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Some Diagnostic Approaches to Verify the Etiology of Acute Tonsillopharyngitis in Children

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Abstract

Introduction. Considerable occurrence of acute tonsillopharyngitis (ATP) among children stipulates topicality of the issue to make the diagnosis timely and choose the tactics of etiotropic treatment of the pathology.

Purpose. To evaluate the results of application of certain immunological tests in finding non-streptococcal acute tonsillopharyngitis (nATP) in children in order to optimize starting etiotropic treatment and non-relevant antibacterial therapy.

Materials and methods. A prospective study of 102 patients suffering from acute tonsillopharyngitis was conducted. The age of patients was from 3 to 18 years. They were treated at the Department of Respiratory Infection, the Municipal Medical Institution "Regional Children Clinical Hospital" in the town of Chernivtsi, Ukraine. This group of children was divided into 2 clinical subgroups. The first clinical subgroup included 68 patients suffering from non-streptococcal acute tonsillopharyngitis (nATP). The second subgroup included 34 children suffering from streptococcal acute tonsillopharyngitic (sATP). On admission general clinical blood analysis (complete blood count), immunological blood analysis of II–III levels (T-lymphocyte content (CD_3), T-helpers (CD_4), T-killers/suppressors of the blood (CD_8) and B-lymphocytes (CD_{22})) were made for all the children. Nitro blue tetrazolium test (NBT-test) was determined in spontaneous and pyrogenal stimulated variants, determination of interleukin-6 in blood serum.

Results. The content of different leukocyte subpopulations in the peripheral blood of patients in both groups did not differ much, except lymphocytes (in I group – 2.71 ± 0.1 , in II group – 3.21 ± 0.12 ($P < 0.05$)). In children with nATP spontaneous NBT-test more than 25.0% was determined in $35.3 \pm 5.8\%$ of cases, and the stimulated one more than 40.0% of formazan positive cells – in $36.8 \pm 5.85\%$. In patients with sATP the above indices of NBT-test were determined in $26.5 \pm 7.57\%$ and $23.5 \pm 7.27\%$ cases respectively ($P > 0.05$). The use of interleukin-6 (< 10.0 pg/ml), in blood serum, has a high sensitivity (77.1%) for the establishment of non-streptococcal ATP. The results of the stimulated NBT-test of neutrophil granulocytes of the blood more than 40.0% of formazan positive cells were indicative of a reliable risk of non-streptococcal ATP in children available (OR=1.9; 95% CI 1.1–3.5).

Keywords: children, acute non-streptococcal, streptococcal tonsillopharyngitis, NBT-test, IL-6

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Использование отдельных иммунологических тестов для выявления нестрептококкового острого тонзиллофарингита у детей

Конфликт интересов: не заявлен.

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Этическое одобрение. Протокол исследования и форма информированного согласия одобрены Комиссией по биоэтической этике при проведении биомедицинских научных исследований Буковинского государственного медицинского университета (протокол № 36 от 17.11.2016).

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Резюме

Введение. Значительная распространенность острых тонзиллофарингитов (ОТФ) среди детского населения обуславливает актуальность проблемы своевременной диагностики и верной тактики этиотропного лечения данной патологии в педиатрии.

Цель. Оценить результаты применения отдельных иммунологических тестов при выявлении нестрептококкового острого тонзиллофарингита у детей с целью оптимизации начального этиотропного лечения и нерелевантной антибактериальной терапии.

Материалы и методы. Проведено проспективное исследование 102 пациентов с острым тонзиллофарингитом в возрасте от 3 до 18 лет, находившихся на стационарном лечении в отделении воздушно-капельных инфекций КМУ «Областная детская клиническая больница» г. Черновцы, Украина. Данная когорта пациентов была разделена на 2 клинические группы. Первую клиническую группу составили 68 пациентов с нестрептококковым острым тонзиллофарингитом (нОТФ), а вторую клиническую группу образовали 34 ребенка со стрептококковым острым тонзиллофарингитом (сОТФ). Всем детям при поступлении проводилось общеклиническое (общий анализ крови), иммунологическое исследование крови II–III уровней (содержание Т-лимфоцитов (CD3), Т-хелперов (CD4), Т-киллеров / супрессоров крови (CD8) и В-лимфоцитов (CD22)), определение теста с нитросиним тетразолием (НСТ-тест) в спонтанном и стимулируемом пирогеналом вариантах.

Результаты. В периферической крови пациентов обеих групп наблюдения содержание различных субпопуляций лейкоцитов существенно не различалось, за исключением лимфоцитов (в I группе – $2,71 \pm 0,1$, во II группе – $3,21 \pm 0,12$ ($P < 0,05$)). У детей с нОТФ спонтанный НСТ-тест более 25,0% определялся в $35,3 \pm 5,8\%$

случаев, а стимулированный больше 40,0% формазанположительных клеток – в $36,8 \pm 5,85\%$ случаев. У пациентов со сОТФ приведенные показатели НСТ-теста определялись в $26,5 \pm 7,57\%$ и $23,5 \pm 7,27\%$ случаев ($P > 0,05$). Определение интерлейкина-6 ($< 10,0$ пг/мл) в сыворотке крови обладает высокой чувствительностью (77,1%) для установления нестрептококковой природы ОТФ. Показатели стимулированного НСТ-теста нейтрофилов крови у детей с ОТФ более 40,0% формазанположительных клеток свидетельствовали о вероятном риске нестрептококковой этиологии данного заболевания (ОШ=1,9; 95% ДИ 1,1–3,5).

Ключевые слова: дети, острый тонзиллофарингит, диагностика, НСТ-тест, ИЛ-6

■ INTRODUCTION

Acute tonsillopharyngitis (ATP) is one of the most common infectious diseases of the upper respiratory tract in children, manifested by acute inflammation of the tonsils and pharynx, and caused by viruses in the majority of cases [1]. Bacteria as a causative factor play an insignificant role in the development of ATP. *Streptococcus pyogenes*, also known as beta-hemolytic streptococcus of A group (BHSA), is the most important causative agent [2, 3]. One of the leading reasons of attending medical institutions in the whole world is BHSA-tonsillopharyngitis. Approximately 450 million people suffer from it annually [4, 5]. Pediatric population constitutes practically a half of all the cases, mostly at the age of 5–15 years (30–37%), and the rest (5–10%) – younger than 5 years [6].

As a rule, acute tonsillopharyngitis is a self-limiting disease. In the majority of cases it does not require antibiotic treatment [7–9]. Though, an inconsiderable amount of patients develop severe complications, such as scarlet fever and peritonsillar abscess, as well as autoimmune diseases such as post-streptococcal glomerulonephritis and acute rheumatic fever. Early treatment of ATP caused by BHSA by means of appropriate antibiotics is known to decrease intensity and duration of symptoms, stop spread of bacteria and decrease the risk of acute rheumatic fever occurrence [10]. Sickness rate of rheumatic heart disease ranges from 0.03 to 2.1%, considering the status of a country development [11].

Since the majority of tonsillopharyngitis is viral by origin, a clarified diagnosis can reduce useless administration of antibiotics and potential resistance development to them [12, 13]. Meanwhile etiological diagnostics of ATP is complicated due to several reasons. First, making the diagnosis of non-streptococcal or streptococcal ATP by means of clinical signs only is not reliable due to similarity of symptoms between viral and bacterial etiology [14]; physicians do not find up to 50% of cases of BHSA-tonsillitis, and they identify 20–40% cases of non-streptococcal ATP, which treatment does not require administration of antibacterial medicines [15–17]. Second, many children are asymptomatic carriers of BHSA. Its occurrence is about 12% [18, 19]. Third and the most important, a standard procedure of laboratory detection of BHSA, bacteriological culture of the blood agar, as a rule, requires no less than 48–72 hours [20, 21]. It is troublesome for a physician to make the diagnosis on the day of a patient's visit for medical aid [22, 23].

Therefore, the search of new diagnostic criteria able to make early differential diagnostics of acute tonsillopharyngitis of bacterial and viral etiology is, in our opinion, topical and perspective. It will increase the efficacy of a target starting therapy of the disease in children.

■ PURPOSE OF THE STUDY

To evaluate the results of application of certain immunological tests in finding non-streptococcal acute tonsillopharyngitis (nATP) in children in order to optimize starting etiotropic treatment and non-relevant antibacterial therapy.

■ MATERIALS AND METHODS

To achieve the stated purpose a prospective study of 102 patients suffering from acute tonsillopharyngitis aged from 3 to 18 years was conducted. They were treated at the Department of Respiratory Infection, the Municipal Medical Institution "Regional Children Clinical Hospital" in the town of Chernivtsi, Ukraine. The patients were divided into two clinical groups depending on the isolation of beta-hemolytic streptococcus of A group while making culture examination of smears from the mucous membrane of the tonsils/pharynx. The first clinical group (I) included 68 patients without BHSA found in bacteriological test (ATP of non-streptococcal etiology). The second group (II) included 34 children with streptococcal etiology found (streptococcal acute tonsillopharyngitic (sATP)).

On admission general clinical blood analysis (complete blood count), immunological blood analysis of II–III levels (T-lymphocyte content (CD_3), T-helpers (CD_4), T-killers/suppressors of the blood (CD_8) and B-lymphocytes (CD_{22})) were made for all the children by means of immunofluorescence method using the sets of monoclonal antibodies. Activity of oxygen-dependent microbicidal neutrophil blood granulocytes was evaluated by means of histochemical method with determination of a spontaneous and stimulated variant of the test, where granulocytes were stained by nitro blue tetrazolium test (NBT-test) according to Park B.H. et al. method. The serum content of interleukin-6 (pg/ml) was investigated using reagents for enzyme-linked immunosorbent assay of the concentration of this cytokine in human biological fluids (firm "Vector BEST", RF) registration number A-8768.

The results of the study obtained were analyzed from the position of biostatistics and clinical epidemiology by means of the computer packages Statistica7 StatSoft Inc. and Excel XP for Windows. Confidence level p was bilateral, the criterion of statistical confidence was $p < 0.05$.

The study was performed according to the principles of the Declaration of Helsinki. An informed written consent to conduct examination from parents or tutors was obtained.

■ RESULTS AND DISCUSSION

On admission to the hospital all the children underwent laboratory general clinical and immunological examinations. The Table 1 presents an absolute content of leukocytes in the peripheral blood of children with non-streptococcal and streptococcal acute tonsillopharyngitis and full-scaled [comprehensive] blood leukogram.

The data obtained give the evidence that both children with streptococcal and non-streptococcal acute tonsillopharyngitis do not develop considerable differences in the content of various subpopulations of leukocytes in the peripheral blood, except lymphocytes. Substantial differences in erythropoiesis were not found either. Thus, children with non-streptococcal acute tonsillopharyngitis presented RBCs in the peripheral blood $4.2 \pm 0.06 \times 10^9/L$ (95% CI 4.10–4.32), an average hemoglobin concentration was

Table 1
Leukogram of the peripheral blood in children from the groups of comparison (g/L) on admission to the hospital

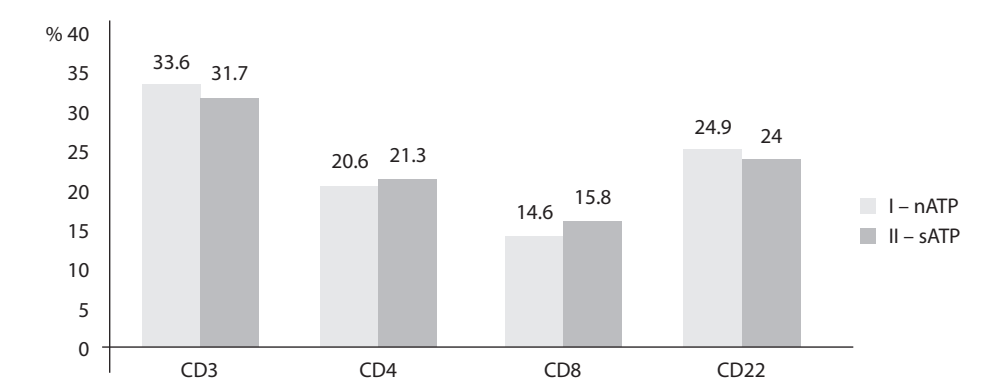
Clinical groups	Number of patients	Leukocytes	Neutrophils		Eosinophils	Lymphocytes	Monocytes
			Stabs	Segmented			
I – nATP	68	8.9±0.50	1.33±0.45	4.33±0.21	0.16±0.02	2.71±0.1	0.38±0.02
II – sATP	34	10.0±0.74	0.66±0.10	4.70±0.35	0.19±0.01	3.21±0.12	0.44±0.04
P		<0.05	>0.05	>0.05	>0.05	<0.05	>0.05

Notes: P – Student criterion; nATP – non-streptococcal acute tonsillopharyngitis; sATP – streptococcal acute tonsillopharyngitis.

129.6±1.78 g/L (95% CI 126.0–133.1), and color index 0.92±0.003 (95% CI 0.92–0.93). In patients with signs of streptococcal acute tonsillopharyngitis the above indices were 4.0±0.11×10⁹/L (95% CI 3.7–4.2), 121.2±2.48 (95% CI 116.2–126.3) g/L and 0.94±0.03 (95% CI 0.88–1.0) (P>0.05) respectively. The content of platelets in patients with non-streptococcal ATP was on an average 234.3±5.78 (95% CI 220.1–248.4) g/L. In children with streptococcal ATP an average content of platelets in the blood was 337.0±6.28 (95% CI 330.0–352.0) g/L (P>0.05).

Since considerable increase of the lymphocyte content was found in the peripheral blood of patients with streptococcal acute tonsillopharyngitis, we found it reasonable to examine the content of immune-competent cells in children of the both groups of comparison (Figure).

The data presented give the evidence to consider that there were no considerable differences found in the content of immune-competent lymphocytes and their subpopulations in the peripheral blood of children from the both groups of comparison. An absolute content of these cells in the blood did not differ either. Thus, in patients with nATP an absolute content of CD3 was 0.89±0.087 (95% CI 0.72–1.07) g/L, and CD22 – 0.71±0.097 (95% CI 0.52–0.91) g/L. In patients with sATP the content of the immune-competent cells was 0.89±0.12 (95% CI 0.65–1.14) g/L and 0.86±0.19 (95% CI 0.46–1.26) g/L (P>0.05) respectively.



Relative content of immune-competent lymphocytes in the peripheral blood of children from the both groups of comparison on admission to the hospital

Table 2
Results of NBT-test of neutrophils in children from the groups of comparison on admission to the hospital ($M \pm m$)

Clinical groups	Number of patients	Spontaneous NBT		Stimulated NBT	
		%	CCC, s.u.	%	CCC, s.u.
I – nATP	61	22.7 $\pm$ 1.26	0.28 $\pm$ 0.02	39.1 $\pm$ 1.5	0.52 $\pm$ 0.04
II – sATP	30	21.9 $\pm$ 1.20	0.26 $\pm$ 0.03	30.4 $\pm$ 1.66	0.39 $\pm$ 0.03
P		>0.05	>0.05	<0.05	<0.05

Notes: P – Student criterion; nATP – non-streptococcal acute tonsillopharyngitis; sATP – streptococcal acute tonsillopharyngitis; CCC – integral cytochemical coefficient.

Since general inflammatory response with ATP is mediated by the blood neutrophils mainly [24], we consider it reasonable to examine oxygen-dependent microbicidal neutrophil granulocytes in the peripheral blood in children from the groups of comparison. The Table 2 presents the results of the test with nitro blue tetrazolium in spontaneous and pyrogenal stimulated variants, in percentage of formazan positive cells and in the form of integral cytochemical coefficient (CCC).

In spite of the lack of considerable differences in the results of spontaneous NBT-test in children from the groups of comparison, higher indices were found more frequently in patients with non-streptococcal acute tonsillopharyngitis. Thus, spontaneous NBT-test more than 25.0% was found in 35.3 $\pm$ 5.8% cases, and the stimulated one more than 40.0% of formazan positive cells – in 36.8 $\pm$ 5.85%. In patients with sATP the above indices of NBT-test were determined in 26.5 $\pm$ 7.57% and 23.5 $\pm$ 7.27% cases respectively ($P > 0.05$). The data obtained enabled to consider that in case of streptococcal ATP the exhaustion of the reserve of neutrophil ability to respiratory "explosion" occurs with decrease of oxygen dependent metabolism.

A diagnostic value of the spontaneous test with nitro blue tetrazolium of the blood neutrophil granulocytes more than 25% of formazan positive cells in finding non-streptococcal acute tonsillopharyngitis was the following: sensitivity – 35.3%, specificity – 73.5%, predicted value of a positive result – 57.1%, predicted value of a negative result – 53.2%, odds ratio – 1.5 (95% CI 0.8–2.8). The indices of a diagnostic value of the stimulated NBT-test more than 40% of formazan positive cells in finding non-streptococcal acute tonsillopharyngitis concerning acute streptococcal acute tonsillopharyngitis did not differ considerably from the spontaneous NBT-test and were the following: sensitivity – 36.8%, specificity – 76.5%, predicted value of a positive result – 61%, predicted value of a negative result – 54.8%, odds ratio – 1.9 (95% CI 1.1–3.5).

With the use of spontaneous and stimulated NBT-test in patients with acute tonsillopharyngitis the probability of non-streptococcal etiology of ATP with positive results 11.0% increased, and in case of negative results it 5.0% decreased only.

A relative risk of non-streptococcal acute tonsillopharyngitis available with the indices of the spontaneous NBT >25% of formazan positive cells was 1.2 (95% CI 0.8–1.9), and an attributive risk was 0.10. The stimulated NBT >40% of formazan positive cells was associated with the risk of non-streptococcal etiology of ATP in the following way: relative risk – 1.4 (95% CI 1.0–2.1), attributive risk – 0.16.

Therefore, only high values of the stimulated NBT-test of the blood neutrophils were indicative of a reliable risk of non-streptococcal nature of acute tonsillopharyngitis in children.

Table 3
Diagnostic value of Interleukin-6 in the detection of non-streptococcal GTP when children are admitted to the hospital

Indexes	Diagnostic value, % (95% CI)				The relationship of plausibility	
	sensitivity	specificity	Prognostic value		positive result	negative result
			positive result	negative result		
IL-6 <10.0 pg/ml	77.1 (67.6–85.0)	51.6 (41.3–61.8)	61.4 (52.3–70.0)	69.3 (57.4–79.5)	1.6	0.4

Note: IL – interleukin.

In infectious inflammation, a special case of which is acute tonsillopharyngitis, its mediators are determined in the blood, which have a pro-inflammatory effect, in particular interleukin-6. The level of this cytokine depends on the severity of inflammatory changes, which would distinguish viral infection from bacterial. In our study, we analyzed the diagnostic value of interleukin-6 in children with GTP, the results are shown in Table 3.

These data indicate that the lack of a clear general inflammatory response of the body in acute tonsillopharyngitis can be used to establish the non-streptococcal etiology of the disease. This is due to the fact that the use of interleukin-6 in serum has a high sensitivity and moderate prognostic value of a negative result.

The risk indicators of interleukin-6 in establishing the non-streptococcal etiology of GTP when children were admitted to the hospital were as follows: the odds ratio was 3.6 (95% CI 2.0–6.6), the relative risk – 2.0 (95% CI 1.6–2.5), attributive risk – 0.31, which probably indicated a high risk of non-streptococcal etiology of acute tonsillopharyngitis.

■ CONCLUSIONS

1. Considering a low ratio of likelihood of paraclinical indices in children, there is no reason to use them to verify non-streptococcal and streptococcal etiology of acute tonsillopharyngitis.
2. The results of the stimulated NBT-test of neutrophil granulocytes of the blood more than 40.0% of formazan positive cells were indicative of a reliable risk of non-streptococcal ATP in children available (OR=1.9; 95% CI 1.1–3.5).
3. In the presence of interleukin-6 <10.0 pg/ml, in the serum the risk of non-streptococcal etiology of acute tonsillopharyngitis is 3.6 (95% CI 2.0–6.6), and the sensitivity of this test is 77.1%.

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