ORIGINAL ARTICLE

PECULIARITIES OF THYROID STATUS OF PRESCHOOL CHILDREN WITH ACUTE BRONCHITIS

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ABSTRACT

The aim: The aim of this study was to determine the characteristics of thyroid status (thyroid hormone, total and free fractions of triiodothyronine and thyroxine, reversible triiodothyronine, antibodies to thyroperoxidase) of preschool children with acute bronchitis.

Materials and methods: We examined 135 preschool children (from 3 to 6 years old) with acute bronchitis (main group) and 28 apparently healthy subjects who were in the control group. It used clinical-anamnestic, laboratory and instrumental research methods. Evaluation of the course of acute bronchitis was carried out in the acute period of the disease. All results were statistically processed using the SPSS 26 package.

Results: In 33 % of patients with acute bronchitis there are subclinical abnormalities of thyroid hormones, which manifest themselves in the form of euthyroid sick syndrome. Namely, we found an increased concentration of reversible triiodothyronine in the serum, as well as a decrease in total triiodothyronine and its free fraction.

Conclusions: In patients with acute bronchitis in almost every third case there are functional shifts in hormonal status, which are manifested in the form of the first variant of the euthyroid sick syndrome.

KEY WORDS: acute bronchitis, children, euthyroid sick syndrome, triiodothyronine, thyroxine

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INTRODUCTION

An analysis of scientific publications shows that over the last century, acute infectious diseases of the respiratory system among children of all ages occupy a leading place and as a result form an important medical, social, economic and scientific problem. Respiratory tract diseases account for the vast majority, up to 90 %, of reported cases among children. According to the WHO, every year 50 % of children under the age of 5 suffer from acute respiratory infections, and from 5 to 12 years – 30 %. Acute infections of the respiratory system are 7 – 7.5 times higher than the incidence of all other infections and 1.5 – 3 times higher than in adults [1].

Acute bronchitis with its various clinical forms occupies a significant share in the structure of nonspecific acute infectious diseases of the respiratory system of children. Thus, the incidence of this nosology averages about 100 per 1,000 children [2]. Acute bronchitis is one of the five reasons for outpatient treatment by a pediatrician [3]. Among the hospitalized patients in children's infectious wards with respiratory lesions in every 2 – 4 cases in the history of the disease there is a diagnosis of acute bronchitis [4].

Acute pathological processes accompanied by inflammation, including acute bronchitis, in the course of stressful changes involve the hypothalamic-pituitary-thyroid system. Therefore, the state of thyroid status depends on the resistance and adaptive stability of the organism, which can determine the features of acute bronchitis and the consequences for the patient [5, 6, 7]. In particular, such an adaptive state as euthyroid sick syndrome (ESS) is developing, which is manifested by various combinations of changes in thyroid hormone concentrations at the subclinical level [8-10]. Most often there is the first variant of this pathology: ESS-1 or "low T3 syndrome" [8, 11]. The study of this condition will better understand the interdependence of hormonal and immune systems, their response to acute inflammatory process of the respiratory tract in children and the stress that accompanies it, as well as further use the data to predict the course of acute bronchitis and improve treatment approaches.

After analyzing the available sources of information, we found that the state of the thyroid system of preschool children with acute bronchitis remains unresolved. Therefore, we see the relevance in the study of this problem, which will improve the early diagnosis of the features of acute bronchitis and predict the consequences for the patient.

THE AIM

The aim of this study was to determine the characteristics of thyroid status (thyroid hormone, total and free fractions of triiodothyronine and thyroxine, reversible triiodothyronine, antibodies to thyroperoxidase) of preschool children with acute bronchitis.

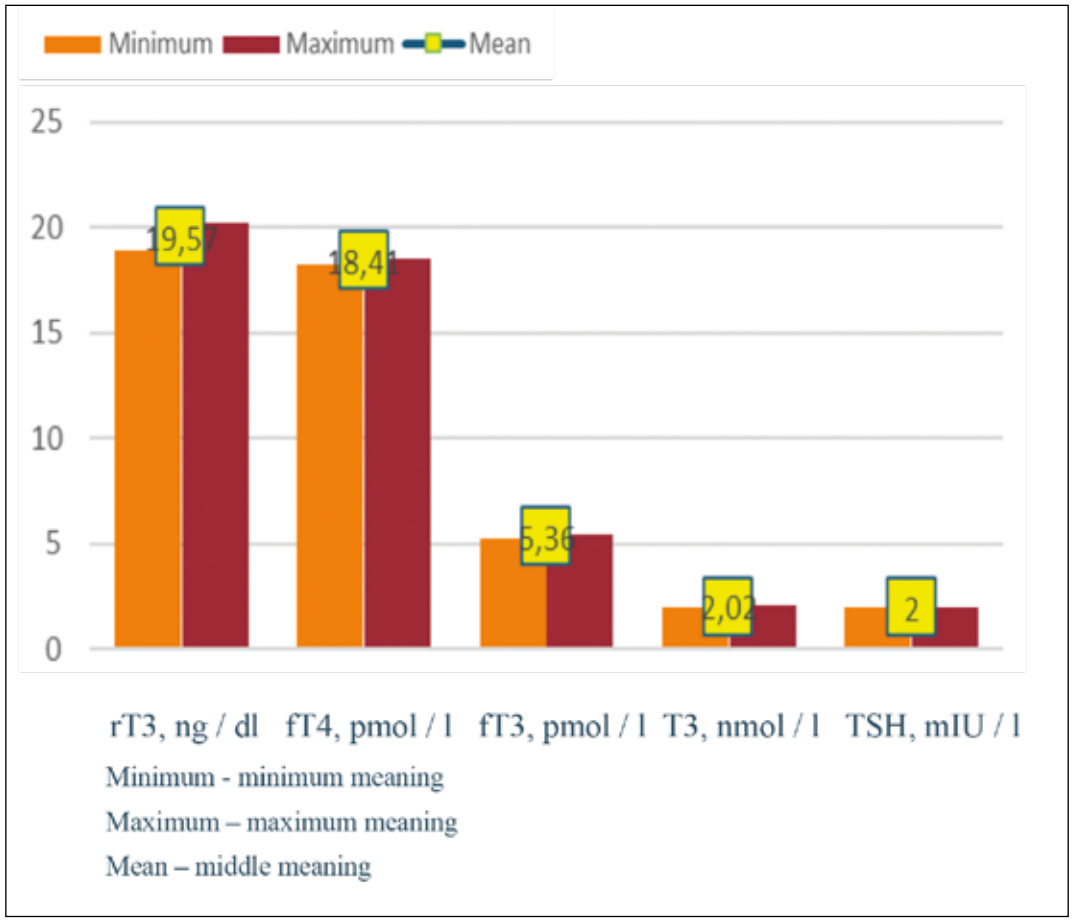

Fig. 1. Levels of thyroid hormones in the serum of the main group in the acute period of the disease

Table I. Condition of thyroid hormones in the serum of children with acute bronchitis (main group) in the acute phase of the disease

Hormones	N	Minimum	Maximum	Mean	
	Statistic	Statistic	Statistic	Statistic	Std. Error
T4, nmol / l	135	118,60	150,40	122,7178	0,41377
rT3, ng / dl	135	9,40	37,60	19,5733	0,68367
fT4, pmol / l	135	6,00	21,70	18,4126	0,15247
fT3, pmol / l	134	3,50	6,70	5,3597	0,10433
T3, nmol / l	135	1,01	2,74	2,0225	0,05069
TSH, mIU / l	135	1,13	3,58	1,9956	0,04281

N – number
Statistic – meaning
Minimum – minimum meaning
Maximum – maximum meaning
Mean – middle meaning
Std. Error – standart error

MATERIALS AND METHODS

We examined 135 preschool children (3 to 6 years old) with acute bronchitis (main group) who were treated in the infectious diseases departments of the Municipal Non-Profit Enterprise "Children's Clinical Hospital of St. Zinaida" Sumy City Council and 28 healthy children (control group) who were under supervision pediatrician in the Municipal Non-Profit Enterprise "Center for Primary Health Care № 2" Sumy City Council. The first group consisted of 92 children with acute bronchitis, the second group included 43 patients with acute bronchitis with signs of ESS.

The examination of the children included in the study was agreed with their parents (informed consent) and met the requirements of bioethics, as evidenced by the protocol of the Commission on Biomedical Ethics of the Municipal Non-Profit "Children's Clinical Hospital St. Zinaida" Sumy City Council.

Clinical and anamnestic assessments were used to comprehensively assess the patient's thyroid status (collection of complaints, anamnesis of disease and life, physical examination), laboratory (determination by solid-phase

Table II. The state of thyroid hormones in children with acute bronchitis with signs of ESS and without them (main group) in the acute phase and control groups

Groups		TSH, mIU / l	T3, nmol / l	fT3, pmol / l	rT3, ng / dl	T4, nmol / l	fT4, pmol / l
I	Mean	2,0059	2,4134	6,1620	14,5478	122,6707	18,5652
	N	92	92	92	92	92	92
	Std. Error of Mean	0,04940	0,01581	0,02418	0,23458	0,52575	0,14839
II	Mean	1,9735	1,1863	3,6024	30,3256	122,8186	18,0860
	N	43	43	42	43	43	43
	Std. Error of Mean	0,08383	0,01195	0,01050	0,62251	0,65813	0,35646
Control group	Mean	1,8857	2,3732	6,2107	15,8679	121,8571	19,0357
	N	28	28	28	28	28	28
	Std. Error of Mean	0,04437	0,02619	0,03014	0,16011	0,60477	0,32060
Total	Mean	1,9767	2,0828	5,5068	18,9368	122,5699	18,5196
	N	163	163	162	163	163	163
	Std. Error of Mean	0,03637	0,04345	0,09004	0,57706	0,35834	0,13860

Mean – middle meaning
N – number
Std. Error of Mean – standart error of middle meaning
Total – total

Table III. Dispersion analysis of differences in the state of hormones of children with acute bronchitis with signs of ESS and without them (main group) in the acute phase and control groups

Hormones			Sum of Squares	Df	Mean Square	F	Sig.
TSH, mIU / l	Between Groups	(Combined)	0,031	1	0,031	0,123	0,726
	Within Groups		33,123	133	0,249		
			33,154	134			
T3, nmol / l	Between Groups	(Combined)	44,124	1	44,124	2497,172	0,000
	Within Groups		2,350	133	0,018		
	Total		46,474	134			
fT3, pmol / l	Between Groups	(Combined)	188,916	1	188,916	4902,456	0,000
	Within Groups		5,087	132	0,039		
	Total		194,002	133			
rT3, ng / dl	Between Groups	(Combined)	7294,793	1	7294,793	835,988	0,000
	Within Groups		1160,551	133	8,726		
	Total		8455,344	134			
T4, nmol / l	Between Groups	(Combined)	0,641	1	0,641	0,028	0,868
	Within Groups		3096,416	133	23,281		
	Total		3097,057	134			
fT4, pmol / l	Between Groups	(Combined)	6,728	1	6,728	2,162	0,144
	Within Groups		413,820	133	3,111		
	Total		420,549	134			

Sum of Squares – sum of squares
Df – definition degrees of freedom
Mean Square – mean values of squares
F - the value of Fisher's calculation criterion
Sig. – significant - p-value (materiality)
Between Groups | (Combined) – intergroup (combined)
Within Groups – in the middle of groups (average of groups)
Total - total

enzyme-linked immunosorbent assay) of serum hormones such as thyroid-stimulating hormone (TSH), total and free (T3 and fT3) and thyroxine (T4 and fT4), reversible triiodothyronine (rT3), antibodies to thyroperoxidase), as well as instrumental research methods (chest radiography, ultrasound examination of the thyroid gland).

In children of the main group, the diagnosis of acute bronchitis was verified on the basis of complaints of children and their parents, anamnesis, objective symptoms, results of laboratory and instrumental research methods according to the clinical protocol on medical care for children in "Pediatric Pulmonology" from 13.01.2005 № 18 with changes and additions made by the order of the Ministry of Health of Ukraine from July 16, 2014 № 499 (Unified clinical protocol of primary care for adults and children "Acute respiratory infections"), Adapted clinical guidelines based on evidence, " Influenza and acute respiratory infections ", 2014. Assessment of acute bronchitis, including the use of laboratory and instrumental methods, was carried out in the acute period of the disease (1 – 2 days of hospitalization).

In addition, we studied children in the main group of ESS, namely the first option, known as "low T3 syndrome". This is an adaptive state in which non-thyroid diseases with euthyroidism cause subclinical changes in serum thyroid hormone levels: decreased T3, fT3 and increased rT3.

All results were statistically processed using the SPSS 26 package. Descriptive statistics and comparisons of mean values were used to characterize the course of acute bronchitis in preschool children. Differences between groups were confirmed or refuted by analysis of variance for quantitative characteristics and the chi-square criterion, for features of nominal or rank scale.

RESULTS

Dynamic determination of hormonal status was performed on all 135 preschool patients of the main group and 28 children of the control group. Clinically pronounced hypo- or hyperthyroidism was not detected in the examined children. With the help of ultrasound examination of the thyroid gland was ruled out the presence of organic pathology of these organs. The diagnosis of pneumonia was refuted in doubtful clinical cases after X-ray examination of the chest. Determination of the concentration of antibodies to thyroperoxidase made it possible to exclude the autoimmune etiology of changes in thyroid hormones.

The concentrations of hormones in the serum of the control group corresponded to the age norm. Their average values were: T3 – 2.37 ± 0.03 nmol / l, fT3 – 6.21 ± 0.03 pmol / l, T4 – 121.86 ± 0.60 nmol / l, fT4 – 19.04 ± 0.32 pmol / l, TSH – 1.89 ± 0.04 mIU / l and rT3 – 15.87 ± 0.16 ng / dl.

Compared with the indicators of the control group, the children of the main group had significant deviations and variance in the values of thyroid hormones. In general, in the acute period of the disease, the level of T3 in the serum varied from 1.01 to 2.74 nmol / l, in fT3 – from 3.5 to 6.7 pmol / l, T4 – from 118.6 to 150.4 nmol / l , fT4 – from 3.5 to 6.7 pmol / l, TSH – from 1.13 to 3.58 mIU / l and rT3 – from 9.4 to 37.6 ng / dl (table I).

Average values of concentrations of hormones of the main group of the population: T3 – 2,02 ± 0,0,5 nmol / l, fT3 – 5,36 ± 0,10 pmol / l, T4 – 122,7 ± 0,41 nmol / l, fT4 – 18.41 ± 0.15 pmol / l, TSH – 1.99 ± 0.04 mIU / l and rT3 – 19.57 ± 0.68 ng / dl (Figure 1).

Studies in children with acute bronchitis with signs of ESS and without them revealed an imbalance in changes in thyroid hormones (table II).

Analyzing the data in Tables II and III, it was found that the average level of TSH, T4 and fT4 with a probability of 95 % ($p > 0.05$) did not differ statistically for the group of children with acute bronchitis with signs of ESS, without signs of ESS and in the group control.

In contrast, the level of rT3 was significantly higher in the group of children with acute bronchitis with signs of ESS (30.32 ± 0.62) ng / dl against (14.55 ± 0.23) ng / dl in the group of children with acute bronchitis without signs of ESS in the control group (15.87 ± 0.16) ng / dl) ($p < 0.001$), respectively). The level of T3 was significantly lower in the group of children with acute bronchitis with signs of ESS (1.18 ± 0.01) nmol / l against (2.41 ± 0.02) nmol / l in the group of children with acute bronchitis without signs of ESS and in the control group (2.37 ± 0.03) nmol / l ($p < 0.001$), respectively; and fT3 in the group of children with acute bronchitis with signs of ESS (3.6 ± 0.01) pmol / l against (6.16 ± 0.2) pmol / l in the group of children with acute bronchitis without signs of ESS and in control group (3.6 ± 0.01) pmol / l ($p < 0.001$). The above features of changes in the concentrations of thyroid hormones in the serum and gave us grounds for selection within the main group of children with manifestations of "low T3 syndrome".

The share of functional shifts in hormones is quite large. Almost every third patient (43 (31.85 ± 4.02) %)) showed changes in ESS.

DISCUSSION

The problems of euthyroid sick syndrome in non-thyroid diseases are widely discussed in the modern medical literature. Thus, a number of authors observed euthyroid sick syndrome in patients with COVID-19, which was significantly associated with the severity of the disease and baseline parameters [12]. Other researchers have shown that levels of free T3 can serve as a prognostic criterion for determining the severity of the disease in the early manifestations of COVID-19 [13].

It is interesting to note that low levels of T3 are common among patients who are not in critical condition. Serum T3 levels, alone or in combination with other prognostic estimates, have been shown to be a simple and valuable tool for stratification of disease risk [14]. In addition, this hormone plays an important role in regulating the immune response, inducing protection against systemic inflammation in response to endotoxemia. Moreover, the key role of T3 is assigned to inhibit the differentiation of monocytes into macrophages [15]. At

the same time, new experimental and clinical studies show the evolutionary effect of T3 on the adaptation of affected tissue in hypoxia and on the immune response and viral load in infected tissue [16]. Some authors suggest that changes in the concentration of thyroid hormones in severe disease are a protective reaction, as it prevents excessive tissue catabolism [17].

A number of authors found that T3 was significantly correlated with lymphocyte counts in patients with bacterial sepsis, and lower hormone levels were found in patients with severe lymphopenia. In patients with severe lymphopenia, COVID-19 showed significantly lower plasma concentrations of TSH, T4, fT4 and T3 compared to patients without lymphopenia. At the same time, the indicators of inflammatory markers increased significantly: interleukin-6, C-reactive protein and ferritin [18].

Researchers believe that an increase in rT3 is a predictor of both short-term and long-term mortality. A decrease in the concentration of fT3 is a contributing factor to subsequent cardiac disorders [19].

The relationship between thyroid hormones and immune cells is complex, and T3 can model various aspects of innate and adaptive immune responses through both genomic and non-genomic mechanisms. Thyroid hormones have also been shown to affect the activity of natural killer cells and the cellular immune response [20].

Studies by Mei-Xian Xu and others (2020) have shown that children with sepsis often have euthyroid syndrome, which the authors believe is associated with high levels of interleukin-6 [21]. During the experiment, other researchers found that in patients with irritable bowel syndrome, changes in thyroid hormone levels are associated with a moderate increase in proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-1β, interleukin-6 and interleukin-8) and decreased anti-inflammatory cytokine. (interleukin-10) [22].

The problem of a clear distinction between low T3 syndrome and central hypothyroidism has been addressed by a number of researchers and proposed to determine the serological threshold of the ratio of fT3 to fT4 (pg / ml, ng / dl, respectively) at 2.0 [23].

It is possible that in the acute phase of the disease euthyroid sick syndrome is part of the body's favorable adaptation to reduce energy expenditure and activation of the innate immune response, which is important for recovery [24]. At the same time, in chronic disease, such a hypometabolic state leads to thyroid allostasis type 1, in which the amount of energy consumed and mobilized from reserves is less than the need for it [25]. To emphasize the compensatory-adaptive orientation, other researchers suggest a new name for this condition – the syndrome of adaptive thyroid imbalance. Speaking of classification, the authors point to both immobilizing (inhibitory) and mobilizing (activating) shifts in thyroid hormones [26].

Thus, the euthyroid sick syndrome occurs in a significant proportion of hospitalized patients and includes many changes in the axis of the hypothalamus-pituitary-thyroid gland. One of the hallmarks of the syndrome is a decrease in the concentration of thyroid hormones in the serum, which is often seen as an adaptive mechanism for energy savings. Cytokines released during the disease affect a number of genes involved in the metabolism of thyroid hormones, and therefore are considered the main determinants of euthyroid sick syndrome [27].

CONCLUSIONS

Thus, in patients with acute bronchitis in the acute period of the disease in almost every third case there are functional shifts in hormonal status, which manifests itself in the form of "low T3 syndrome" (ESS-1). It should be noted that all changes are subclinical in nature, so no signs of hypo- or hyperthyroidism were detected. Thus, in children of the selected subgroup with signs of euthyroid sick syndrome, an increased concentration of reversible triiodothyronine in the serum, as well as a decrease in the total and free fraction of triiodothyronine. Our research has shown that, in response to inflammation, children with acute bronchitis may have a physiological adaptive state involving the hypothalamic-pituitary-thyroid system.

Prospects for further research are to expand the study of hormonal homeostasis, including the hypothalamus, pituitary gland and thyroid gland, to understand the role of thyroid hormones in children with acute bronchitis in age. In addition, it is important to link thyroid hormone levels to the function of the immune system and respiratory pathology. Further research in this area is needed, which is especially important in children with infectious diseases. This will allow a more accurate understanding of the pathogenetic processes of the disease and in the long run to optimize early diagnosis, the severity of acute bronchitis and predict the consequences for the patient.

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The Authors declare no conflict of interest.

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