American Journal of Medicine and Medical Sciences 2019, 9(5): 170-173
DOI: 10.5923/j.ajmms.20190905.03

Clinical and Anamnestic and Laboratory Criteria for Diagnostic Pre-Thrombotic Conditions in Patients with Hemostasiopathy

Aziza Dzhumanovna Makhmudova[1], Inna Viktorovna Berger[2,*], Nigora Abduvalievna Tursunova[3], Lola Valievna Ashurova[1]

[1]Administration, Scientific-Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan
[2]Research Department, Scientific-Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan
[3]Day Stay Department, Scientific-Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan

Abstract The Hematology Research Institute examined patients with thrombophilia, determined the frequency and nature of violations in different parts of the hemostasis system. Clinical, anamnestic and laboratory criteria for the diagnosis of prethrombotic conditions in patients with chronic melastoplastic disease (CMD) have been established. Studies were conducted on the basis of a study of hemostasiogram data, as well as studies of Protein C, lupus anticoagulant and D-dimer. Studies have shown and confirm that violations in different parts of the hemostasis system for CMD are frequent and are characterized not only by vascular and platelet, but also deep plasma disorders.

Keywords Thrombophilia, Thrombotic complications, Hemostasis, Hypercoagulation

1. Introduction

Pre-thrombotic state (thrombophilia, hypercoagulability) is a condition of increased blood clotting resulting from changes in one or several hemostatic components - platelets (thrombocytosis, increased platelet function), coagulation factors (increased content of prothrombin, fibrinogen), fibrinolysis factors (decrease in plasma levels). Its activators, an increase in the activity of inhibitors), vascular wall factors (decrease in the synthesis of prostacyclin, a decrease in the activity of the active plasminogen ator) [1]. Often, instead of the term “prethrombotic state”, the term “thrombophilia” is used [4, 5].

According to some foreign studies, thrombophilia, in this variant in hematological patients is acquired and detected in more than 40% of patients. Most often, thrombogenic risk factors in patients with the above pathologies include genetic abnormalities as well as individual characteristics of the organism [2]. It has been established that if a patient’s age exceeds 45 years, the risk of a thrombotic state increases by another 25% and may lead to the development of thrombotic readiness [2]. Thrombophilic conditions are clinically manifested in the form of venous thrombosis, thromboembolism, ischemia, infarction of various organs, strokes, pulmonary thromboembolism, which inevitably can be fatal [3].

The study of blood coagulation and thrombosis, the value of each phase of hemocoagulation and fibrosis during the formation of a prethrombotic state will significantly increase the number of indicators for its diagnosis, which can be grouped as follows: 1) the results obtained using instrumental methods (thromboelasto and electrocoagulography); 2) total blood coagulation activity (blood clotting time, heparin tolerance, recalcination time); 3) functional properties of platelets (adhesion and aggregation) and erythrocytes; 4) fibrinogen and products of its transformation and degradation; 5) stabilizing fibrin factor; 6) anticoagulant activity (antithrombins, especially antithrombin III, heparin, their inhibitors); 7) total fibrinolytic activity of blood and fibrinolysis inhibitors; 8) antithrombogenic properties of the vascular wall. [four].

2. Main Body

2.1. The Purpose of Our Research

Establish clinical-anamnestic and laboratory criteria for

* Corresponding author:
innaberger@mail.ru (Inna Viktorovna Berger)
Published online at http://journal.sapub.org/ajmms

the diagnosis of pre-thrombotic conditions in patients with CMP (chronic myeloproliferative diseases).

2.2. Material and Methods of Study

In the research work used the blood and plasma of patients suffering from CMD. The control group consisted of 20 healthy donors. All persons in the control group conducted a study of the parameters of the blood coagulation system used in the work.

When studying prethrombotic conditions in hematological patients who are hospitalized at Scientific Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan (SRI of H and BT) for 2016-2017, it was found that they occur in pathologies such as: chronic myeloid leukemia (250 patients), erythremia (68 patients), subleukemic myelosis (49 patients), multiple myeloma (413 patients), Waldenstrom's disease (30 patients), chronic megakaryocytic leukemia (23 patients), as well as vasculitis (69 patients). In total, 902 patients with these pathologies were registered for 2017, which is significantly more than in 2015 (850) and 2014 (835 patients).

2.3. Results of the Study

During the period of 2018, a comprehensive clinical and laboratory examination of 63 patients suffering from CMP (48 men and 15 women) aged from 18 to 62 years was conducted. Of them: 42 patients with Multiple myeloma, 13 - with Erythremia, 8 - with chronic myeloid leukemia. Signs of thrombophilia confirmed by clinical and laboratory studies were found in 13 patients from the examined (21%) patients. The diagnosis of myeloproliferative diseases was established on the basis of clinical symptoms, laboratory tests, and cytological and immunohistochemical studies of the bone marrow.

Signs of thrombophilia confirmed by clinical and laboratory studies were found in 13 patients from the examined (21%) patients. All examined patients with suspected thrombophilia are tested for D-dimer, Protein C and lupus anticoagulant, the level of factor VIII previously not included in the examination algorithm.

Table 1. Characteristic manifestations of hypercoagulation syndrome and thrombosis localization in patients with the 1st (main) group

№	Manifestations	Number the sick	
		abs.	%
1	Deep leg vein thrombosis	10	72
2	Myocardial infarction	12	4
3	Ischemic stroke	22	3,8
4	Retinal vein thrombosis	2	1

The incidence of thrombosis in patients with nosological groups of myeloproliferative diseases (n = 54) was determined by collecting anamnestic data, and the incidence of the hypercoagulative syndrome and localization of thrombosis were determined with the calculation of the percentage of localization occurrence (Table 1), so in 72% of cases deep venous thrombosis was detected. tibia, 4% myocardial infarction, 3.8% ischemic stroke, retinal vein thrombosis was recorded in 1% of cases (confirmed by ophthalmoscopy).

The study of the vascular-platelet, plasma-coagulation and fibrinolytic units of the hemostasis system was carried out in accordance with modern methodological guidelines Z.S. Barkagan, A.P. Momot (2001, 2004). The control group consisted of 20 practically healthy people of similar age (median age 21 ± 9 years), who were blood donors residing in Uzbekistan in Tashkent.

All patients with myeloproliferative diseases were studied for coagulation and vascular-platelet hemostasis, the indicators and the frequency of violations of which are shown in Table 2.

From Table 2 it can be seen that in almost all groups of patients with myeloproliferative diseases, frequent and reliable shortening of the APTT, lengthening of XIIa-dependent fibrinolysis is observed. When analyzing the indicators of coagulation and platelet hemostasis in patients with myeloproliferative diseases in the group with and without thrombosis of thrombosis, there are no significant differences. However, hypercoagulation by APTT and thrombin time is more often observed in the group with thrombosis. In patients with thrombosis, an increase in fibrinogen concentration is 1.5 times more common. Disturbances in the system of fibrinolysis are twice as often found in patients with thrombosis.

Table 2. The study of coagulation and vascular platelet hemostasis

The studied indicators	Patients with CMP (n=63) (M±m)	Control group (n=20) (M±m)	P
APTTV, sec	30,6±2,5	41,95±0,43	≤ 0,05
Prothrombin time, %	98.6±1,1	95,55±1,09	≤ 0,05
Thrombin time, s	12,5±1,4	16,4±0,46	≤ 0,05
Fibrinogen, g / l	5,5±2,8	2,99±0,1	≤ 0,05
Platelet count, 10 ^ 9 / l	489±106,8	235±39,7	≤ 0,05
Heparin plasma tolerance, s	9,1±08	8±09	≤ 0,05
Fibrinolysis, min	14,3±3,8	6,09±3,2	≤ 0,05

Notes: p - significant differences compared with the control;

From Table 2 it can be seen that in almost all groups of patients with myeloproliferative diseases, frequent and reliable shortening of the APTT, lengthening of XIIa-dependent fibrinolysis is observed. When analyzing the indicators of coagulation and platelet hemostasis in patients with myeloproliferative diseases in the group with and without thrombosis of thrombosis, there are no significant differences. However, hypercoagulation by APTT and thrombin time is more often observed in the group with thrombosis. In patients with thrombosis, an increase in fibrinogen concentration is 1.5 times more common. Disturbances in the system of fibrinolysis are

twice as often found in patients with thrombosis.

Additionally, we determined D – dimer, Protein C, Factor VIII and Lupus anticoagulant (Table 3).

D-dimer is a protein fraction, the result of the breakdown of fibrin in the process of dissolving blood clots (fibrinolysis). D-dimer is considered to be a rather informative indicator of thrombosis, since the mechanism of its production starts simultaneously with the process of formation of a thrombus. The analysis on D-dimer allows to evaluate 2 factors in a complex at once: coagulation (blood coagulation) and fibrinolysis (clot dissolution) [4]. The marker makes it possible to timely detect an imbalance between them in case of diseases of the circulatory system.

Violation of the integrity of blood vessels is usually accompanied by bleeding, which requires fibrin to stop [4, 5]. This protein is involved in the formation of blood clots (blood clots), and they, in turn, clog bleeding gaps. Increasing the concentration of fibrin in the blood provokes the formation of a greater than necessary amount of blood clots. A similar condition is fraught with the development of thrombosis of the veins and arteries [2, 3]. To regulate the process, a special enzyme plasmin is produced in the body, which dissolves excess fibrin [4, 5, 6]. The result of this chemical reaction is D-dimer. Its level should be directly proportional to the degree of intensity of fibrinolysis.

Violations in the protein C system (Table 3) were observed only in patients with thrombosis, its deficiency was detected 1.7 times compared with the control group, which was 68 ± 6.6 and 106%, respectively. Much more often in the group with thrombosis, a high level of factor VIII and (or) von Willebrand factor was observed: 136 ± 21.6% in the examined group and 86.0 ± 1.5 in the group of healthy donors, while the hyperaggregal syndrome in both groups of the examined patients occurred in approximately the same percentage cases. The difference coefficient in all studies was ≤ 0.005 (high confidence level).

Table 3. Determination of markers of coagulation and fibrinolysis

The studied indicators	Patients with CMP (n=63) (M±m)	Control group (n=20) (M±m)	P
Protein C (70-140%)	68±6,6	106	≤ 0,005
D-dimer (0-0,24мкг/мл)	8,17	0,06	≤ 0,005
Lupus anticoagulant (0.8-1.2)	HO 1,72±0,8	0.6±0,1	≤ 0,005
Factor VIII, % (50-100%)	136±21,6	86.0±1.5	≤ 0,005

Notes: p - significant differences compared with the control;

We also examined patients with a history of thrombophilia (n = 50) and carried out a comparative analysis of hemostasis parameters in patients who currently have acute thrombosis (n = 13). As can be seen from tables 4, 5 and 6 for the surveyed 1st group (with a history of thrombosis in history), the shortening of the Coalin-Kefalin time was characteristic compared with the control of -33.7 ± 2.5, (p <0.05), and in 2 group with acute thrombosis (30.2 ± 1.9 sec; P2 <K <0.05 and P3 <1-2 <0.5). Indicators of the prothrombin index (PTI) were within the normal range (p≥0.05), which made it possible to exclude in all patients a defect of phase II coagulation factors. As for fibrinogen, as a marker of any inflammatory reaction, there is a high level of fibrinogen in patients with acute thrombosis, relative to group 1 (P3 <1-2 <0.05).

Table 4. Hemostasiological parameters in patients with hypercoagulation (outside acute thrombosis)

Indicators of coagulation hemostasis	Patients with hypercoagulable syndrome		
	Control (n=20)	Outside acute thrombosis (1 group)	P1 < K
APTTV, s	41,95±0,43	33,7±2,5	0,05
PTI,%	95,55±1,09	93,1±1,4	0,05
Fibrinogen, g / l	2,99±0,1	4,9±0,2	0,05
Thrombin time, s	14,4±0,46	14,8±1.2	0,5
D - dimer, µg / ml	0,06	6,17±1,1	0,001
Protein C,%	106	88±9,6	0,01
Platelet count, 10 ^ 9 / l	235±39,7	379±98,1	0,01
Heparin plasma tolerance, s	8±09	9,0±0.7	0,05
Fibrinolysis, min	6,09±3,2	11,7±3,1	0,01

Notes: p1, p2 - significant differences compared with the control; p3 - significant differences between the compared groups.

Table 5. Hemostasiological parameters in patients with hypercoagulation (with acute thrombosis)

Indicators of coagulation hemostasis	Patients with hypercoagulable syndrome		
	Control (n=20)	With acute thrombosis (2 group)	P2 < K
APTTV, s	41,95±0,43	30,2±1,9	0,05
PTI,%	95,55±1,09	92.93±0,79	0,5
Fibrinogen, g / l	2,99±0,1	7,7±0,15	0,005
Thrombin time, s	14,4±0,46	11.2±0,26	0,01
D - dimer, µg / ml	0,06	7,1±1,6	0,01
Protein C,%	106	64±6,5	0,01
Platelet count, 10 ^ 9 / l	235±39,7	503±36,8	0,001
Heparin plasma tolerance, s	8±09	9,9±1.5	0,05
Fibrinolysis, min	6,09±3,2	12,6±2.7	0,001

Notes: p1, p2 - significant differences compared with the control; p3 - significant differences between the compared groups.

The data obtained during the study allows us to identify another form of hypercoagulative syndrome - post-thrombotic hypercoagulative syndrome that occurs after suffering a thrombosis and speaks about the activation of the blood coagulation system, which can lead to acute thrombosis with certain provoking factors. Diagnosis of such a condition is extremely important, as it will allow to prescribe antithrombotic therapy in time or to carry out

correction of the anticoagulation treatment already underway.

Table 6. Hemostasiological parameters in patients with hypercoagulation (Compare I and II group)

Indicators of coagulation hemostasis	Patients with hypercoagulable syndrome		
	Outside acute thrombosis (1 group)	With acute thrombosis (2 group)	P3 < 1-2
APTTV, s	33,7±2,5	30,2±1,9	<0,5
PTI,%	93,1±1,4	92.93±0,79	<0,5
Fibrinogen, g / l	4,9±0,2	7,7±0,15	<0,05
Thrombin time, s	14,8±1.2	11.2±0,26	<0,5
D - dimer, µg / ml	6,17±1,1	7,1±1,6	<0,001
Protein C,%	88±9,6	64±6,5	<0,5
Platelet count, 10 ^ 9 / l	379±98,1	503±36,8	<0,5
Heparin plasma tolerance, s	9,0±0.7	9,9±1.5	<0,5
Fibrinolysis, min	11,7±3,1	12,6±2.7	<0,5

Notes: p1, p2 - significant differences compared with the control; p3 - significant differences between the compared groups.

Despite the fact that the level of thrombin time (TV) in patients with CMD1 group was within the normal range (p1,2,3 p≥0.5), the thrombin time in the representatives of the 2nd group was significantly shortened compared with the control (p1≤ 0.01). In this connection, the identified changes in these patients can be interpreted as combined thrombophilia, since here will play the role of additional tests for hereditary thrombophilia. Along with this, in the majority of patients there was a significant (p1,2,3 ≤ 0.01) deficit in plasma protein C level (p1 ≤ 0.01) in both 1 and 2 groups 88 ± 9.6% and 64 ± 6.5% respectively. Obviously, this points to an acute process marker due to a decrease in the main function of the protein C by inhibition of activated coagulation factors V and VIII after interaction with thrombin associated with thrombomodulin. The D-dimer of 6.17 ± 1.1 µg / ml in a group of patients and 7.1 ± 1.6 µg / ml in group 2 showed a high level of significance of differences between groups (p1,2,3≤ 0.01). being in the phase of an acute thrombosis process, relative to the control group, where this indicator was 0.06 µg / ml..

3. Conclusions

Based on clinical and laboratory studies, the frequency and nature of violations in different parts of the hemostasis system in a group of patients with CMD were determined. As part of the problem of high growth in the number of patients with thrombophilic complications, further study of this condition is necessary, which makes knowledge of clinical features and algorithms particularly important. Patients have a state of increased blood clotting due to changes in one or more components of hemostasis - platelets (thrombocytosis, increased functional activity of platelets), blood coagulation factors (increased prothrombin content, fibrinogen), fibrinolysis factors (reduced content of plasminogen and its activators, increased inhibitors), vascular wall factors (reduced synthesis of prostacyclin, reduced activity of plasminogen activators) in persons suffering from CMD.

In contrast to the control group of comparison, which has the same age characteristics, there were no changes in the hemostasis system and no patients had any changes indicating the onset of thrombosis. Thus, our studies show and confirm that violations in different parts of the hemostasis system in CMD are frequent and are characterized not only by vascular and platelet, but also deep plasma disorders.

REFERENCES

[1] Alekseev N.A. Hemorrhagic diathesis and thrombophilia guide for physicians / Alekseev N.A. St. Petersburg: Hippocrates, 2005. - 606 p.

[2] Barkagan Z.S. On the methods of diagnosis of thrombophilia caused by abnormalities in the C / Z.S. protein system. Barkagan, A.N. Mamaev, L.P. Tsyvkina // Clinical. lab diagnostics. - 2002. - №6. - C. 17.

[3] Barkagan Z.S. Pathology of the hemostasis system. Hemorrhagic diathesis and syndromes. Thrombophilia: a guide for doctors and students. Pathological physiology // edited by V.V. Novitsky, E.D. Goldberg / Z.S. Barkagan Tomsk Tomsk University Press, 2001. - p. 428-221.

[4] Rudakova V.E. Abstract of the thesis "Hypercoagulative syndrome: pathogenetic, diagnostic and therapeutic features" Moscow 9 2 GENE 2008.

[5] Makhmudova A.D., Berger I.V. On the problem of prethrombotic conditions in hematological patients. Collection of scientific papers. IV International Congress of Hematology and Transfusiology. Tashkent 2018.S-62.

[6] Tursunova N.A., Makhmudova A.D., Shadibekova O.B., Berger I.V. Thrombosis in hematological practice. European Scientific Review. 2018 No. 5-6.C-175-177.