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Abstract

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INFLUENCE OF THYROID HORMONES AND CORTISOL ON IMMUNE RESPONSE IN CASE OF CHILDREN'S BRONCHOPULMONARY DISEASES

The problem of acute respiratory tract infections (including acute bronchitis) remains urgent in the whole world independent of human age, especially when disease rates are considered. The World Health Organization reports annually on 1.5 billion cases of acute respiratory diseases. In Ukraine, the disease rate is 3.6 times higher among children than among adults (totally, it is equal to 67,000 cases per 100,000 individuals). The highest rate is observed among under-6-year-old children. In contrast to the average bronchopulmonary disease rate in Europe, the same Ukrainian index remains slightly higher for the last decades. Among children, the acute bronchitis rate is 6.2–25.0% within all bronchopulmonary diseases, reaching 50.0–90.0% if there are recurrences.

Our literature review aims to compare different researchers' perspectives, selecting articles and analyzing data as to how thyroid hormones and cortisol influence immune response in children's bronchopulmonary diseases. In the literature review, the modern perspective of children's hormonal state in bronchopulmonary diseases is studied. The hypothalamus-hypophysis-thyroid and hypothalamus-hypophysis-paranephros interaction roles in bronchopulmonary adaptive responses are explained. The thyroid hormone and cortisol importance for organism resistance are regarded. The manifestation, pathogenetic progress mechanisms, diagnosing methods, and treatment of different subclinical hormonal shifts (particularly euthyroid sick syndrome) are researched. The interconnection of hormonal and immunological indicators is covered (whose change is a predictively significant marker – that can foresee the disease progress, its duration and consequences for patients). Therefore, the relevance consists in researching the influence of thyroid hormones and cortisol on immune response by different pathological states of children's bronchopulmonary diseases.

Key words: children, bronchopulmonary diseases, euthyroid sick syndrome, hormones, triiodothyronine, thyroxine, cortisol, immunity.

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Резюме

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ВПЛИВ ГОРМОНІВ ЩИТОПОДІБНОЇ ЗАЛОЗИ ТА КОРТИЗОЛУ НА ІМУННУ ВІДПОВІДЬ ПРИ БРОНХОЛЕГЕНЕВИХ ЗАХВОРЮВАННЯХ У ДІТЕЙ

Проблема гострих інфекцій дихальних шляхів, у тому числі гострого бронхіту, з огляду на високу захворюваність та поширеність залишається актуальною в усьому світі незалежно від віку. Про близько 1,5 млрд. випадків гострих респіраторних захворювань ВООЗ рапортує щороку. В Україні розповсюдженість гострих респіраторних інфекцій серед дітей в 3,6 разів вища за аналогічних показник серед дорослих і становить 67 тисяч випадків на 100 тисяч населення. Найбільше випадків реєструють у дітей віком від 0 до 6 років. Порівняно з середнім рівнем захворюваності й поширеності бронхолегеневих захворювань в країнах Європи аналогічні показники по Україні залишаються дещо вищими в останні десятиріччя. Гострий бронхіт з питомою вагою 6,2–25,0 % займає провідне місце серед захворювань даної групи у дітей, а при їх рекурентному перебігу частка збільшується до 50,0–90,0 %.

Метою нашого огляду літератури було порівняння різних думок дослідників, підбір статей та аналіз даних про вплив гормонів щитоподібної залози та кортизолу на імунну відповідь при різних патологічних станах у дітей з акцентом на бронхолегеневі захворювання. У літературному огляді нами було досліджено сучасне розуміння гормонального статусу дітей при бронхолегеневих захворюваннях. Обговорили роль гіпоталамо-гіпофізарно-тиреоїдної та гіпоталамо-гіпофізарно-наднирникової системи в адаптаційних реакціях при вищезазначеній патології. Висвітлили важливість впливів тиреоїдних гормонів та кортизолу в підтриманні резистентності організму. Дослідили особливості прояву, патогенетичні механізми розвитку, методи діагностики й доцільність терапії різних варіантів субклінічних зсувів гормонального статусу, а саме синдром еутиреоїдної патології. Також висвітлили питання взаємозв'язку гормональних і імунологічних показників, ступінь тяжкості змін яких є прогностично важливим маркером, що може дозволити вже на ранніх етапах хвороби передбачити характер перебігу, її тривалість та наслідки для пацієнта. Тому, ми вбачаємо актуальність в дослідженні впливу гормонів щитоподібної залози та кортизолу на імунну відповідь при різних патологічних станах у дітей з акцентом на бронхолегеневі захворювання.

Ключові слова: діти, бронхолегеневі захворювання, синдром еутиреоїдної патології, гормони, трийодтиронін, тироксин, кортизол, імунітет.

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Introduction/Вступ

In the whole world, paediatricians are focused on acute respiratory tract infections rising for the last decade. In Ukraine, the highest disease rate is traced among the most densely populated areas – Kyiv, Lviv and Odesa Oblasts. The case distribution in male and female groups is equal [35]. The high mortality rate caused by acute respiratory tract infections among under-1-year-old children vividly reflects how relevant this problem is, which requires studying [34]. Acute bronchitis is one of the most widely spread respiratory diseases among children. This pathology often affects physical and sexual development, which leads to chronic diseases of different organs and systems [3, 57, 100, 108]. Recurring bronchitis can provoke children's asthma [57, 71, 92] and chronic bronchitis [37].

A significant role in children's endocrine regulation of vital processes and adaptive responses (short-term and long-term ones) is performed by the hypothalamus-hypophysis-thyroid and hypothalamus-hypophysis-paranephros interactions. Such an influence is provided usually by some effector hormones: triiodothyronine (T_3), thyroxine (T_4) and cortisol [9, 51, 59, 96].

The conducted researches revealed the thyroid hormone influence on a range of diseases: psoriasis, Down syndrome, gastrointestinal disorders, obesity, insulin-dependent and non-insulin-dependent diabetes mellitus, acute ischemic stroke and critical conditions [1, 18, 44, 61, 62, 69, 72, 73, 80, 82, 83, 89, 98, 107].

For example, in chronic plaque psoriasis, thyroid hormones influence the keratinocyte division speed and support the active disease state [1]. Some authors regard a low T3 level within critical conditions as inhibiting the thyroid deiodinase function after depletion of selenium, leptin and adenosine triphosphate [18, 62, 69, 89, 107]. By acute decompensated heart failure, a low free T_3 amount correlated with patients' lethality, which allows using concentration rates of thyroid hormones for predicting harmful health risks [69]. Besides, dependence between thyroid hormones and some gastrointestinal disorders (functional dyspepsia, irritable bowel syndrome, hypo- and hyperkinetic functional gall disorders, Sphincter of Oddi dysfunctions) was proved as well [61]. For obesity and subclinical hyperthyroidism, thyroid hormones influence insulin resistance and cardiovascular risks [73].

Meanwhile, it is also argued that consequences of metabolic syndrome with coronary heart disease and non-insulin-dependent diabetes mellitus are determined by thyrotropin and cortisol [12]. In the case of diabetes mellitus, hyper- and hypothyroidism and autoimmune thyroiditis, and subclinical thyroid dysfunctions occur much more often. Such changes are more typical for juvenile diabetes mellitus. Among a third of examined children with this disease, some thyroid dysfunctions were detected [72].

In particular, by bronchopulmonary diseases (especially, community-acquired pneumonia), a tight connection was defined between thyroid hormones and some clinical laboratory disease indexes [74].

Research purpose

Our literature review aims to compare different researchers' perspectives, selecting articles and analyzing data as to how thyroid hormones and cortisol influence immune response in children's bronchopulmonary diseases.

Materials and methods

One hundred nine sources were studied to produce data on how thyroid hormones and cortisol influence immune response in children's bronchopulmonary diseases. The search was done via the Scopus, PubMed, Web of Science and Google Scholar bases. If a source matched the research purpose, it was taken into consideration.

As a research result, some functional biological T_3 and T_4 effects were established. Mainly, in the fetus and newborns, these hormones differentiate brain cells and promote their architectonics, synaptogenesis and myelination. Moreover, they perform a significant role in thermogenesis and metabolism (that of proteins, carbohydrates and fats). Besides, they increase aerobic metabolism, erythropoiesis, gastrointestinal motility, structural protein synthesis; provide inotropic and chronotropic heart effects; raise β-adrenoreceptors in skeletal and heart muscles, lymphocytes and adipose; regulate ion transport, respiratory centre, CNS activity, endocrine functions and organism immune responses [4, 22, 26, 56, 57, 70, 75, 105].

One of the main thyroid features is that its hormones produce an anabolic effect. By average concentration, they regulate metabolism and energy exchange, promote protein and antibody synthesis [6, 8, 11, 30, 63, 94]. Thyroid hormone decrease leads to metabolism and general reactivity fall, which can be a possible reason for autoimmune and oncology diseases [7, 10, 45, 47, 109].

Thyroid hormone decrease can cause vessel wall dysfunctions, blood rheology changes, antioxidative activity disorders [6]. Moreover, alveolocyte and surfactant maturation depend on iodothyronines and glucocorticoids [20, 95]. In addition, thyroid hypofunction can provoke respiratory disturbances. That occurs because of the respiratory centre and breathing muscle depressions (which leads to lung ventilation decrease) and a high mucopolysaccharide and protein production in the throat and tongue [33]. The primary disease progress is usually severe within thyroid dysfunctions [21, 31], especially for children with bronchopulmonary problems [28].

T_3 concentration decrease can be regarded as an organism adaptive disease response when the need for nutrients is low. By severe and prolonged diseases, biochemical reactions are inhibited, and thyroid hormones fall in blood serum [6, 13, 30, 63, 94]. The primary disease severity correlates directly with such changes [6, 23, 52, 55]. Simultaneously, hypothyroidism and thyrotoxicosis are not traced clinically [23].

Such an adaptive response is called a euthyroid sick syndrome. There are some other names in literature sources: non-thyroidal disease syndrome, thyroid pseudo-dysfunction syndrome, euthyroid patient syndrome, euthyroid pathological syndrome [6, 29, 36, 52, 55, 64, 106]. It is caused by various diseases (infectious, inflammatory, traumatic, neoplastic ones) by no concomitant thyroid pathology and its integrity. In literature, the euthyroid sick syndrome is described in adult acute bronchitis [6, 52, 55].

The euthyroid sick syndrome progress during different diseases (especially children's) is still not thoroughly studied. However, the thyroid change triggers are considered to be the T_4-T_3 peripheral conversion, a disorder in thyroid hormones binding with the thyroxine-associated globulin, thyrotropin secretion disorder, the reverse T_3 (rT_3) clearance inhibition, the T_3 tissue recycling increase, proinflammatory cytokine effects (TNF-α, IL-1 etc.) [102].

In 2000, Braverman L.I. singled out main components in the euthyroid sick syndrome progress: the thyroid hormone metabolism and transport disorder, the thyrotropin production shift [7, 102].

There is still no unified euthyroid sick syndrome classification. However, most scientists define three variants of the euthyroid sick syndrome (ESS):

1) ESS-1 (the T_3 low-level syndrome) – the T_4 content is normal;

2) ESS-2 – the T_4 content is low, which is traced by more prolonged and more severe diseases;

3) ESS-3 – the T_4 content is high [90, 102].

Also, many researchers distinguish ESS-4 (with thyrotropin changes) [39, 52]. Some authors even distinguish its two subtypes: ESS-4 itself (the low-level thyrotropin syndrome) and ESS-5 (the high-level thyrotropin syndrome) [23, 29].

If there is an ESS suspected case, differential diagnosing with hypothyroidism is required. Clinically, such patients are in the euthyroid state. The blood serum thyrotropin concentration can be low, normal or slightly high (although it does not reach any significant changes as by hypothyroidism). For ESS, the rT_3 high level is also typical [29].

In ESS, the cortisol high level (produced by paranephros) is observed as well. However, hypothyroidism can decrease [29].

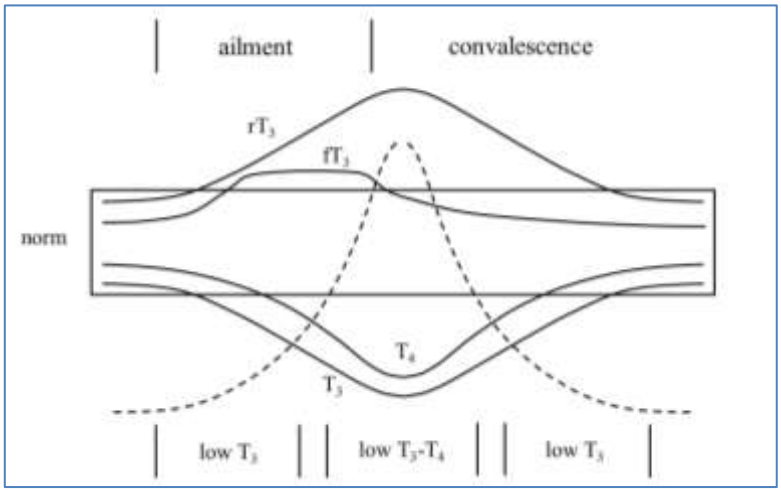

Figure 1 – Iodothyronines shift in blood serum by acute diseases

Glucocorticoids and catecholamine (as stress hormones) inhibit T_3 secretion caused by thyrotropin [68]. Besides, cortisol affects peripheral deiodination [66, 97, 104]. Along with T_3 decrease, there is fall of free iodothyronine, triiodothyronine and thyroxine, which leads to their improper binding with transport proteins and tissue catabolism. It results in a biological effect shift of these hormones (Figure 1) [87, 102].

Glucocorticosteroids inhibit thyrotropin synthesis via decreasing thyrocyte response to thyrotropin-releasing hormone. Thus, in severe cases (when stress hormones are released – e.g. by acute bronchitis), thyrotropin concentration and its reaction to thyrotropin-releasing hormone fall [102].

As a rule by the ESS, thyroid hormone shifts in blood serum rise gradually as to disease severity degrees. Firstly, T_3 drops. Secondly, T_4 sinks. Simultaneously, rT_3 rises. The deeper hormone concentrations vary, the higher mortality risk is predicted (Figure 2) [52, 64, 102].

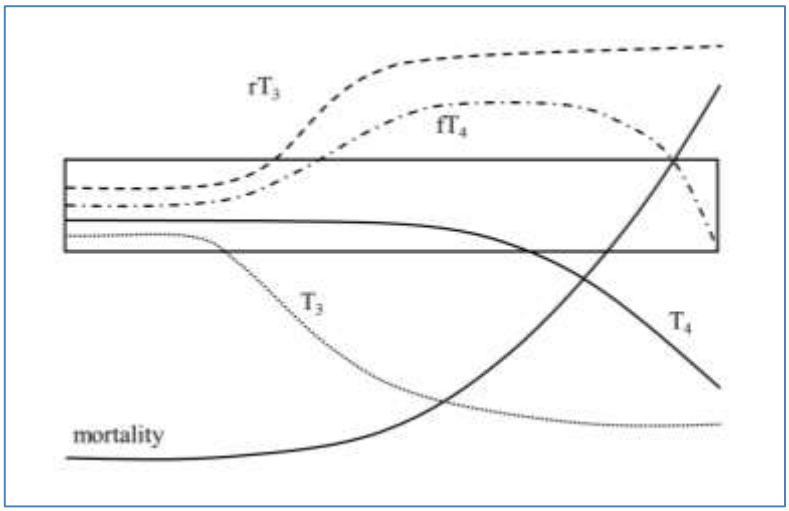

Figure 2 – Thyroid hormone shifts in blood serum with regard to increasing severity of a non-thyroid disease

According to its progress, ESS-1 is the mildest variant of such a syndrome. It occurs most often among children by different diseases. Thus, in 1973, Sullivan P.R. et al. were the first to describe the T_3 low-level syndrome among patients with severe general diseases [99]. In journals, one can find the ESS-1 clinical cases of patients with myocardial infarct, tuberculosis, insulin-dependent and non-insulin-dependent diabetes mellitus, osteoarthrosis, burns, chronic renal insufficiency, tumours and liver diseases. Many authors concluded that the primary mechanism of the T_3 low-level syndrome progress is the T_4-T_3 peripheral conversion disorder [14, 17, 58, 88]. They also argue that the most significant role in it is performed by the type I deiodinase activity fall [29, 85]. Moreover, this ESS kind is accompanied by the T_4 tissue grabbing decrease, which causes the T_3 synthesis drop [29, 64].

Meanwhile, ESS-2 is connected with other pathogenetic mechanisms. It is caused by the T_4 metabolism clearance growth and the T_3 and T_4 inhibitor appearance in blood serum. If a patient has ESS-2, that is a sign of a very severe state with bad predictions. Usually, such a syndrome is observed among in-patients with decompensation (intensive care units). The T_4 level in blood serum directly defines mortality risks. For example, the T_4 level of under 4 μg/100 ml leads to death in 50% of cases. By the T_4 level of under 2 μg/100 ml, people die in 80% of cases [43, 52, 101].

ESS-3 is described among pregnant women and patients who took iodine-containing medicines (amiodarone, radiocontrast agents) and those with liver diseases, mental disorders, tuberculosis [13, 48, 54, 86, 88].

There can be a thyrotropin drop within shocked patients and those treated by glucocorticoids and dopamine (ESS-4) [6, 17, 103].

Among respiratory tract diseases, the thyroid hormone adaptive changes are detected for patients with tuberculosis [25, 86], asthma [60], chronic obstructive pulmonary disease [76], pneumonia [32] and respiratory disturbance [67].

During asthma, the thyrotropin rise is accompanied by the T_3 and T_4 fall [60]. The sign for the negative tuberculosis progress is the T_3 and T_4 increase, most often observed in destructive pathology [86].

Research reports inform where an inverse dependence was detected – between T_3 and thyrotropin, T_4 transport fall and selenium availability (selenium participates in deiodinase synthesis) [29, 36, 52].

When analyzing clinical cases of community-acquired pneumonia, the low thyroid iodothyronine production was traced since the disease beginning. The disease progress led to higher thyrotropin synthesis. By chronic obstructive bronchitis, a long low cortisol concentration was observed [53].

The T_3 and T_4 drop with the normal thyrotropin level was detected during ARVI. Attention was paid to a correlation of hormone changes with toxicosis [38, 57].

Transient inhibition of thyroid hormone production was observed by respiratory distress syndrome, severe infectious diseases and hypoxia neonatorum (while thyrotropin remained stable) [93].

As a rule, patients with such a syndrome do not require thyroid hormone correction because ESS is an adaptive physiological organism response. In most clinical cases, it is enough to treat the primary disease. In addition, hormone normalization of the hypothalamus-hypophysis-thyroid system is a predictively positive index [29]. Exclusion is a situation when the blood serum T_4 concentration is under 4 μg/100 ml. L-thyroxine should be prescribed as a replacement dose [42, 55].

During clinical research of treating community-acquired pneumonia, a positive effect was traced if some T_3/T_4-containing medicines had been taken. There was a relatively earlier physiological stabilization of clinical and laboratory indexes among such patients, the lung infection nidus disappeared [53].

Invasion of viral or bacterial infectious agents during respiratory tract diseases causes some stress organism reactions. The hypothalamus-hypophysis-paranephros interaction is activated first for adaptive organism resistance (as a response to such an influence). Adrenotropic hormone and cortisol realize this process via correcting the protein, carbohydrate and fat metabolism. These changes result in providing an additional energy pool [78, 84].

The deficient glucocorticosteroid synthesis can provoke an allergic respiratory tract inflammation (because lungs promote glucocorticosteroid metabolism and biologically active substances regulating the bronchial smooth muscle tonus) [40].

During stress, the adrenotropic hormone and cortisol concentration change can be two-phase or three-phase. The first variant consists of hormone decrease after their increase. The second one defines a recurring hormone rise after a wave of their growth and fall [19, 30].

Also, researchers detected dependence between the acute laryngostenosis severity and the blood serum glucocorticoid change. At the first stage, the adrenotropic hormone level rises; there is the adrenotropic hormone and cortisol growth at the second stage. Simultaneously, the compensatory mechanism exhaustion leads to both hormones dropping [77].

By examining children with asthma, it was established that a moderately severe asthmatic attack makes cortisol increase while a severe one makes it decrease [24].

In a range of children's clinical asthma cases, the T_3 fall was observed with the subsequent T_4 and cortisol drop tendency (depending on the disease severity) [24, 60].

Although the immune system cell processes are highly autonomous, the interactions with the CNS and endocrine glands on the organ and organism levels are much tighter [2, 6, 15, 16, 46, 47, 91].

Thus, exerting an immunomodulatory influence, thyroid hormones (by their exogenous release) affect the functional activity of some specific immunocompetent cell subpopulations and the immune system in general. For example, T_3 trigger cytotoxic T-cells while T_4 promotes the leucocyte phagocytic activity [47, 79, 91].

Relation between the thyroid hormone amount and antibody responses is traced, which results in immunoglobulin synthesis growth [45, 46, 47, 51].

In 1999, Yehorova I.L. et al. established dependences between thyroid hormones and immune indexes of tuberculosis patients. There was a direct relationship between the T_3 and T-lymphocyte/T-helper amounts, between the T_3/T_4 and T-suppressor/B-lymphocyte content. An inverse relation was found between the T_3 and T-suppressor quantity [25].

Also, an inverse relation is proved between some immune indexes and T_3. In particular, this effect is traced among TNF-α [65], IL-1 and IL-6 [14, 27, 41, 49, 63, 81]. It is revealed via experiments that if INF-α or TNF-α are administered for healthy humans, the T_3 level falls [5, 49, 65].

Proinflammatory cytokines provoke the thyrotropin drop. Thus, within healthy humans,

INF-α or TNF-α administering caused the thyrotropin decrease [5, 49, 65].

Among children with inflammatory bronchopulmonary diseases, tests were conducted as well. As a result, shifts in thyroid hormone concentrations were detected: T_3 and T_4 fell, thyrotropin rose. Besides, immune changes were observed: the IgG, IgA, IgM and T-lymphocyte levels dropped in blood serum [49, 67].

Other researchers described a tight interrelation between the immune and endocrine systems within children with acute and latent viral infections (e.g. herpes). In such cases, T_4 decreased while T_3 and cortisol increased [50].

Conclusions/Висновки

The endocrine, nervous and immune systems are interconnected. Together they form an integrated system and support adaptive organism functions. The proper immunity work significantly depends on hormones and antigenic signals. Within the endocrine system, a significant role is performed by the thyroid and paranephros hormones. As a part of such a highly organized union, iodothyronines and glucocorticoids influence immunogenesis. Since during inflammatory respiratory tract diseases (e.g. acute bronchitis), there are some dysadaptative processes, local immunity disorders and general immune reactivity, we can see a connection of this disease with the hypothalamus-hypophysis-thyroid and hypothalamus-hypophysis-paranephros interactions.

Therefore, by inflammatory respiratory tract diseases of bacterial and viral aetiology, there is a metabolism disorder in thyroid and glucocorticoid hormones. This change depends on the disease severity degree. However, it is a predictively significant marker – that can be used to foresee the disease progress, its duration and consequences for patients.

The literature analysis showed that the hypothalamus-hypophysis-thyroid, hypothalamus-hypophysis-paranephros and immune responses to different children's pathologies (especially bronchopulmonary ones) are still not thoroughly studied. Above all, it concerns predictive hormone shifts within the endocrine interactions mentioned above.

Therefore, future research prospects consist of studying the thyroid hormone and cortisol influence on the immune response and their interrelation among children with acute bronchopulmonary diseases.

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