

ASSESSMENT OF THE COURSE AND SEVERITY OF RESPIRATORY RECURRENT PAPILLOMATOSIS IN CHILDREN AND THE CHOICE OF TREATMENT TACTICS

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INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a chronic disease of the respiratory tract with proliferation of papillomas in any part of it, which is multiple and often recurrent. RRP affects patients of all ages, but has different clinical manifestations and course in adults and children.

RRP is classified into two categories: juvenile and adult. Such a division is associated not only with the onset of the age of the disease, but also with the route of infection and its course, which also determines the prognosis.

The incidence of RRP in developed countries is estimated annually at 4.3 per 100,000 children (1, USA), while the prevalence is from 1.69 to 2.59 per 100,000^[2] In European countries, for example, in Denmark, this level is also not so high and amounts to 3.5 per 1 million people per year.^[3] The national RRP prevalence in Australia between 2000 and 2013 was 0.81 per 100,000 aged <15 years, peaking between 5 and 9 years of age (1.1 per 100,000).

Human papillomaviruses (HPV) are a widespread and variable group of viruses that infect the epithelium of the skin and mucous membranes and have oncogenic potential. HPV is transmitted by close contact with the infected epithelium, therefore the main routes of infection are sexual and contact-household. Transmission of HPV from an infected mother to the fetus is possible.

RRP is caused by human papillomavirus (HPV), usually types 6 and 11, which are also the cause of most cases of anogenital warts and respiratory papillomas.^[4] HPV is one of the most common sexually transmitted infections. So in the United States; more than 75% of women have genital HPV at some point in their life. 30-60% of mothers of children with RRP have genital HPV, compared with 5% of mothers whose children do not. The incubation period for infection with orogenital papillomas can last from 2 months to 2-10 years. In 30% of cases, the virus can be cleared within 6-12 months. Diagnosis of latent HPV infection is carried out only by PCR.

Although the mode of transmission of HPV is still unclear, vertical transmission (intrauterine or during

delivery through an infected birth canal) is considered the main route of transmission to children. HPV deoxyribonucleic acid has been detected in the peripheral blood of pregnant women and newborns.^[5] With a single sexual contact, the probability of HPV infection reaches 80%, but in most cases the virus spontaneously eliminates within 9-15 months from the moment of infection. Risk factors for infection are considered early onset of sexual activity, promiscuous sexual intercourse, unprotected sex, concomitant infections and inflammation affecting the cervix.

The course of juvenile RRP, in comparison with adult RCC, is characterized by frequent recurrence with the need for more surgical interventions and usually affects several areas of the respiratory tract. The larynx is most often affected.^[7-9]

In terms of the prevalence of gender differences, one of the researchers did not note either.^[6,8,9] Most often, in juvenile RRP, the first symptoms appear very early - at the age of 2 to 4 years and the most common symptom is dysphonia. The adult form usually appears in the third or fourth decade of life, rarely in patients over 60 years of age. In both adults and children, one of the first symptoms is dysphonia, less often cough and dysphagia, while in children the second common symptom is shortness of breath and stridor. The earlier the symptoms appear, the more aggressive the disease and the larger the lesion (more than one anatomical region) and the more often the need for surgical interventions. Children who are diagnosed before the age of three are 3.6 times more likely to need more than four operations per year and have more than one anatomical focus of the disease.^[8]

The main therapeutic method is surgical - this is the resection of papillomas using various instruments (cold tweezers, CO2 laser and microdebrider) to restore adequate airway patency and improve voice quality.^[21]

However, surgical excision does not guarantee the cessation of papilloma growth. In children under 5 years of age, on average, five operations are recorded per year to control relapses.^[8,9]

Antiviral drugs are widely used, mainly in adults with RRP, which is associated with the risks of side effects of antiviral drugs in general on the body. There have been reports of the use of the prophylactic vaccine Gardasil^[6,11,16,18] for RRP to reduce relapses during the latency period.

MATERIAL AND RESEARCH METHODS

A study was carried out of 71 patients with recurrent respiratory papillomatosis, aged 1 to 17 years (mean age was 4.23 ± 2.1), there were 52.1% boys ($n = 37$), 47.9% girls ($n = 34$). In the age aspect, the group of preschool children (4-6 years old) prevailed, amounting to 43.7%, the group of schoolchildren (7-10 years old) was small, accounting for 11.3% of children (Table 1). The second largest group was the group of young children (1-3 years old, which amounted to 32.4%.

Table 1: Distribution of patients by gender and age.

Gender	Age, years				Total	
	1-3 y	4-6 years	7-10 years	11-17 years	abs.	%
boys	13	20	1	3	37	52.1
girls	10	11	7	6	34	47.9
Total	abs	23	31	8	71	100, 0
	%	32.4	43,7	11.3		

The first clinical manifestations of respiratory recurrent papillomatosis is a change in voice, the first signs of which parents pay little attention to. With the progression of the growth of papillomas, voice changes intensify, signs of respiratory failure are added, and therefore patients turn to a medical institution. The study of the anamnesis of children with RRP revealed that the period between the appearance of the first symptoms of the disease in the form of a change in voice and the visit to a doctor is from six months to a year. At the same time, the development of the clinic, its course, recurrence is influenced by the age of the onset of the disease, which

is determined by us by the age of the first clinical manifestations. We analyzed the age of onset of RRP, while it was revealed that in 80.3% of children, hoarseness of the voice appeared before the age of 3 years, of which changes in voice at the age of 1 to 3 years were noted by the parents of 63.4% of children, and in 16.9% of children, voice changes were recorded even before the age of 1 year - this is evidence of a more severe course of the disease in most children with RRP. Hoarseness first appeared at the age of 4-6 years in 19.7% of children (Table 2).

Table 2: Data on the appearance of the first clinical signs of RRP by age (according to anamnesis).

Gender	The number of patients in whom a change of voice for the first time appeared in age, n = 71			Total	
	Up to 1 year	13 years	4-6years old	Abs.	%
boys	7	24	6	37	52.1
girls	5	21	8	34	47.9
Total	abs	12	45	71	100
	%	16.9	63.4		

Diagnosis of papillomas was based primarily on laryngoscopic examination - accumulations of small-point formations were detected, with uneven growth along the surface of the larynx. In young children, the degree of narrowing of the glottis was determined laryngoscopically, in older children, a more thorough examination was performed to determine the prevalence of papillomas.

The following data were collected from medical records and examinations:

1. Gender
2. Age of onset
3. Symptoms
4. Age at first surgery
5. The presence or absence of complications from the larynx.
6. Type of laryngeal complication.

7. The total number of operations for the treatment of RRP or the number of procedures (per year).
8. Duration of the disease or the interval between diagnosis and detection of consequences.
9. Applied surgical technique (instruments used in surgical interventions)
10. Topographic and calibration setting.
11. The degree of airway obstruction.

Based on the data in points 7 and 8, the annual frequency of operations for each patient was obtained. Based on the data in paragraphs 10 and 11, the RRP was classified according to the stage scoring system proposed by Derkay et al. (22), which assesses the degree of disease in the anatomical regions of the digestive tract. Depending on the size of the lesion, each affected area is scored in the range from "0" to "3": "0" - no damage, "1" - superficial damage, "2" - protruding lesions, and "3" -

obstructive lesions. The sum gives the anatomical score (Table 3). To analyze the results, the maximum degree of respiratory impairment presented by the patients (their representatives) during their observation was taken into account (the worst estimate presented during the observation).

Table 3: Anatomical scale of the spread of papillomas proposed by Derkay et al.

scale score: 0 - no, 1 - superficial lesion, 2 - protruding lesion, 3 - volumetric lesion	
Epiglottis (lingual surface)	
Epiglottis (laryngeal surface)	
Right scapular-laryngeal fold	
Left scapular laryngeal fold	
Right vestibular fold	
Left vestibular fold	
Right vocal fold	
Left vocal fold	
Right arytenoid	
Left arytenoid	
Anterior commissure	
posterior commissure	
Sub-voice department	
Trachea upper third	
Trachea middle third	
Trachea lower third	
Right bronchus	
Left bronchus	
Trachestoma	
Nose	
Palate	
Pharynx	
Esophagus	
Lungs	
other	
Total	

A quantitative study was carried out to monitor papillomavirus infection and identify a possible relationship between the viral load in a laboratory sample

and the clinical course (prevalence, recurrence rate), as well as predict its course (Mairand MH et al., 2009; Von Karsa et al., 2015).

Methods of measurement Absolute concentration • Copies of HPV DNA in the sample volume (1 ml)
Relative concentration • Copies (lg copies) of HPV DNA per cell (genome) - per 1 cell - For 10^3 cells - For 10^5 cells

HPV monitoring and prognosis criteria

- The amount of HPV DNA is not determined in the absence of the virus in the test sample or its minimum amount (below the detectable level) - the risk of developing a pathological process associated with HPV is minimal.
- Clinically insignificant concentration of the virus (less than 10 copies of HPV DNA per 10^3 cells) - minimal risk of relapse, transient course of the viral process.
- A clinically significant concentration of the virus (more than 10 copies of HPV DNA per 10^3 cells) is a chronic infection with a high risk of developing neoplastic processes.
- More than 1000 copies of HPV DNA per 10^3 cells with an established fact of persistent infection (HPV has been detected for more than 1 year) - increased viral load.
- Reduction of viral load by 10 times in 6 months - transient infection.
- An increase in viral load 6 months or more after treatment indicates the possibility of a relapse. Statistical information was initially presented in a descriptive manner. Independent samples Student's t test and Fisher's exact test were the inference criteria used to confirm the evidence. A 5% significance level was used for all statistical results ($p < 0.05$).

RESEARCH RESULTS

The gender distribution was 44 (51.8%) males and 41 (48.2%) females. The age at onset of symptoms ranged from one month to 6 years (mean age = 2.71 years).

Table 4: The incidence of clinical indicators of RRP in children.

sign		indicator	
Age of first symptoms		2.71	
symptoms	Dysphonia	100% (71)	
	Dyspnea	85.4 % (60)	
	Dysphagia	26.8 % (19)	
	cough	11.3% (8)	
Age of first surgery (number of patients)	Up to 3 years old	26.8% (19)	
	3-7 years old	49.3% (35)	
	Over 7 years old	23.9% (17)	
complications	Availability	Available +	No -
		39.4% (28)	60.6% (43)
Number of operations per year	Type of complications and number	scarring	trachestomy
		36.6% (26)	2.8% (2)
Number of operations per year	Up to 7 years	3.2	
	Over 7 years old	0, 8	

Number of patients who needed > or <3 operations per year	> 3 operations	36,6% (26)
	<3 operations	63.4% (45)
Based on Derkay score	localized process	2.75 ± 0.23
	moderately widespread process	6.01 ± 1.2
	common process	29.45 ± 3.05

Among children, the appearance of the first symptoms of papillomatosis before the age of 3 years was noted by 67 patients, which amounted to 94.4%, however, the first procedures (operations) were carried out before 3 years in 19 patients, which amounted to 26.8%. It is worth noting the interval between the appearance of the first symptoms and the establishment of the diagnosis, which ranged from 6 months to 3 years, which is associated with the difficulties of examining the larynx in young children, as well as the fact that parents pay little attention to the change in voice in young children. The first symptoms in patients were noted: dysphonia, shortness of breath and cough. At the same time, in 67.6% of cases (58 patients), the patients were associated with a previous cold; therefore, in most cases, the primary diagnosis in children was acute laryngitis. The most frequent symptoms were dysphonia 100% (71 patients), shortness of breath - 85.4% (60 patients), cough occurred in 11.3% (8 patients).

The age at onset of first symptoms in adults was 39.2 ± 5.1, with the only symptom being dysphonia of varying degrees.

Severe complications were observed in 39.4% (n = 28) of cases. At the same time, complications in the form of cicatricial changes in the airway tube and tracheostomy developed in childhood, 36.6% and 2.8%, respectively. The imposition of a tracheostomy in 2 cases was caused - in the first case, by rapid progression and spread into the bronchi, in the second case - by cicatricial changes at the level of the vocal cords with a narrowing of its lumen. Cicatricial adhesions were observed mainly along the anterior commissure - 17 patients, with the capture of vestibular folds - 6 patients, 6 patients - vocal cords without scarring of the anterior section.

Before 3 years, the first operations were performed in 14.1% of patients, over 7 years - 20% of patients. It is

worth noting that one child whose papillomas were found at the age of 6 months to 14 years did not undergo any surgical procedure, although he had a score of 21 on the Derkay score. The frequency of operations in children under 7 years old was 3.2 procedures per year. , for children over 7 years old 0.8 procedures per year. At the same time, the number of patients who needed more than 3 operations per year was 36.6% (n = 26), while all of them were under 3 years of age.

In RRP, the vocal cords were always affected (100%), extra-laryngeal lesions were noted in 16 cases (17.4%): 2 - into the trachea, 1 - into the trachea and bronchi, the mouth of the esophagus and the initial section in 11 cases, into the pharynx - 2 ...

We conditionally divided the prevalence according to Derkay into a localized process, a moderately widespread process and a widespread process. A localized process according to Derkay occupying no more than two areas with a maximum volumetric lesion is no more than 6 points; moderately widespread process - occupies no more than three areas with a maximum volumetric lesion or more than 3 areas with minimal lesions is not more than 10 points; a common process - in which the lesion is more than 10 points with spread to more than 4 areas with various lesions of the mucosal surface.

At the same time, the average score according to Derkay with a localized process in children was 2.75 ± 0.23 points, with a moderately widespread process in Derkay children was 6.01 ± 1.2 points. The widespread process according to Derkay was 29.45 ± 3.05 points in children. So in childhood, the higher the Derkay score, the more the symptoms of both dysphonia and shortness of breath increase.

Table 5: Characteristics of the degree of narrowing of patients with RRP at the first visit according to the data of laryngoscopy.

Narrowing degree	grade I	grade II	grade III	grade IV	Total
Quality	31	24	11	5	71
%	43,7	33.8	15.5	7.0	100

At the same time, the degree of narrowing at the first visit prevailed of the first degree - 43.7% of patients, more pronounced degrees of narrowing were noted in 15.5% (3 degrees) and 7.0% (4 degrees) of children, which in total, however, amounted to almost a quarter from all sick children with RRP. However, given the age of children, these data on stenosis can be considered

indirect, since a full examination with the determination of the degree of narrowing and the prevalence of the process in children is possible only with direct laryngoscopy, in fact, the degree of narrowing during operational revision in children is much higher than with laryngoscopy without sedation. Examination was possible in all patients with flexible laryngoscopy or a

rigid endoscope with an angle of view of 70° without the use of sedation methods, which made it possible to establish the diagnosis in all children without the use of sedation methods.

A survey of 71 children was carried out, typing revealed only HPV types 6 and 11, other genotypes were not detected. A quantitative analysis revealed the presence of HPV 6, 11 in 83.1% of patients (n = 59), in 16.9% of cases (n = 12) HPV was not detected, however, the

presence of papillomas was noted in patients with RRP, it should be noted that these were children with repeated relapses over the age of 7 years, while papillomas persisted stably, were not removed for some period after the start of growth. In patients with HPV, there were significant discrepancies in the quantitative analysis of viral load: for example, a larger percentage of patients (40.8%) were detected when exceeding 1,000,000 viral particles (HPV) per 1,000 human cells.

Table 6: Clinical characteristics of patients with RRP with determination of HPV viral load.

HPV copies / 1000 cells	Number of patients	%	Number of copies M ± m	Number of relapses per year, M ± m	By Derkay points, M ± m	p
Not determined	12	16.9	-	0.5 ± 0.025	2.75 ± 0.23	$\chi^2 = 0.2$ p > 0.05
Up to 10 ⁴	6	8.5	2.5 ± 0.88x10	0.77 ± 0.05	6.01 ± 1.2	$\chi^2 = 0.42$ p > 0.05
Up to 10 ⁵	6	8.5	2.87 ± 2.31x10 ⁴	0.98 ± 0.15	12.2 ± 0.83	$\chi^2 = 0.51$ p > 0.05
10 ⁵ to 10 ⁶	eighteen	25.4	4.02 ± 3.74x10 ⁵	2.58 ± 0.65	29.45 ± 3.05	$\chi^2 = 8.58$ p < 0.01
Over 10 ⁶	29	40.8	2.14 ± 1.63x10 ⁶	3.01 ± 1.45	48.65 ± 7.4	$\chi^2 = 18.0$ p < 0.001
Total	71	100				

Note: $\chi^2 = 4.8$ p < 0.05, $\chi^2 = 12.2$ p < 0.01, $\chi^2 = 8.58$ p < 0.01, $\chi^2 = 18.0$ p < 0.001 - the data are reliable; p > 0.05 - data are not reliable

When comparing the viral load and clinical data, it can be stated that with a viral load of up to 10,000 copies per 1000 cells, there was a weak growth of papillomas with rare relapses up to 1 time per year or less, while on the Derkay scale, the spread occurs within 2-3 areas. to the easy flow of RRS. With a virus concentration of up to 1000 copies or less per 1000 cells, we determine a mild course of RRP with the capture of one or two anatomical regions with rare relapses associated with previous colds or concomitant viral diseases. A more severe clinical course of RCP with frequent relapses was observed when the virus concentration was more than 1,000,000 copies per 1,000 cells with relapses up to 3-4 times a year and spreading to 5-6 areas with a narrowing of 2-3 degrees. Moderately severe course with control of the degree of narrowing by surgical methods is observed with a viral load of less than 1,000,000 and above 100,000 copies per 1,000 cells - with this recurrence 2-3 times a year, patients with constant observation are well controlled, but require special treatment.

The therapeutic measures carried out by us in the form of systemic interferon therapy showed the best effect in the group with severe RRP with a viral load of more than 1,000,000 copies per 10³ cells, while side effects were leveled against the background of a decrease in the recurrence of papillomatosis, but the duration of treatment was 1 year. In the group of patients with a viral load of 100,000 copies per 10³ cells, a good effect was noted when using interferon therapy for 3 months to six months, with minimal side effects. In groups with a viral

load of up to 10,000 copies per 10³ cells, we consider it inappropriate to use systemic interferon therapy, given the large number of side effects, and shortening the intake also does not reduce the number of relapses. The best effect is observed when the Gardasil vaccine is used for prophylactic purposes - so its use leveled the growth of papillomas for more than 3 years in groups with a viral load of less than 100,000 copies per 10³ cells. In groups of up to 10,000 copies per 10³ cells, special therapy is not required and should be limited to surgical removal of papillomas.

The scheme developed by us for the prognostic determination of the HPV viral load with the determination of treatment tactics on its basis led to a sharp reduction in the number of relapses in all groups with an increase in the duration of remission and a decrease in the number of surgical interventions. This tactic allows you to avoid the development of side effects of the use of systemic interferon therapy and at the same time makes it possible to reduce the number of surgical procedures and reduce the possibility of cicatricial complications.

We have developed prognostic criteria for monitoring the viral load of molecular biological determination of HPV in biopsies from papilloma tissue taken during operations and recommendations for conducting therapeutic tactics.

Table 7: CRP monitoring criteria when determining viral load.

critierion	Clinical manifestations	Forecast	recommendation
not determined	Papillomas in one area m / w are voluminous, there is no growth dynamics for 6 months with any volume of damage	not recur (or very rarely)	surgical
HPV up to 10^4 per 10^3 cells	Papillomas can occupy up to 3 areas without narrowing the lumen of the larynx	rarely recur, less than 1 time per year	surgical
HPV up to 10^5 per 10^3 cells	Papillomas can occupy up to 5 areas, narrowing the lumen without causing signs of respiratory distress	recur up to 1 time per year	Surgical, vaccine prophylaxis
HPV from 10^5 to 10^6 per 10^3 cells	Papillomas can span more than 5 areas, narrowing the larynx, causing signs of respiratory distress	recur up to 2-3 times a year	interferon therapy
HPV over 10^6 per 10^3 cells	Papillomas can spread extra-larengally , narrowing the larynx, causing signs of respiratory distress	recur very often more than 3 times a year, poorly controlled	Long-term interferon therapy with local injection into the area of papilloma growth

A viral load of less than 100,000 is considered a prognostically positive moment in the development of relapses and a criterion for the use of a vaccine to prevent recurrence of papillomas. At the same time, the presence of papillomas without determining HPV in any part of the respiratory tract is a chronic HPV infection with the possibility of recurrence under unfavorable conditions, frolicking in the respiratory tract. Determination of the viral load of more than 100,000 copies per 10^3 cells is evidence of a severe course with a prognosis of a high risk of recurrence with the development of respiratory failure and the capture of more than 3 zones of papilloma growth.

DISCUSSION

According to the literature, there is no data on a unified classification of RRP of juvenile age. There are data from some authors who divide papillomas into aggressive and non-aggressive (Doyle D.J. et al., 1994), depending on the number of procedures during the entire treatment period. However, we believe that such a division is incorrect, since the infection is chronic and its control depends on many factors. So we found that the onset of the onset of symptoms significantly affects the course of the disease, however, we consider the frequency of procedures per year to be more significant, and the severity of the disease is characterized by the total number of procedures (operations) performed. The Derkay score also has a relative influence, the higher the score, the more severe the course and more aggressive the virus. This is confirmed by other authors who also claim that the severity of RRP increased with the early age of onset of the disease, the age of the first operation, the total number of operations, the frequency of operations and the number of affected areas.^[3,4,8,23]

When analyzing the lesion, we used the Derkay rating scale as the most systematized scale and is applicable in the world as an anatomical characteristic of mucosal lesions. The system proposed by Derkay et al. 22 was

chosen as the most used in the world. The most common symptoms were dysphonia and shortness of breath, commonly seen with RRP, as the larynx is the most commonly affected area.^[7-9]

CONCLUSION

Respiratory recurrent papillomatosis of childhood is one of the most common diseases of the larynx in children, taking up a significant share of its chronic pathology. The urgency of the problem is due to the development of not only voice changes, but most of all life-threatening respiratory failure in young children, in addition, frequent recurrence and difficulties in controlling the growth of papillomas make the problem of RRP in children a global one, especially given the fact that this disease affects families of a socially lower category. in which children are the most vulnerable.

Despite the high cost of PCR diagnostics, HPV has a high specificity and sensitivity, which makes it possible to conduct prognostic parallels. We consider the differentiation of the type of papillomas to be not relevant and not carrying important information. Determination of the total viral load is an important prognostic criterion for the course of the disease and determination of the tactics of managing a patient with RRP. In addition, it is worth noting about the need to inform medical workers about the possibility of a high risk of infection of a child in the presence of papillomas or genital warts in women, as well as informing the population about the need to vaccinate against HPV in girls, introduced into the national vaccination calendar since 2019 in Uzbekistan - that is one of the important points in the development of a modern approach to the treatment and prevention of viral diseases in women and children.

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