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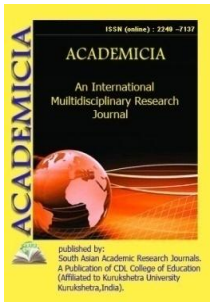

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VALUE OF HEMOSTASIS SYSTEM INDICES IN RESPIRATORY RECURRENT PAPILLOMATOSIS

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ABSTRACT

For the solution of objectives there were studied patients aged from 2 years up to 45 years with benign formation of a throat respiratory recurrent papillomatosis – 59 patients. The 1st group - 38 patients with a recurrent respiratory papillomatosis of children's age, the 2nd group - 21 patients with a recurrent respiratory papillomatosis of adult age, the 3rd group made 12 almost healthy people. Study of hemostasis system indicators; activated partially thromboplatin time (APTT), thrombin time, antithrombin-III, fibrinogen was tested by the conventional method using sets from HUMAN. As it can be seen from the presented results of the studies, the number of platelets in blood plasma in patients of group 1 has a decrease dynamic, in particular, when compared with healthy persons, the concentration of platelets in blood plasma decreases by an average of 30%, while in group 2 the platelet content tends to decrease by an average of 43%. The detected disorders in the hemostasis system can serve as a marker of endothelial dysfunction that contributes to the constant maintenance of inflammation, increased neoplastic effects, which can lead to frequent recurrence of RRP of the infant contingent and stunning of RRP - an adult, and require appropriate targeted correction of the detected disorders.

KEYWORDS: *Respiratory Recurrent Papillomatosis, Study, Hemostasis System Indicators, Dysfunction Of Vascular Endothelial Cells*

INTRODUCTION

Benign tumors and tumor-like changes are found in the larynx much more often than malignancies. According to various authors, benign laryngeal neoplasms are found in 55-70% of cases among productive processes of the upper respiratory tract [1,2,6].

Tumor pathology is characterized by involvement in the pathogenesis processes of integral homeostasis regulation systems, including endocrine, immune, and hemostatic ones. At the same time, tumor cells can directly produce various procoagulants and anticoagulants. It is known that tumor cells activate the procoagulant link of the hemostasis system due to the formation of the factor V receptor. This receptor is located on the surface of the membranes of tumor cells and accelerates the formation of the prothrombinase complex (factor V + factor X + calcium + platelets). Proinflammatory cytokines secreted by tumor cells significantly increase the expression of tissue factor monocytes. Pro-inflammatory cytokines released by the tumor and blood cells also disrupt the regulation of thrombomodulin in endothelial cells, as well as increase the expression of tissue factor and fibrinolysis inhibitors - a plasminogen-1 activator inhibitor (PAI-1) in endothelium. Impaired control function of the endothelium reduces the synthesis of antithrombin III and protein C by the liver. This leads to increased procoagulant and decreased anticoagulant and fibrinolytic activity of the vascular wall, which is essential in the formation of vascular blood clots [8]. Tumor cells and circulating particles of tumor cell membranes affect the platelet link of the hemostasis system, increasing platelet adhesion and aggregation [3,4,5,7].

Thus, activation of a system of a hemostasis as a result of influence of tumoral pro-coagulants, inflammatory cytokines, a fabric factor of monocytes, fabric macrophages and endothelial cells and also leads to increases in functional activity of platelets to emergence of thrombin and deposition of fibrin in and around tumoral fabric. Modern researches showed that local accumulation of fibrin forms a matrix for growth of a tumor and angiogenesis. Tumor cells are capable to express all proteins necessary for regulation of a fibrinolisis on the surface. The constant fibrinolytic activity, i.e. formation of plasmin, promotes a tumor invasion.

On the basis of the above presented the purpose of this research was to reveal a contribution of system disorders in the haemocoagulation of blood to pathogenesis of benign tumors and throat cancer and also to define their predictive and diagnostic importance.

Material and methods of a research

For the solution of objectives from 2016 for 2018 on the basis of the Republican scientific and practical medical center of pediatrics there were studied patients aged from 2 years up to 45 years with benign formation of a throat respiratory recurrent papillomatosis – 59 patients. From them 34 children (aged from 2 years up to 6 years) with a frequent recurring form, and 28 adults from 18 to 45 years.

The 1st group - 38 patients with a recurrent respiratory papillomatosis of children's age, the 2nd group - 21 patients with a recurrent respiratory papillomatosis of adult age, the 3rd group made 12 almost healthy people.

The developed clinical diagnosis was established on the basis of the nature of complaints, of the anamnesis, results of clinical examinations, investigations of ENT organs: otoscopy, pharyngoscopy, front and back rhinoscopy, indirect laryngoscopy. Specialized methods of

inspection: a videolaryngoscopy by means of a rigid pharyngo-laryngotelescope with a point of view 70 ° or 90 ° (diameter of trunk is 10 mm, useful length is 15 cm), "KarlStorz" with removal of the image on the monitor and an opportunity photo, and video documenting for the subsequent analysis; an indirect microlaryngoskopy at increase 6x8x12 with an operational microscope of Zeiss; a fibrolaryngocopy, a laryngostroboscopy with photo and video documenting of the image output to the monitor for the further analysis of time-lapse reproduction of a video; Neck MSCT; a research of acoustic indicators of a voice (in Hz, before operation); a direct microlaryngoscopy for a research and sounding of pathologically changed departments of a throat under control of big increase in a microscope (6x 8x12) and also rigid endoscopes viewing angles 0 °, 30 °, 70 °, sufficient operating length, for the final decision about the of surgical intervention and a possibility of its rying out. Additional tool methods: measurement of pH in the lower and middle third of a throat, and the top third of a gullet (according to indications).

The mandatory plan for the examination of patients included generally accepted clinical-laboratory and instrumental diagnostic methods. Study of hemostasis system indicators; activated partially thromboplatin time (APTT), thrombin time, antithrombin-III, fibrinogen was tested by the conventional method using sets from HUMAN.

Statistical processing of the obtained results was carried out using the application package "STATISTICA" (version 6.0, StatSoft Inc, 2001). Differences and correlation coefficients were considered significant at $p < 0.05$.

RESEARCH RESULTS AND DISCUSSION

We used global (screening) methods for assessing of hemostasis: determining APTT, TV and fibrinase concentration, as well as a refinement test - determining antithrombin AT III. The patients we examined had an increase in the level of fibrinase, a shortening of APTT and an increase in TV with a decrease in the level of antithrombin AT III, which appeared to be the signs of the hypercoagulation syndrome.

As it can be seen from the presented results of the studies, Table 1, the number of platelets in blood plasma in patients of group 1 has a decrease dynamics, in particular, when compared with healthy persons, the concentration of platelets in blood plasma decreases by an average of 30%, while in group 2 the platelet content tends to decrease by an average of 43%.

Therefore, in patients with RPP, a state of thrombocytopenia is observed in blood plasma.

As it can be seen from the results obtained (Table 1), the activated recalcification time in patients with RRP decreased by 35% on average ($P < 0.05$). ABP contraction indicates an acceleration of chronometric hypercoagulation due to the state of the external pathway of the hemostasis system, i.e. activation of the vascular-platelet link of the hemostasis system by tissue factors.

Activated partial thromboplastin time (APTT) is used as a screening test to evaluate the internal plasma clotting cascade, which uses reagents containing contact activation phospholipids rather than tissue factors. In our study, APTT in 28 children with recurrent respiratory papillomatosis was 25.9 ± 1.07 sec, and in 10 of them less than 25 s. This is 19% ($P < 0.05$) lower than in the comparison group. This coagulogram index is closely related to the structure of the thrombus formed and is due to the state factors of the blood coagulation system. Activation of the vascular-platelet unit of the hemostasis system along the cascade chain activates its plasma unit and leads

to chronometric and structural hypercoagulation. When analyzing the results in children with RRP, the often recurrent form of the disease is on average 1.2 times lower when compared with the indicators of a group of healthy patients. As is known, APTT is directly dependent on the level of endogenous anticoagulants. Therefore, the elongation in time of the APTT index in patients with RRP indicates disorders in the plasma unit of the hemostasis system, which may be one of the causes of frequent recurrence as a result of maintaining inflammation. As it is known, one of the factors disrupting the procoagulant link of the hemostasis system is enhanced thrombin synthesis, which plays a dual role in the hemostasis system. It can activate the process of thrombosis and fibrinolysis, worsening the local rheology leading to dystrophic mucosal changes supporting inflammation, which increases the possibility of relapse.

To prevent this situation, vascular endothelial cells synthesize antithrombin-III, which, when endogenous heparin is involved, binds thrombin. In our studies, the observed increase in thrombin levels is accompanied by a significant decrease in plasma antithrombin-III. So, in patients of group 1, there was a decrease in the level of antithrombin-III by an average of 33% when compared with the control group. As is known, the dynamics of thrombin time may indicate the risk of developing thrombohemorrhagia in a given contingent of patients. Analysis of the obtained research results showed the risk of thrombohemorrhagia in patients of both groups, while in the second group the risk is higher than in the first. It is worth noting that hemorrhages in the postoperative period lead to the development of microthrombus and damage of mucosal trophies, deterioration of local blood flow. Endothelin serves as a compromising factor. Under the action of factors that activate or damage the endothelium (viral endotoxins, CEC, cytokines, inflammatory mediators), a sharp change in the para- and autocrine activity of the endothelium occurs with the loss of its inherent property of thromboreactivity and the enhancement of procoagulant and proaggregant effects: increased formation of Willebrand factor, type 1 plasminogen activator inhibitor (IAP-1), tissue thromboplastin, fibronectin, decreased synthesis of tissue-type plasminogen activator, thrombomodulin, antithrombin, prostacycline, nitric oxide, endothelium included in synthesis of prooxidants, vasoconstrictors to enhanced thrombosis, disorder local homeostasis and endothelial dysfunction, which increases the risk of papilla staining of adults with RRP.

The state of hypercoagulation that we observe in patients of group 1 can lead to compensatory activation of the fibrinolytic unit of the hemostasis system, expressed by an increase in fibrinolytic activity of blood plasma, due to an increase in thrombin levels. The increased consumption of thrombin and fibrinogen against the background of the depletion of antithrombin II is reflected in the properties of the resulting clot. This is expressed by an increase in the activity of factor XIII - fibrinase, in which additional crosslinking is formed in the fibrin clot, partially dehydrates it, and the clot becomes more dense. That is, in patients of group 2, the level of fibrinase increases by 27.0% ($P < 0.05$). Thrombin formed in the cascade chain binds to antithrombin III. The mediator and activator of this complex is endogenous heparin. Plasma tolerance to heparin indirectly indicates the content of endogenous heparin, an increase in the level of which indicates the depletion of antithrombin II.

Thus, in patients with RRP, the fibrinolytic link of the hemostasis system is activated against the background of disruption of the plasma link of the hemostasis system and dysfunction of vascular endothelial cells. The detected disorders in the hemostasis system can serve as a marker

of endothelial dysfunction that contributes to the constant maintenance of inflammation, increased neoplastic effects, which can lead to frequent recurrence of RRP of the infant contingent and stunning of RRP - an adult, and require appropriate targeted correction of the detected disorders.

TABLE 1 DYNAMICS OF THE CHARACTERISTICS OF THE HEMOSTASIS SYSTEM IN THE PATIENTS OF THE RECURRENT RESPIRATORY PAPILLOMATOSIS

Characteristics	Healthy patients n=12	Patients with recurrent respiratory papillomatosis, children n=38	Patients with recurrent respiratory papillomatosis, Adults n=21
Thrombocites (x109/l)	228,14±9,34	158,46±7,89	131,15±8,56*
Activated partially thromboplastin time APTT (cec)	31,78±2,57	25,90±1,07*	38,69±2,94*
Prothrombin time PT(cec)	16,43±1,22	20,41±2,65	33,86±3,72*
Antithrombin AT III (%)	101,12±7,84	70,86±5,12*	62,84±7,05*
Activated recalcification ART(cec)	58,21±3,44	41,42±3,12*	37,64±2,38*
Fibrinolitic activity, (cec)	0,91±0,05	1,28±0,03*	1,45±0,04*
Fibrinasa , %	64,21±4,33	70,30±5,01	85,30±6,01*
Tolerability of plasma to heparin, %	7,6±0,48	6,9±0,56	18,2±1,48*

Notes : *- differences reliability at P< 0,05

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