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ENDOTOXIN AGGRESSION IN PATHOGENESIS OF DISORDERS IN THE SYSTEM OF HEMOSTASIS IN PATIENTS WITH ONCOPATHOLOGY

Эндотоксиновая агрессия в патогенезе нарушений системы гемостаза у больных с онкопатологией

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Abstract

There are the reports, which indicate, that leading role in initiation of all disorders in hemostasis system can belong to lipopolysaccharide of gram-negative bacteria. In this connection the aim of our research was the complex study of the basic indices of hemostasis system and endotoxin-antiendotoxin system in patients

with benign and malignant tumours of laryngopharynx. 20 donors, 20 patients with benign tumours of laryngopharynx, and 20 patients with diagnosed malignant neoplasms of laryngopharynx like planocellular cancer, confirmed by histological examination, have been examined. As a result of research it has been revealed that considerable increase of the total endotoxin concentration in bloodstream has been observed both in benign and malignant tumours. Development of chronic endotoxin aggression, which results in disbalance both in external and internal cascade of hemopexis has been diagnosed. Development of subacute endotoxin aggression resulting in formation of the first (hypercoagulative) stage of disseminated intravascular clotting syndrome.

Резюме

Встречаются сообщения, указывающие, что в инициации всех нарушений системы гемостаза ведущая роль вполне может принадлежать липополисахариду грамотрицательных бактерий. В связи с этим целью исследования явилось комплексное изучение основных показателей системы гемостаза и эндотоксин-антиэндотоксиновой системы у больных с доброкачественными и злокачественными опухолями гортаноглотки.

Нами обследовано 20 доноров, 20 больных с доброкачественными опухолями гортаноглотки и 20 больных с диагностированными злокачественными новообразованиями гортаноглотки, с диагнозом – плоскоклеточная форма рака, подтвержденным гистологически.

В результате исследования выявлено, что как при доброкачественном, так и при злокачественном течении опухолевого процесса отмечено значительное увеличение общей концентрации эндотоксина в кровяном русле. У больных с доброкачественными опухолями диагностировано развитие хронической эндотоксиновой агрессии, которая вызывает дисбаланс, как во внешнем, так и во внутреннем каскаде свертывания. У больных со злокачественными опухолями гортаноглотки отмечено развитие

подострой эндотоксиновой агрессии, которая влечет за собой формирование первой (гиперкоагуляционной) стадии ДВС синдрома.

Despite a certain independence, tumours cells are in close interaction with protective system of body and they are under their permanent influence [4, 6]. System of hemostasis is one of such systems, it retains the blood in liquid state within blood vessels and assures thrombopoiesis in area of wall damaged in the vessels [7]. Dynamic state of hemostasis system including permanent physiologic microactivation, provides high mobility and ability for fast response on external and internal conditions by passage into qualitatively new state, that is, hyper- or hypocoagulation [2]. The available information points out, that various neoplastic processes during their development can result in sever changes in hemostasis system, and their clinical manifestations (such as, thromboses and embolies) take second place among mortality causes and patients disability [1, 5].

However, there are reports which testify, that leading role in initiation of processes, described above, both in the norm and in the development of syndrome of disseminated intravascular clotting syndrome can belong to lipopolysaccharide (LPS) of gram-negative bacteria [11]. Under standard conditions, endotoxin (ET), executing adaptive functions of organism to the conditions of external and internal milieu permanently changing, supports all its systems, including hemostasis, consequently all systems taking part in its regulation, in state of permanent physiologic tone [9].

In insufficiency of functions of endotoxin binding and endotoxineliminating systems LPS from intestine stipulates the development of endotoxin aggression (EA). In case of EA, LPS, being an initial agent of microvascular endothelium damage causes modulation of secretion by endothelial cells of bioactive substances, favouring, according to the opinion of many authors, activation in coagulating blood system, which in manifested clinically by thrombohemorrhagic

syndrome [8, 10]. In this connection, it seems ultimately interesting to study probable correlation between activity of endotoxin-antiendotoxin system, on the one hand, and hemostasis status on the other one. Thus, carrying out the complex research, of this aspect in oncologic patients is considered expedient.

Aim of the research is complex study of the main indices of hemostasis system and endotoxin-antiendotoxin system in patients suffering from benign and malignant tumours of laryngopharynx.

Materials and methods

We have examined 20 donors and 40 patients, divided into two groups: the first one (20 persons) were patients suffering from benign tumours of laryngopharynx, the third group included the malignant neoplasia diagnosed of laryngopharynx and diagnosis histologically confirmed, that is, planocellular cancer.

The study of endotoxin-antiendotoxin system has been conducted under assistance of academician of Academy of natural sciences of Russia professor M.Y. Yakovlev on the base of clinical and diagnostic department of the Institute of general and clinical pathology (Moscow).

Determination of total concentration of endotoxin gram-negative bacteria in blood serum in Eu/ml (international unit of activity) has been executed by Micro-LAL-test (Patent of RF № 2169367).

Determination of integral indices of humoral link activity of antiendotoxin immunity has been performed by technique SOIS-IEA (Patent of RF № 2019993).

Determination of prothrombin complex activity is based on pointing time of blood plasm clotting, if there are tissue thromboplastin and calcium chloride. The results are presented as prothrombin index (PI), corresponding to the ratio of the time of standard donor's blood plasm clotting to the time of patient's blood plasm clotting; the ratio is presented in per cent [3].

Determination of activated partial thromboplastin time (APTT) is based on determination of clotting time of poor in thrombocytes plasm and adding optimal

quantity of calcium under conditions of both standard contact (by kaolin) and phospholipid (by kephalin) clotting activation [3].

Fibrinogen quantity in blood plasm has been determined by weighing: fibrin clot formed in blood plasm clotting by calcium chloride [3].

Statistic analysis of data has been carried out by the routine method of variation statistics with using set of applied programs «Excel». It has been calculated arithmetic mean (M), mean error (m). The authenticity of research results has been defined on 1 criterion of Student. Comparative results were considered as authentic at $P < 0,05$.

Results of research

After studying results it has been revealed that total concentration of endotoxin in the blood of patients with benign tumours exceeded donor's values for 1089 %.

Examining indices, which permit estimate by integral way humoral link activity of antiendotoxin immunity, it has been revealed, that in patients with benign tumours antibody titer to glycolipid Re-chemotype (At to GLP) as well as antibody titer to general antigen of enterobacteria (At to GAE) were decreased by 39 % and 15 % relatively, as compared with donor's values (Table 1).

Table 1

Endotoxin-antiedotoxin system status in patients with benign and malignant tumours of laryngopharynx (M ± m)

	Concentration of ET EU/ml	At to GLP, c.u.o.d.	At to GAE, c.u.o.d.
Donors (n=20)	0,19 ± 0,03	195,0 ± 2,2	389,3 ± 0,8*
Benign tumours (n=20)	2,25 ± 0,10*	119,0 ± 1,4*	331,5 ± 4,7*
Malignant tumours (n=20)	2,60 ± 0,20*,**	201,0 ± 1,3*	349,8 ± 3,9*

Notes: * - authentic difference ($P < 0,05$) relative to the donors' group;
** - authentic difference ($P < 0,05$) relative to the group with benign tumours.

While studying endotoxin-antiendotoxin system status in patients with malignant tumours it has been established, that the total endotoxin concentration exceeded control donor's values by 1268 %. Merely tendency towards increasing antibody titer to glycolipid (At to GLP) by 7 % relatively to donor's values has been observed. Antibodies' titer to general antigen of enterobacteria (At to GAE) in patients with malignant neoplasm has been decreased relatively to donor's values by 11 %.

Thus, research performed permits to reveal in patients with benign tumours of laryngopharynx the symptoms of chronic endotoxin aggression: considerable increase of endotoxin concentration in blood secondary to insufficiency of functioning endotoxinconnecting and endotoxineliminating of the body (decrease of antibodies' titer to GLP and antibodies' titer to GAE).

Proceeding from the results obtained, one may suspect development of subacute endotoxin aggression in patients with malignant neoplasms of laryngopharynx: it has been observed that secondary to the sharp increase of endotoxin concentration in bloodstream, activity of humoral link of antiendotoxin immunity is preserved.

In the issue of studying coagulative hemostasis it has been established that in patients with benign tumours decrease of activated partial thromboplastin time (APTT) by 18 % and tendency to increasing of prothrombin index (PI) by 8 % relative to donors' values, that give evidence concerning disbalance both in external and internal cascade of blood clotting. Increasing fibrinogen content by 14 % is observed too. It shows prevalence of hypercoagulation (Table 2).

While studying the values of coagulative hemostasis in patients with malignant neoplasms, considerable differences of PI relative to donors' values haven't been revealed statistically. It has been revealed chronometric index of APTT by 7 % (relatively 43,9 and 41,0 at $p = 0,000$), that is significant difference. At the same time, increasing fibrinogen content in the blood by 23 % relative to donors' values is observed. All data testify prevalence of hypercoagulation and

enables formation of the first stage of disseminated intravascular clotting (DIC) syndrome.

Table 2

Values of coagulative hemostasis in patients with benign and malignant tumours of laryngopharynx (M ± m)

	APTT, sec	PI, %	Fibrinogen, g/l
Donors (n=20)	43,9 ± 1,7	84,6 ± 4,9	3,0 ± 0,1*
Benign tumours (n=20)	36,0 ± 3,1*	90,9 ± 8,5*	3,4 ± 0,2*
Malignant tumours (n=20)	41,0 ± 4,7*,**	82,4± 4,1**	3,7 ± 0,2*,**

Notes: * - authentic difference (P <0,05) relative to the donors' group;
** - authentic difference (P <0,05) relative to the group with benign tumours.

Decreasing coagulative potential shows the development of „hypocoagulative consumption" by one side, and by other side, is an unfavourable symptom for prognosis, that gives evidence of probable development of DIC syndrome.

Thus, oncologic process secondary to endotoxin aggression, occurring in both groups under research, disturb physiologic process of hemostasis system functioning in different directions.

Conclusions

As a result of our research it has been determined:

1. Considerable increase of total concentration of ET in the bloodstream has been observed both in benign and malignant course of a tumoral process.

2. In patients with benign tumours the increase of ET concentration occurs secondary to insufficiency of humoral link of antiendotoxin immunity, testifying

development of chronic EA, which results in disbalance both in external and in internal clotting cascade.

3.In patients with malignant tumours of laryngopharynx a sharp increase of total endotoxin concentration secondary to increase of antibodies' titer to GLP at decreasing antibodies' titer to GAE, that testifies the development of subacute EA which results in formation of the first (hypercoagulative) stage of DIC syndrome.

References in original

1. Аяпбергенова Г. О. Профилактика тромбоэмболических осложнений у больных раком легкого / Г. О. Аяпбергенова // Сибирский онкологический журнал. - 2009. - Приложение № 1. - С. 22 - 23.

2. Баркаган З. С. Диагностика и контролируемая терапия нарушений гемостаза / З. С. Баркаган, А. П. Момот. – М.: Ньюдиамед-АО, 2001. – 296 с.

3. Горячковский А. М. Клиническая биохимия в лабораторной диагностике / А. М. Горячковский. – Одесса: Экология, 2005. – 616 с.

4. Козлова О. Д. Изменение показателей системы гемостаза и риск тромбоэмболических осложнений у больных доброкачественными и злокачественными новообразованиями / О. Д. Козлова // Тромбоз, гемостаз и реология. – 2006. – № 2 (26). – С. 74 – 79.

5. Тромбопрофилактика при эндопротезировании крупных суставов и онкологических поражений костей / Н. А. Корж, Л. Д. Горидова, Ф. С. Леонтьева [и др.] // Український журнал екстремальної медицини ім. Г.О. Можаєва. – 2010. - Т. 11, № 4. – С. 73-76.

6. Фактор роста эндотелия сосудов в опухолях и сыворотке больных раком молочной железы: связь с клинико-морфологическими факторами / Е.

С. Герштейн, А. М. Щербаков, С. К. Алиева [и др.] // Вестник Российского Онкологического Научного Центра имени Н.Н. Блохина РАМН. - 2005. - Вып. 1 - 2. - С. 26 - 30.

7. Шилова А. Н. Современные данные о частоте и патогенезе онкотромбозов / А. Н. Шилова, З. С. Баркаган // Тромбоз, гемостаз и реология. – 2006. – № 1 (25). – С. 6 – 15.

8. Lynn W. A. Anti-endotoxin therapeutic option for the treatment of sepsis / W. A. Lynn // J. Antimicrob Chemother. – 1998. – Vol. 41 (A). – P. 71 – 80.

9. Overbeek B. P. Role of antibodies and antibiotic in aerobic gram-negative septicemia: possible synergism between antimicrobial treatment and immunotherapy / B. P. Overbeek, E. M. Veringa // Rev. Infect. Dis. – 1991. – Vol. 13, № 7 – 8. – P. 751 – 760.

10. Stoll L. L. Potential role of endotoxine as a proinflammatory mediator of atherosclerosis / L. L. Stoll, G. M. Denning, N. L. Weintraub // Arterioscler. Thromb. Vasc. Biol. – 2004. – Vol. 24, № 12. – P. 2227 – 2236.

11. Yakovlev M. Yu. Elements of endotoxin theory of human physiology and pathology: systemic endotoxinemia, endotoxin aggression and endotoxin insuffcoencyi / M. Yu. Yakovlev // J. Endotoxin Research – 2000. – Vol. 6. – P. 120 – 124.

References in transliteration

1. Ajapbergenova G. O. Profilaktika tromboembolicheskih oslojneniy u bolnih rakom legkogo / G. O. Ajapbergenova // Sibirskiy onkologicheskiy jurnal. - 2009. - Prilojenie № 1. - S. 22 - 23.

2. Barkagan Z. S. Diagnostika i kontroliruemaja terapija narusheniy gemostaza / Z. S. Barkagan, A. P. Momot. – M.: Newdiamed-AO, 2001. – 296 s.

3. Goriachkovskiy A. M. Klinicheskaja biokhimija v laboratornoiy diagnostike / A. M. Goriachkovskiy. – Odessa: Ekologija, 2005. – 616 s.

4. Kozlova O. D. Izmenenie pokozateley sistemy gemostaza i risk tromboembolicheskih oslojneniy u bolnih dobrokachestvennymi i zlokachestvennymi novoobrazovanijami / O. D. Kozlova // Tromboz, gemostaz i reologija. – 2006. – № 2 (26). – S. 74 – 79.

5. Tromboprofilaktika pri endoprotezirovanii krupnyh sustavov i onkologicheskih porajeniy kostey / N. A. Korj, L. D. Goridova, F. S. Leontieva [i dr.] // Ukrainskiy jurnal eksperementalnoy mediciny im. G.O. Mojaeva. – 2010. - T. 11, № 4. – S. 73-76.

6. Faktor rosta endotelija sosudov v opuholiah i sivorotke bolnikh rakom molochnoy jelezy: sviaz s kliniko-morfologicheskimi factorami / E. S. Gershtein, A. M. Tscherbakov, S. K. Alieva [i dr.] // Vestnik Rossijskogo Onkologicheskogo Nauchnogo Tsentra im. N.N. Blokhina RAMN. - 2005. - Vip. 1 - 2. - S. 26 - 30.

7. Shilova A. N. Sovremennie dannie o chastote i patogeneze onkotrombozov / A. N. Shilova, Z. S. Barkagan // Tromboz, gemostaz i reologija. – 2006. – № 1 (25). – S. 6 – 15.

8. Lynn W. A. Anti-endotoxin therapeutic option for the treatment of sepsis / W. A. Lynn // J. Antimicrob Chemother. – 1998. – Vol. 41 (A). – P. 71 – 80.

9. Overbeek B. P. Role of antibodies and antibiotic in aerobic gram-negative septicemia: possible synergism between antimicrobial treatment and immunotherapy / B. P. Overbeek, E. M. Veringa // Rev. Infect. Dis. – 1991. – Vol. 13, № 7 – 8. – P. 751 – 760.

10. Stoll L. L. Potential role of endotoxine as a proinflammatory mediator of atherosclerosis / L. L. Stoll, G. M. Denning, N. L. Weintraub // Arterioscler. Thromb. Vasc. Biol. – 2004. – Vol. 24, № 12. – P. 2227 – 2236.

11. Yakovlev M. Yu. Elements of endotoxin theory of human physiology and pathology: systemic endotoxinemia, endotoxin aggression and endotoxin insuffcoencyi / M. Yu. Yakovlev // J. Endotoxin Research – 2000. – Vol. 6. – P. 120 – 124.

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