а показники функціонального стану дихальної системи необхідно враховувати як для визначення типу вентиляційних порушень у дітей з бронхіальною астмою, так і для диференціальної діагностики хронічного алергійного запалення респіраторного тракту і супутньої ортодонтичної патології у дітей з алергічним ринітом.

Ключові слова: бронхіальна астма, алергічний риніт, діти, спірометрія.

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ОЦЕНКА ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ДЫХАТЕЛЬНОЙ СИСТЕМЫ У ДЕТЕЙ С БРОНХИАЛЬНОЙ АСТМОЙ И АЛЛЕРГИЧЕСКИМ РИНИТОМ

Шумная Т.Е., Федосеева Е. С., Зинченко Т. П.

Исследование функции внешнего дыхания методом спирометрии проводилось у 138 детей от 7 до 17 лет, из них, I группу наблюдения составило 78 детей с бронхиальной астмой; II группу – 40 детей с аллергическим ринитом; III группу – 20 практически здоровых детей. Установлено, что у детей с бронхиальной астмой, вентиляционная функция легких по обструктивному типу была нарушена в 67,95% случаев, по рестриктивному – в 16,67% и по смешаному – у 2,56% пациентов. У детей с аллергическим ринитом обструктивные вентиляционные нарушения в 32,5% случав были обусловлены наличием сочетанной ортодонтической патологией, а именно, дистальным прикусом и в 12,5% - наличием хронического аллергического воспаления респираторного тракта без зубо-челюстных аномалий, что требовало индивидуального подхода в выборе лечения и профилактики. Спирометрию необходимо проводить всем детям с клиническими симптомами респираторной аллергии, а показатели функционального состояния діхательной системы не обходимо учитывать как для определения типа вентиляционных нарушений у детей с бронхиальной астмой, так и для дифференциальной диагностики хронического аллергического воспаления респираторного тракта и сопутствующей ортодонтической патологии у детей с аллергическим ринитом.

Ключевые слова: бронхиальная астма, аллергический ринит, дети, спирометрия.

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GLUCOCORTICOIDS AS IMMUNOSTIMULATORS IN PATHOGENETIC THERAPY OF TUBERCULOSIS

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The immunostimulating effect of corticosteroids in the complex treatment of tuberculosis patients when they are administered in a double physiological dose, every other day, taking into account the circadian rhythm of the function of the hypothalamic-pituitary-adrenal axis was substantiated in the article. Whereas with daily administration, corticosteroids have shown an immunosuppressive effect. Peripheral blood B-lymphocytes are not sensitive to glucocorticosteroid drugs.

Key words: tuberculosis, pathogenetic therapy, glucocorticosteroids.

This work is a fragment of the research project "To study the effectiveness of pathogenetic agents in the complex treatment of destructive pulmonary tuberculosis with resistance to antibacterial drugs", state registration No. 0117U000304.

Tuberculosis (TB) disease is the result of the organism's immune response to infection with Mycobacterium tuberculosis (Mtb), but becoming infected with Mtb does not mean being sick. According to data of the World Health Organization, no more than 10% of infected people become ill during their lifetime, which indicates the high effectiveness of the human body's defense system. The main condition for tuberculosis development is immunodeficiency disease. The modern medical guideline for tuberculosis

treatment involves only antibacterial drugs, and such a resource as pathogenetic therapy, aimed at restoring the protective capacity of the patient's organism, remains unused.

An important means of pathogenetic therapy of tuberculosis are glucocorticoid (GCs) medications, in which product label tuberculosis is on the list of contraindications due to their immunosuppressive effect. Because of the wide range of biological activity, anti-inflammatory and desensitizing action, GCs are still used in the treatment of patients with tuberculosis [3, 5, 7].

The regulatory effect of GCs on lymphocytes is characterized by a circadian rhythm, while in the morning lymphocytes are more resistant to the cytotoxic effects of GCs, and in the evening their sensitivity increases [6]. The circadian rhythm of quantitative changes in subpopulations of lymphocytes and cortisol shows a high correlation. In physiological concentrations, cortisol is a necessary factor in the formation of the inductive phase of the immunological response [2, 10]. Moreover, in high doses, GCs suppress, and in low doses they increase a resistance to infections of experimental animals. High doses of GCs can even show cytolytic activities on lymphocytes [6]. That is why in the early period the use of GCs in the treatment of tuberculosis and non-specific diseases was accompanied by the development of "steroid" tuberculosis [1]. Similar reports have contributed to limit the use of GCs in the treatment of patients with tuberculosis. Prescribing them to such patients was considered illogical and harmful, since immunodeficiency is the main condition for the development of tuberculosis.

Given the results of scientific studies on the circadian rhythm of quantitative changes in GCs and lymphocytes, we have developed a method of hormone therapy for patients with tuberculosis with the administration of corticosteroids every other day, taking into account the circadian rhythm of the hypothalamic-pituitary-adrenal (HPA) axis. As a result, their negative impact on the immune system was leveled, which made it possible to carry out the entire course of hormone therapy at a dose of 20-30 mg of prednisolone, lasting at least 2 months and to withdraw it simultaneously without tapering the dose. Complications and immunosuppression with this method of hormone therapy are absent.

The purpose of the study was to substantiate the immunostimulatory effect of corticosteroids when administered in a double physiological dose, every other day, taking into account the circadian rhythm of HPA axis functioning in the conditions of complex treatment of patients with tuberculosis.

Materials and methods. The effectiveness of treatment of 304 patients with pulmonary tuberculosis was studied. 134 of them were in the 1st group: received only anti-tuberculosis chemotherapeutics. The 2nd group consisted of 67 patients who received chemotherapy and prednisolone daily in three doses with gradual dose reduction before GCs withdrawal. The 3rd group consisted of 103 patients who received chemotherapy and prednisolone according to the proposed method, with simultaneous GCs withdrawal, without dose tapering.

The functional state of the immune system was determined in 141 patients aged 19-65 years (mean age was 35.9±1.3 years), there were 38 women (27.0%), 103 (73.0%) men. Distribution by clinical forms of pulmonary tuberculosis: in 34 (24.1%) it was focal, in 45 (31.9%) – infiltrative, in 48 (34.0%) – disseminated and in 14 (10.0%) – fibrous–cavernous one. In 108 (76.6%) patients the tuberculous process was destructive and bacteriologically proven.

Overall quantitative indices of cellular, humoral, and phagocytic immunity were determined. The functional state of T-lymphocytes was determined by skin sensitivity to tuberculin with PPD 2 T.U. The humoral immunity was determined by the number of circulating B-lymphocytes, and their functional activity by quantitative changes in plasma immunoglobulins A, M, G. Phagocytic system state was determined by phagocytic activity and phagocytic index of polymorphonuclear neutrophils (PMNs) and mononuclear phagocytic system (MPS).

Examinations were performed at hospitalization of patients, after 2-3 months and at the end of standard treatment guidelines. In accordance with the purpose of the study, we carried out an analysis of the results obtained in 2-3 months, when the intensive phase of chemotherapy of patients with tuberculosis was completed. This made it possible to make a comparative assessment of the effect of GCs on the immune system when administered daily in 3 doses and once, in the morning, every other day.

The selection and examination of patients complied with the principles of biomedical ethics. Study results were analyzed with an Excel computer package for Windows XP, the difference was considered statistically significant at $p < 0.05$.

Results of the study and their discussion. Results of the study showed that, depending on the treatment regimen, GCs had different effects on the immune system of patients. Thus, after 2-3 months of treatment, the total count of lymphocytes in patients of Group 1 who received only anti-TB chemotherapy, was 2.02 ± 0.12 g/l, which corresponded to the norm. The situation was similar in patients of the 3rd group who received GCs every other day, in the intermittent regimen. In them, this index increased to the normal

level from 1.65±0.08 G/l to 2.03±0.07 G/l (p0.01). And only in the group of patients who received GCs daily in three doses, the level of lymphocytes remained at the initial value level (1.49±0.10 G/l) and amounted to 1.64±0.12 G/l (p >0.05).

T-lymphocytes count was characterized by ambivalent indices. Thus, in patients of the 1st group after 2-3 months of treatment, their number was 0.96±0.11 G/l with a tendency to increase (0.74±0.12 G/l, p> 0.05). In patients of the 2nd group, their number decreased to 0.61±0.05 G/l compared with the initial level (0.79±0.08, p> 0.05). And only in patients of the 3rd group T-lymphocytes' count increased to normal value and amounted to 1.21±0.04 G/l, which significantly exceeded the initial level (0.71±0.05, p <0.01). Correlation analysis of the results confirmed the relationship between changes in the number of lymphocytes and their T-subpopulation with the administration regimen of corticosteroids (r=0.515). The results confirmed that GCs with daily administration showed an immunosuppressive effect on the T-cell immune system, whereas with intermittent administration, their action was characterized by an immunostimulatory effect with the T-cell immunity normalization by the end of hormone therapy.

Humoral immunity was less sensitive to GCs administration. Thus, the number of B-lymphocytes in the peripheral blood of patients with tuberculosis averaged 0.30±0.03 G/l, which reflected a tendency to increase compared to healthy patients (0.23±0.03 G/l, p> 0.05). After 2-3 months of treatment, the number of B-lymphocytes was characterized by a tendency to decrease in patients of the 1st group from 0.30±0.03 G/l to 0.25±0.03 G/l (p> 0.05), in the 2nd group – from 0.30±0.02 G/l to 0.27±0.02 G/l (p>0.05) and in the 3rd group – from 0.31±0.03 G/l up to 0.24±0.002 G/l (p>0.05), approaching the normal range.

Functional activity of B-lymphocytes by determining the amount of serum immunoglobulins also changed little. In patients with tuberculosis, a significant increase was found only in IgG, and averaged 12.53±0.37 G/l, which exceeded the normal range of 10.21±0.21 G/l (p<0.001). IgA and IgM were 2.33±0.15 G/l and 1.14±0.12 G/l, respectively, which significantly exceeded the corresponding control values (2.10±0.14 G/l and 1.21±0.07 G/l, p>0.05). After 2-3 months of treatment, IgA tended to decrease: in patients of the 1st group from 2.28±0.13 G/l during hospitalization to 2.20±0.13 G/l (p>0.05), in the 2nd group – from 2.01±0.23 G/l to 1.60±0.23 G/l (p>0.05), and in the 3rd group – from 2.39±0.13 G/l to 2.20±0.09 G/l (p>0.05).

A similar trend was typical for IgM, the amount of which compared to baseline varied in patients of Group 1 – from 1.25±0.15 G/l to 1.15±0.17 G/l (p>0.05), in Group 2 from 1.04±0.17 G/l to 0.96±0.22 G/l (p>0.05) and in Group 3 – from 1.16±0.07 G/l to 1.17±0.08 G/l (p>0.05).

The amount of IgG in patients of the 2nd group was dependent on hormone therapy and was characterized by a decrease from 11.99±0.42 G / l to 10.35±0.25 G/l (p<0.05), whereas in patients of the 1st and 3rd groups this indicator did not change significantly from 12.98±0.31 G/l to 12.17±0.39 G/l (p>0.05) and from 12.80±0.34 G/l to 12.03±0.15 G / l (p>0.05), respectively.

The effect of corticosteroid therapy regimens on the phagocytic system after 2-3 months of treatment was ambivalent. Thus, in patients of the 1st group, the functional activity indicators PMNs and MPS in comparison with the initial level, respectively, showed a tendency to increase the neutrophil phagocytic rate (NPR), neutrophil phagocytic count (NPC), monocytes phagocytic activity (MPA) and monocyte phagocytic count (MPC) from 45.5±2.3% to 49.8±2.4% (p>0.05), from 2.4±0.3 to 2.7±0.2 (p>0.05), from 29.5±2.2% to 33.7±0.2% (p>0.05) and from 1.5±0.2 to 1.7±0.2 (p>0.05).

In patients of the 2nd group, phagocytosis indices remained at the level of initial values with a downward trend and, respectively, amounted to 53.2±1.5% and 51.5±1.5% (p>0.05), 2.5±0.1 and 2.4±0.1 (p>0.05), 28.6±0.9% and 28.4±1.0% (p>0.05), 1.8±0.1 and 1.7±0.3 (p>0.05).

And only in patients of the 3rd group there an increase of these indicators: from 50.8±1.6% to 57.1±1.4% (p<0.05), from 2.5±0.1 to 2.9±0.1 (p<0.01), from 32.1±1.4% to 33.8±1.3% (p>0.05) and from 1.7±0.1 to 1.8±0.1 (p>0.05).

More accurate results of the corticosteroids effect on phagocyte function were obtained in vitro studies under the influence of a stress dose (100 μg%) of cortisol. The NPR, NPC, MPA and MPC indices in healthy people decreased, respectively, from 72.8±0.98% to 50.5±2.2% (p<0.01), from 3.96±0.12 to 2.80±0.14 (p<0.01), from 44.0±1.0% to 35.8±1.34% (p<0.01), and from 3.3±0.14 to 2.5±0.17 (p<0.05).

Similar changes in these indicators of phagocytic function of PMNs and MPS were found in patients with tuberculosis. The decrease in NPR, NPC, MPA and MPC was from 54.3±1.6% to 38.9±1.9% (p<0.01), from 2.8±0.14 to 2.23±0.09 (p<0.01), from 37.2±1.1% to 31.3±1.4% (p<0.01), and from 2.1±0.08 to 2.0±0.1 (p<0.05).

The study showed that antibacterial therapy received by patients with tuberculosis is directed against the pathogen and, according to the results of Group 1, had no direct effect on immunological protection. The use of corticosteroids in the complex treatment of patients with tuberculosis had an effect

on various parts of the body's immune defense and depended on the administration regimen. With daily administration, GCs suppressed T-cell and phagocytic immunity, as evidenced by their performance after 2-3 months of treatment of patients of Group 2, in which they were reduced and corresponded to the level of the initial values detected during hospitalization, which explained the reasons for the development of complications therapy with GCs. At the same time, when GCs were administered for a long time, they inhibited the functional activity of mononuclear phagocytes (MNF) to a lower level of migration and adhesion, and inhibited chemotaxis and functional activity [9].

GCs also affected PMNs, reducing the superoxide production, inhibiting the release of lysosomal enzymes, and with prolonged action it suppressed the cytotoxic effect of phagocytes, which led to a decrease in phagocytic protection [1].

In patients with tuberculosis, changes in the functional activity of peripheral blood phagocytes showed only a downward trend, while in vitro addition of hydrocortisone to the incubation medium in a stress dose showed a statistically significant suppressive effect on PMNs and MPS in both healthy volunteers and patients with tuberculosis.

The results of examination of patients of the 2nd group after 2-3 months of chemotherapy showed that GCs in the daily administration regimen caused a decrease in peripheral blood of the total number of lymphocytes and their T-helper (CD4+) subpopulation. This could be due to the redistribution of lymphocytes in the organism. However, it is known that GCs can inhibit the ability of T-helper cells (CD4+) to proliferate, and moreover, they can be an inducer of apoptosis of various subpopulations of lymphocytes [4]. Hypersecretion of cortisol is a natural factor in the induction of programmed death of peripheral blood leukocytes, which makes it a logical and understandable immunosuppressive effect of GCs in patients of Group 2 when administered daily.

With the administration of GCs in the morning, every other day, there was a positive effect on T-cell immunity and phagocytosis. Indices of T-cell and phagocytic immunity in patients of the 3rd group reached normal levels after 2-3 months of hormone therapy, which can be explained by the preservation (restoration) of the synchrony of GCs administration and physiological biorhythm of HPA axis activity. The results showed that pharmacotherapeutic doses of corticosteroids when administered taking into account the circadian rhythm of HPA axis function played the role of a physiological regulator of the immune system and had an immunostimulatory effect on lymphocytes. The absence of immunosuppressive effects of low doses of corticosteroids has been pointed out by other authors [7].

The lack of influence of GCs on humoral immunity in our studies confirmed the fact that mature B-lymphocytes are not sensitive to their action [8].

Therefore, the GCs therapy by synchronization with the HPA axis functional activity showed that under such conditions, corticosteroids have a positive effect on T-cell and phagocytic immunity, as evidenced by a significant increase in the total number of peripheral blood lymphocytes, as well as subpopulations of T-lymphocytes after 2-3 months of treatment of patients receiving corticosteroids in the intermittent regimen, which contributed to the normalization of the physiological biorhythm of the HPA axis functional activity, restored the regulatory effect of the neuroendocrine system on the immune defense system, showing an immunostimulatory effect.

Conclusions

1. Antibacterial drugs used in the treatment of tuberculosis have virtually no effect on the immune system at the end of the intensive phase of treatment.

2. Supplementation of antibacterial therapy with corticosteroids in the daily administration regimen with dose tapering after completion of the intensive phase of treatment of tuberculosis has a negative impact on the indicators of immunological protection: GCs suppress the restoration of T-cell and phagocytic immunity and reduce IgG levels without affecting other indicators of humoral immunity.

3. GCs drugs when administered taking into account the physiological biorhythm of the HPA axis functional activity, in the morning, once a daily dose, every other day give the opportunity to perform hormone therapy in a pharmacotherapeutic dose throughout the course of the intensive phase of complex treatment of tuberculosis with drug withdrawal without dose tapering. GCS have a stimulating effect on T-cell and phagocytic immunity, which is manifested by the normalization of their indices by the end of the intensive phase of treatment.

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Реферати

ГЛЮКОКОРТИКОЇДИ ЯК ІМУНОСТИМУЛЯТОРИ В ПАТОГЕНЕТИЧНІЙ ТЕРАПІЇ ТУБЕРКУЛЬОЗУ

Ярешко А. Г., Куліш М. В.

В статті обґрунтований імуностимулюючий ефект кортикостероїдів в комплексному лікуванні хворих на туберкульозу при введенні їх в подвійній фізіологічній дозі, через день з урахуванням добового біоритму функції гіпоталамо-гіпофізарно-наднирникової системи, тоді як при щоденному введенні вони проявляють імуносупресивний ефект. В-лімфоцити периферійної крові не чутливі до дії глюкокортикостероїдних препаратів.

Ключові слова: туберкульоз, патогенетична терапія, глюкокортикостероїди.

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ГЛЮКОКОРТИКОИДЫ КАК ИММУНОСТИМУЛЯТОРЫ В ПАТОГЕНЕТИЧЕСКОЙ ТЕРАПИИ ТУБЕРКУЛЕЗА

Ярешко А. Г., Кулиш М.В.

В статье обоснован иммуностимулирующий эффект кортикостероидов в комплексном лечении больных туберкулезом при введении их в двойной физиологической дозе, через день с учетом суточного биоритма функции гипоталамо-гипофизарно-надпочечниковой системы, тогда как при ежедневном введении они проявляют иммуносупрессивный эффект. В-лимфоциты периферической крови не чувствительны к действию глюкокортикостероидных препаратов.

Ключевые слова: туберкулез, патогенетическая терапия, глюкокортикостероиды.

Рецензент Костенко В.О.