International Journal of Medical Sciences And Clinical Research
(ISSN – 2771-2265)
VOLUME 03 ISSUE 08 PAGES: 39-51
SJIF IMPACT FACTOR (2021: 5. 694) (2022: 5. 893) (2023: 6. 184)
OCLC – 1121105677
Publisher: Oscar Publishing Services

Journal Website: https://theusajournals.com/index.php/ijmscr

Research Article

THE ROLE OF INFLUENCE OF THE MAIN CYTOKINES OF THE IMMUNE SYSTEM IN CHILDREN WITH PAPILLOMATOSIS OF THE LARYNX ON THE BACKGROUND OF ANTIVIRAL THERAPY

Submission Date: August 14, 2023, Accepted Date: August 19, 2023,
Published Date: August 24, 2023
Crossref doi: https://doi.org/10.37547/ijmscr/Volume03Issue08-06

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ABSTRACT

The purpose of the study was to study the role of cytokines and major interferons in children with laryngeal papillomatosis in the dynamics of antiviral therapy in the postoperative period. To achieve this goal, 252 children with laryngeal papillomatosis aged 3 to 9 years were examined. All children were examined and treated in the surgical department of otolaryngology of TMA. In order to determine the effectiveness of the treatment of children, the following division into groups was carried out: Group I - children with a continuously recurrent course of papillomatosis of the larynx were divided into two subgroups: Subgroup I - the comparison group received standard treatment surgery + IFN preparations (reaferon) - one course per 28 days; Subgroup I - study group surgery + IFN preparations (alpha-IFN / inosine) - according to the scheme for 1 year. Group II - children with a frequently relapsing course of PH: II a subgroup - received standard treatment surgery + IFN preparations (reaferon) - one course for 28 days; II in the subgroup - surgery + IFN preparations (alpha-IFN / inosine) - according to the scheme for 6 months. Group III - children with a rarely recurrent course of PH: III a group - surgery; Group III - surgery + licopid. It was revealed that the analysis of the main interferons and cytokines of the immune system made it possible to establish that the changes obtained in a comparative analysis of clinical variants of laryngeal papillomatosis are amenable to immunotropic therapy, which is expressed by the use of an antiviral drug. Moreover, there is an improvement in the values of cytokines and interferons, which is expressed in a decrease in the production of pro-inflammatory cytokines and in an increase in the production of IFN-α and IFN-γ, which have pronounced antiviral properties. The clinical result of therapy was a

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Crossref doi Google Scholar WorldCat MENDELEY
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decrease in the number of recurrences of papillomatosis in children, an improvement in general well-being, and clinical and laboratory indicators of the disease.

KEYWORDS

papillomatosis of the larynx in children, interferons, cytokines, interleukins, interferon inducers.

INTRODUCTION

The problem of papillomatosis of the larynx today remains one of the most difficult in otorhinolaryngology in relation to treatment. Recently, there has been an increase in the number of children with larynx papilomatosis, with more than 70% of patients having severe common recurrent forms [4,9,11,12]. As is known, the recurrence process is difficult to control with modern drugs , and therefore the question of prescribing antiviral therapy along with surgical therapy remains open. It is believed that the cause of relapses is that in the case of surgical treatment, only the visible pathological focus is excised , and not the etiological factor. Remaining in the tissues of HPV again leads to the development of the tumor process. Most often, HPV types 6 and 11 of the virus are detected in papillomatosis of the larynx, but the detection of viruses of types 8, 16, 18, 30 and 31 has also been described [9,12,15]. Researchers have no consensus on differences in the clinical course of the disease depending on the type of virus [12]. But the fact that the pathological recurrent process is due to a deficiency of immunological factors of immunity and features of the immune response, of course, there is no doubt. In this regard, it was shown that before the start of treatment in children with laryngeal papillomatosis, suppression of IFN-α, which is a powerful antiviral cytokine, against the background of activation of IFN-γ production, was found, which indicates the presence of a pronounced inflammatory process. Also, spontaneous and induced production of IFN-α was significantly reduced, indicating a low potential reserve of antiviral cytokine and clinically indicating the presence of persistent viral infection and recurrence of the pathological process. Our data are consistent with the data of a narrow number of scientists and doctors with scientific potential, who observed the dependence of interferon deficiency and their production on the severity of the clinical manifestation of the disease [1,3,6]. Therefore, a comprehensive diagnosis of laryngeal papillomatosis in children also requires immunological studies at various levels of immunity, ranging from cellular to molecular. At the same time, studies are carried out on the state of immunoreactivity and the main interferons and cytokines. In connection with the above, as usual, we set a goal to study the role of cytokines and major

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interferons in children with laryngeal papillomatosis in the dynamics of antiviral therapy in the postoperative period.

Material and research methods. 252 children with laryngeal papillomatosis aged 3 to 9 years were examined. All children were examined and treated in the surgical department of otolaryngology of the Tashkent Medical Academy (TMA). In order to determine the effectiveness of the treatment of children, the following division into groups was carried out: Group I - children with a continuously recurrent course of papillomatosis of the larynx were divided into two subgroups: Subgroup I - the comparison group received standard treatment surgery + IFN preparations (reaferon) - one course per 28 days; Subgroup I - study group surgery + IFN preparations (alpha-IFN / inosine) - according to the scheme for 1 year. Group II - children with a frequently relapsing course of PH: II a subgroup - received standard treatment surgery + IFN preparations (reaferon) - one course for 28 days; II in the subgroup - surgery + IFN preparations (alpha-IFN / inosine) - according to the scheme for 6 months. Group III - children with a rarely recurrent course of PH: III a group - surgery; Group III - surgery + licopid. The control group was represented by 29 practically healthy children of the same age and gender.

And studies of cytokines and interferons were carried out against the background of therapy after surgical removal for 6 months of therapy. Immunological studies were carried out at the NDC "Immunogen-test" at the RNCI of the Ministry of Health of the Republic of Uzbekistan on the basis of a scientific agreement. Determination of cytokines and interferons in the serum of peripheral blood on an empty stomach was carried out using the test systems "Vector-Best", Novosibirsk, Russia according to the standard instructions by ELISA.

The results obtained and their discussion. Thanks to modern achievements in fundamental and applied immunology, molecular biology and biotechnology, new biologically significant indicators have now appeared that can help in the work of a practicing otolaryngologist, in particular in the diagnosis, treatment and prognosis of diseases, as well as in the selection of immunotropic drugs for complex therapy [2,4]. In recent years, much attention has been paid not only to the study of cellular and humoral factors of immunity, but to the study of the behavior of immunological components depending on the clinical features of the disease, which are a kind of indicators of the nature of the course of the disease, especially against the background of a chronic long-term or recurrent process [2]. Cytokines are proteins that are produced mainly by activated cells of the immune system, providing the functions of intercellular cooperation, positive and negative immunoregulation of the protective functions of the body [2,5,6,7]. It is

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known that cytokines regulate the amplitude and duration of inflammatory and immune responses [2,3]. It is important to note that cytokines can be isolated into a new independent system of regulation of the main functions of the body, which exists along with the nervous and endocrine systems and is primarily associated with maintaining homeostasis [2,3]. It is known that at the tissue level, cytokines are responsible for the development of inflammation, and then the regeneration of tissues of homeostasis [8,9,13,14]. With the development of a systemic inflammatory response, cytokines affect almost all organs and systems of the body involved in the regulation of homeostasis [14]. It should be noted that in recent years, studies of cytokine levels in various human diseases are based on the fact that cytokines are key factors in the immunopathogenesis of a number of immune-dependent conditions and diseases, including infectious and proliferative ones, such as laryngeal papillomatosis in children, where it is quite common the role of infectious etiopathogenesis in its development is recognized and, consequently, the role of almost all factors of the immune system in its development and progression [10,12]. It is known that papillomatosis of the larynx is a serious disease that causes a disorder of the most important functions of the body - respiratory and voice-forming, while recurrence of papillomas, their rapid growth, damage to significant areas of the larynx and trachea pose a threat to the life of the patient [3,4]. A predisposing factor in the occurrence of papillomatosis of the larynx is an acute infectious disease, characterized by a selective lesion of the mucous membrane of the larynx and a decrease in the immunobiological activity of the organism [4,11]. Despite a powerful humoral and cellular immune response in acute viral infections, a chronic viral long-term lesion of the larynx develops, which often has a frequently relapsing character. At the same time, the key role in the mechanisms of virus persistence is played by the relationship between the virus and the factors of the immune system of the macroorganism [5,6]. Despite a significant deepening in the last decade of ideas in the etiology, immunopathogenesis, course and progression of laryngeal papillomatosis in children, many questions regarding the mechanisms of the development of the pathological process and its progression remain open.

As described above, in children with papillomatosis of the larynx, particular importance is attached to the study of the main interferons, which play an important role in the formation of the antiviral and antitumor process [1,9,13]. Many researchers in our country and abroad have devoted their work to laryngeal papillomatosis [6,7], however, despite this, there are still problems regarding the diagnosis and especially the treatment of children, especially with frequently and continuously recurrent forms of the disease. Despite the existing practice and proven mechanisms for the development and progression of laryngeal papillomatosis in children, today there is no way to

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clearly predict the course of the disease, the development of relapses, their frequency and frequency. Our analysis made it possible to identify the following changes in the state of functioning of cytokines, as well as interferons. The data obtained are presented in Table 1. Thus, the analysis showed that the serum content of IFN-α in the dynamics of treatment in the group of children 1a was increased by 7.1 times, and in the group of children 1c - 8 times compared with the group of children before treatment. In turn, IFN-γ in group 1a was increased by 1.22 times, while in group 1 it was also 1.33 times higher compared to the data of children before treatment. The level of antibodies to IFN-α in group 1a was suppressed by 1.05 times, while in group 1 it was suppressed by 1.2 times. Therefore, against the background of the existing potential, i.e. reserve of interferons for induction and when prescribing interferon inducers, there is a significant improvement not only in antiviral immunity, which is expressed in the normal production of IFN-α, but also in the improvement of cellular immunity, as evidenced by an increase in IFN-γ, which is produced by cells of the adaptive immunity link.

Next, we reviewed the main cytokines of the immune system that were studied before treatment - TNF-α and IL-6. At this stage, we have studied the levels of cytokines in the dynamics of treatment. Thus, the analysis showed that the level of IL-6 after treatment compared with the data before treatment in group 1a was suppressed 1.6 times, and in group 1c - 2.7 times. As can be seen, the values of IL-6 in the 1a group of children during therapy remains elevated, even against the background of IFN therapy. And in group 1, the level of IL-6 is significantly reduced, but does not reach the normal value.

TNF-α in group 1a of children with papillomatosis decreased during therapy and was suppressed compared to the data before treatment, where its concentration was significantly increased, by 1.7 times, and in group 1 it was suppressed by 2.5 times. Therefore, the analysis showed that during therapy, suppression of the level of TNF-α is observed, and against the background of IFN-therapy in combination with inosine, a more effective immune response is observed, which is expressed in a significant suppression of IL-6 and TNF-α.

Thus, for children with continuously recurrent papillomatosis of the larynx, taking inosine against the background of standard therapy in the complex in the dynamics of treatment, compared with the data of the standard group, an increase in IFN-alpha by 1.13 times, IFN-γ by 1.1 times was characteristic, decrease in antibodies to IFN-α by 1.14 times, TNF-α decreased by 1.5 times, IL-6 - by 1.74 times. The differences we found were significant. The differences are all valid. Next, we analyzed the results of the analysis of children with a frequently recurrent form of laryngeal papillomatosis. It was found that the content of IFN-α in the dynamics

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of treatment in the group of children 2a was increased by 3.5 times, and in the group of children 2c - 5.5 times compared with the group of children before treatment. In turn, IFN-γ in group 2a was increased by 1.6 times, while in group 2 - by 1.98 times, also compared with the data of children before treatment. The level of antibodies to IFN-α in group 2a was suppressed 1.2 times, in group 2b - 1.5 times.

Table 1.

The study of the dynamics of cytokines in children with papillomatosis of the larynx in the dynamics of therapy, depending on the clinical features of the disease, M± m , ng/ml

Continuously recurrent papillomatosis of the larynx				
Immunological indicators	Norm	Before treatment	Group 1a (standard treatment + IFN)	Group 1c (standard treatment + IFN + inosine pranobex)
IFN-α	44.25±3.4	11.9±1.95*	84.5 ±1.92*^	95.70 ±1.80*#$
IFN-γ	3.86±0.44	13.7±1.9*	16.8 ±1.62* ^	18.2 ±1.61* #
AT to IFN-α	3.5±0.64	8.9±1.45 *	8 , 5 ±0.58*	7.45 ± 0.32* #$
TNF-α	4.82 ±0.91	21.9±2.82*	12.94 ±0.73* ^	8 .62 ±0.41* #$
IL-6	3.58±0.41	19.8±1.25	12.70±0.55 ^	7.3 ±1.42* #$
Frequently recurrent papillomatosis of the larynx				
Immunological indicators	Norm	Before treatment	Group 2a (standard treatment + IFN)	Group 2c (standard treatment + IFN + inosine pranobex)
IFN-α	44.25±3.4	13.4±2.4*	46.40 ±1.65*^	74.20 ±1.94*#$

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IFN-γ	3.86±0.44	9.2±1.9	14.32±1.22*^	18.2±0.58*#$
AT to IFN-α	3.5±0.64	7.8±1.3*	6.52±0.35*	5.28±0.41*#
TNF-α	4.82 ±0.91	23.7±4.1*	11.93±0.80*^	6.20±0.50*#$
IL-6	3.58±0.41	11.6±4.2*	8.12±0.58*^	5.21±0.41*#$
Rarely recurrent papillomatosis of the larynx				
Immunological indicators	Norm	Before treatment	Group 3a (standard treatment	Group 3c (standard treatment + lycopid)
IFN-α	44.25±3.4	18.5±1.42*	39.70 ±0.88*^	42.60 ±1.55#
IFN-γ	3.86±0.44	19.7±2.1*	8.98±0.42*^	6.55±0.42*#
AT to IFN-α	3.5±0.64	6.4±1.29*	5.14±0.85*	4.42±0.63
TNF-α	4.82 ±0.91	34.4±1.35*	14.30±0.81*^	7.40±1.35#$
IL-6	3.58±0.41	6.20±0.55	4.90±0.45	3.29±0.40#

Note: * - significance of differences with the data of the control group, ^ - differences of groups 1a, 2a and 3a with values before treatment; # - differences in groups 1c, 2c and 3c with values before treatment; $ - differences between 1a and 1c, 2a and 2c, 3a and 3c groups.

There is a depletion of interferons in the group of patients with a continuously recurrent form of laryngeal papillomatosis. When comparing the values of IFN-alpha between groups, it can be seen that the lowest content of the antiviral protein IFN-alpha was in the group of children with a continuously recurrent form of laryngeal papillomatosis. Therefore, again, the same picture is observed, which was revealed in the group of children with a frequently recurrent form of laryngeal papilomatosis, which shows a high activity of interferons in the blood serum, which is confirmed clinically by an improvement in the condition, and fewer relapses. The study of TNF-α and IL-6 showed that IL-6 in the dynamics of treatment compared with the values before treatment in group 2a was suppressed by 1.4 times, in group 2c - by 2.2 times. But

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still, the values of IL-6 in both groups of children remain elevated compared to the data of the control group. The data obtained are presented in Table 1. TNF-α in the dynamics of treatment also remains elevated compared to the data of the control group, but significantly reduced compared to the data of children before treatment. Thus, TNF-α in the 2a group of children with papillomatosis decreased 1.9 times, in the 2nd group - 3.8 times. Consequently, a decrease in the level of TNF-α was revealed, and against the background of IFN-therapy in combination with inosine, a more effective immune response is observed, which is expressed in a pronounced anti-inflammatory effect by suppressing pro-inflammatory cytokines. So, for children with frequently recurrent papillomatosis of the larynx, taking inosine in combination with standard therapy in the dynamics of treatment compared with the data of the standard treatment group, an increase in IFN-alpha by 1.6 times, IFN-γ by 1.3 times, a decrease in antibodies to IFN-α by 1.2 times, a decrease in TNF-α by 1.9 times, a decrease in IL-6 by 1.6 times. The differences are all valid. Next, we analyzed the results of the immunological analysis of children with a rarely recurrent form of laryngeal papillomatosis. It was found that the content of IFN-α in the dynamics of treatment in the group of children 3a was increased by 2.14 times, and in the group of children 3b - 2.3 times compared with the group of children before treatment. In turn, IFN-γ in group 3a was reduced by 2.2 times compared with the data before treatment and practically reached the standard values, while in group 3 it was reduced by 3 times in the course of treatment. The level of antibodies to IFN-α in the 3a group was suppressed by 1.3 times, in the 3rd group - by 1.4 times. Consequently, a greater activity of interferons in the blood serum against the background of standard therapy is shown, which is confirmed clinically by an improvement in the condition and fewer relapses. The study of TNF-α and IL-6 showed that IL-6 in the dynamics of treatment compared with the values before treatment in group 3a was suppressed by 1.3 times, in group 3c - by 1.8 times. It should be noted that it is in this group of children that IL-6 values approach the norm and are significantly reduced. TNF-α in the dynamics of treatment also remains elevated compared to the data of the control group, but significantly reduced in comparison with the data of children before treatment. Thus, TNF-α in the 3a group of children with papillomatosis decreased 2.4 times, in the 3rd group - 4.6 times. Consequently, a decrease in the level of TNF-α was revealed, and against the background of IFN-therapy in combination with licopid, a more effective immune response is observed, which indicates a pronounced anti-inflammatory effect of the drug. So, for children with rare recurrent papillomatosis of the larynx, taking against the background of standard therapy in the complex licopid in the dynamics of treatment compared with the data of the standard treatment group, an increase in IFN-α by 1.1 times, IFN-γ by 1.4 times was characteristic, a

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decrease in antibodies to IFN-α by 1.2 times, a decrease in TNF-α by 1.9 times, a decrease in IL-6 by 1.4 times.

When analyzing cytokines between groups, it was shown that the highest content of antibodies to IFN-α was detected in the group of children with a continuously recurrent form of the larynx. Consequently, there is an increase in the formation of antibodies to IFN-α, which contributes to the autoimmunization of the pathological process and its progression. Thus, in the group of children with a continuously recurrent form of laryngeal papillomatosis, the highest value of antibodies to IFN-α is observed, which in turn indicates autoimmunization and clinically a continuously recurrent process. Next, we studied the content of IFN-γ in the blood serum of children with laryngeal papillomatosis. The analysis showed that in all the studied groups of children there is an increase in the level of IFN-γ relative to the control data ($p<0.05$). It was found that the highest value of IFN-γ was typical for children with a rarely relapsing form of laryngeal papillomatosis, while the lowest value was observed with a frequently relapsing form of laryngeal papillomatosis. Data correlations showed that in the group of children with a continuously relapsing form of laryngeal papillomatosis, the content of IFN-γ was increased by 3.5 times, with a frequently relapsing form - by 2.4 times, and with a rarely relapsing form - by 5 times. As can be seen, the highest value of IFN-γ is observed in the group of children with rarely recurrent papillomatosis of the larynx. Based on the data obtained, we can say that as the disease progresses, there is a suppression of IFN- α, an increase in antibodies to IFN-α and a suppression of IFN-γ. It is known that IFN-α, which plays one of the main roles in the elimination of the hepatitis virus, has a direct antiviral effect, as well as mediated immunomodulatory activity. IFN-α is produced by almost all cells of the body, but to the greatest extent by macrophages and lymphocytes. IFN-α is a powerful antiviral protein [4,6].

The highest values of TNF-α serum concentration were found in the group of children with a rarely relapsing form of larynx papilomatosis, and the lowest values were typical for children with a continuously recurrent form of larynx papilomatosis. This picture obviously indicates the depletion of the pro-inflammatory potential in children with a continuous and often recurrent problem. It has been established that microorganisms and their products, the process of phagocytosis itself, serve as inducers of TNF-α formation. Its level increases when infected with viruses [8,14]. Obviously, TNF-α is involved in the implementation of the cytotoxic effect of natural killer cells, which plays an important role in anti-infective and antitumor immunity [8]. Based on the foregoing, it follows that in the group of children with continuously recurrent papillomatosis of the larynx, there is a

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depletion of TNF-alpha reserves against the background of a long and aggressive course of the inflammatory process. In turn, the low content of TNF-α in the blood once again proves and substantiates the suppression of especially cellular immunity in children with continuously recurrent papillomatosis of the larynx. It can be seen from the table that in the group of children with a rarely relapsing form, the level of TNF-α is increased, which confirms the intensity of immunity and an adequate immune response. It is also known from the literature that TNF-α is capable of lysing not only tumor cells, but also virus-infected cells [2,8], which can be seen from our data, a low level of TNF-α contributed to apparently low functional activity, which was often clinically manifested. - and continuously recurrent papillomatosis of the larynx. So, TNF-α is a cytokine, which, according to its properties and spectrum of biological action, is a product of macrophages of the T-lymphocytes themselves. Therefore, we can confidently say that with continuously recurrent papillomatosis of the larynx, a severe course of the disease is observed, which is provoked by suppression of the cellular link of immunity, activation of humoral immunity factors and suppression of TNF-α. Next, we studied the serum concentrations of IL-6 in different groups of children with laryngeal papillomatosis. It can be seen that the concentration of IL-6 was increased in all the studied groups. Moreover, the highest serum value was typical for children with a continuously recurrent form of larynx papilomatosis. And the lowest IL-6 value was found in the group of children with a rarely recurrent form of larynx papilomatosis and did not have a significant difference with the value of the control group. An analysis of the concentration of IL-6 showed that the level of IL-6 in the group of children with a continuously recurrent form of papillomatosis of the larynx was increased by 5.4 times, in the group with a frequently relapsing form - by 3.3 times, and in the group with a rarely relapsing form - 1.4 times. It can be seen that there is an increase in the values of IL-6. Literature analysis shows that IL-6 is a pleiotropic cytokine with a wide range of biological activity, which is produced by both lymphoid and non-lymphoid cells of the body [88,257]. It has been established that IL-6 regulates the immune and acute phase response, inflammation, oncogenesis, and hematopoiesis [6]. One of the main functions of IL-6 is the regulation of the maturation of antibody-producing cells from B-lymphocytes and the production of immunoglobulins itself. IL-6 is involved in the activation of T-lymphocytes, induces the synthesis of many acute-phase proteins: fibrinogen, C-reactive protein, etc. [1,6]. The analysis shows that obviously increased values of IL-6 contribute to the activation of the humoral link of immunity, which we were able to identify, and moreover, an increased level of IL-6 has an immunosuppressive effect on T-cell immunity. Consequently, we found a significant increase in the level of IL-6 in the peripheral blood serum of children

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with laryngeal papilomatosis, with the highest values being typical for children with continuously recurrent laryngeal papilomatosis, which can serve as an important diagnostic and prognostic criterion for the progression of the disease and the frequency of relapses. Thus, our data on the study of TNF-alpha and IL-6 indicate the important diagnostic value of determining the studied cytokines in the progression of a chronic infectious inflammatory process. Summing up the description of the obtained results, it should be noted that these two studied cytokines have an important role in the pathogenesis of larynx papilomatosis in particular. Thus, it is known that TNF-α is one of the most well-known and widely studied pro-inflammatory cytokines, but despite this, our data are top-priority in this area, because there are practically no such studies in the literature. It should be said that the excess content of pro-inflammatory cytokines such as TNF-α and IL-6 contributes to the maintenance of a long-term inflammatory process in the epithelial tissue and may contribute to further damage.

CONCLUSION

Moreover, IFN -γ is known to have a longer lifespan compared to IFN-α, so elevated levels can persist for a long time. It has been proven that IFN -γ is produced under the action of viruses. Also, the production of IFN -γ is enhanced by itself, which, adding up the information together, can explain the increased values of IFN- γ in serum, spontaneous and induced production. IFN- γ has a low antiviral, antiproliferative effect and some immunomodulatory effect [7,8,14]. The most important function of IFN -γ is its participation in the implementation of the relationship between lymphocytes and macrophages in the cellular and humoral components of the immune response, so it serves as a macrophage stimulator [7,8]. Thus, the analysis of the main interferons and cytokines of the immune system made it possible to establish that the identified changes in the comparative analysis of clinical variants of laryngeal papillomatosis are amenable to immunotropic therapy. Moreover, there is an improvement in the values of cytokines and interferons, which is expressed in a decrease in the production of pro-inflammatory cytokines and in an increase in the production of IFN-α and IFN-γ, which have pronounced antiviral properties. The clinical result of therapy was a decrease in the number of recurrences of papillomatosis in children, an improvement in general well-being, and clinical and laboratory indicators of the disease. The cytokine spectrum analyzed by us turned out to be an integral indicator, the determination and analysis of which is a necessary clinical and laboratory criterion in the diagnosis of immunodeficiency conditions, which include papillomatosis of the larynx in children.

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International Journal of Medical Sciences And Clinical Research (ISSN – 2771-2265)
VOLUME 03 ISSUE 08 PAGES: 39-51
SJIF IMPACT FACTOR (2021: 5. 694) (2022: 5. 893) (2023: 6. 184)
OCLC – 1121105677
Publisher: Oscar Publishing Services

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