THROMBOGENICITY IN PATIENTS WITH ISCHEMIC STROKE AND PRE-EXISTING POLYCYTHEMIA VERA

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Thrombogenicity and its causes in patients with ischemic stroke (IS) and pre-existing polycythemia vera (PV) is a significant clinical concern. The aim of this study was to identify the range of factors associated with increased thrombogenicity in patients with IS and pre-existing PV. We performed a physical examination and laboratory tests on 127 patients in the hyperacute stroke stage and 16–18 months after. Of them, 68 patients had PV (the main group) and 59 did not have this condition (the comparison group). Laboratory tests were conducted to evaluate blood rheology, hemostasis, endothelial function, angiogenesis, proinflammatory cytokine levels; we also tested patients for the presence of the V617F mutation in the *JAK2* gene and analyzed the contribution of all studied parameters to the development of thrombotic and hemorrhagic complications. We found that the neurological picture did not differ between the groups: mean NIHSS scores were 12 and 13 points, respectively. Morphological and functional characteristics of red blood cells and platelets, hemostasis and cytokine profiles were compared between patients with IS and pre-existing PV and the comparison group. One of the key elements in potentiating thrombotic complications in patients with IS and PV was JAK2 V617F allele burden. The obtained data suggest the cumulative effect of the identified factors promoting thrombus formation in post-stroke patients with PV and overpowering the effect of antiplatelet therapy.

Keywords: ischemic stroke, polycythemia vera, thrombosis, blood rheology, hemostasis, angiogenesis

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Compliance with ethical standards: the study was approved by the local Ethics Committee (Protocol № 1–4/18 dated February 7, 2018). Informed consent was obtained from all study participants.

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ТРОМБОГЕННОСТЬ У БОЛЬНЫХ ИШЕМИЧЕСКИМ ИНСУЛЬТОМ НА ФОНЕ ИСТИННОЙ ПОЛИЦИТЕМИИ

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Проблема возникновения и возможные причины тромбогенности у пациентов с ишемическим инсультом (ИИ) на фоне истинной полицитемии (ИП) остается актуальной. Целью исследования было определить комплекс факторов, ассоциированных с формированием высокой тромбогенности у пациентов с ИИ на фоне ИП. Проведено комплексное клинико-лабораторное обследование 127 пациентов в острейшем периоде ИИ и спустя 16–18 месяцев: 68 пациентов с ИИ на фоне истинной полицитемии ИП (основная группа) и 59 пациентов с ИИ без ИП (группа сравнения). Лабораторное обследование включало определение гемореологических параметров, показателей системы гемостаза, функции эндотелия, активности ангиогенеза, цитокинового и воспалительного ряда, молекулярно-генетическое исследование мутации V617F в гене *JAK2* и анализ вклада их изменений в развитие тромбогеморрагических осложнений. Обнаружено, что неврологическая картина в обеих группах была без значимых различий со средней оценкой по шкале NIHSS 12 и 13 баллов соответственно. Отмечены особенности морфофункциональных характеристик эритроцитов и тромбоцитов, а также гемостазиологического и цитокинового профиля у пациентов с ИИ на фоне ИП по сравнению с группой сравнения. Одним из ключевых элементов в потенциировании тромботических осложнений у пациентов с ИИ и ИП стала величина аллельной нагрузки мутации V617F в гене *JAK2*. Полученные данные свидетельствуют о совокупном действии комплекса факторов, формирующих высокую тромбогенность у перенесших ИИ пациентов с ИП и преодолевающих суммарный эффект антитромботической терапии.

Ключевые слова: ишемический инсульт, истинная полицитемия, тромбоз, гемореология, гемостаз, ангиогенез

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Despite phenotypic heterogeneity, all subtypes of ischemic stroke (IS) share a common underlying mechanism: interruption of micro-and macrovascular blood flow in brain-supplying vessels.. Thrombosis develops as a complex multifactorial process involving changes in blood rheology, loss of antithrombotic properties by the endothelium, initiation of systemic inflammatory response, and homeostatic imbalance [1, 2]. Cerebrovascular disorders (CVD) often strike in the setting of Ph-negative myeloproliferative neoplasms (MPN) [3, 4]. Polycythemia vera (PV) is a Ph-negative MPN that causes severe, frequent thrombohemorrhagic complications, including CVD. PV arises from myeloproliferation of hematopoietic stem cells in the bone marrow followed by successful terminal differentiation of hematopoietic progenitors into mature cells. This results in the sustained elevation of hemoglobin and erythrocyte count in the peripheral blood [5, 6].

PV can be caused by proliferation of 3 myeloid lineages, including erythroid, granulocytic and megakaryocytic. In recent years, the prevalence of erythrocytosis has been on the rise and is now 0.6–2.8 per 100,000 population. The etiology of PV is still vague and largely attributed to the exposure to genome-damaging environmental or other external factors. The 2005 discovery of the V617F mutation in the *Jak2* gene has dramatically expanded our knowledge of PV pathogenesis and biology: V617F occurs in more than 98% of patients with PV and is a diagnostic criterion [7–9].

Being a hematologic disorder, PV is also recognized as a vascular problem fraught with risk of thrombotic, hemorrhagic and cerebral complications. One of the most common manifestations of vascular pathology in patients with PV is arterial hypertension (AH); it affects 60–80% of patients with PV at any stage of the disease, including clinical and hematologic remission [10–12].

Among the most common and dangerous vascular complications of PV are arterial/venous thrombosis, focal or multifocal hemorrhages or bleeding, and disseminated intravascular coagulation. Clinically, they present as strokes, myocardial infarction, deep vein thrombosis, and pulmonary embolism [13]. On average, patients with PV are at two times higher risk of blood vessel occlusion [14]. In such patients, vein thrombosis in the lower extremities is accompanied by inflammation, edema and hyperemia (similarly to thrombophlebitis). Portal vein thrombosis leads to portal hypertension, splenomegaly, esophageal varices, ascites, and Budd–Chiari syndrome [15, 16].

There are a few factors contributing to thrombosis in the setting of PV: high hematocrit, high red blood cell and platelet counts, reduced fibrinolytic activity, leukocyte activation, endothelial damage, platelet-endothelium interactions, the JAK2 V617F mutation, therapy, and increased blood viscosity [17]. The latter is hypothesized to be the leading factor potentiating thrombosis in patients with PV. The available literature on the role of hemostasis, rheological and microcirculatory factors in promoting thrombotic complications in patients with PV leaves unanswered the question of how such complications develop in patients with IS and comorbid PV [18–20]. In light of the aforementioned facts, the aim of this paper was to study factors associated with increased thrombogenic potential in patients with IS and pre-existing PV.

METHODS

We examined 127 patients with first-time IS, including 68 patients with IS and pre-existing PV (group I, or the main group), and 59 patients with IS but without PV (group II, or the comparison group). The groups did not differ in terms of age or sex.

The following inclusion criteria were applied: 1) age of 42–75 years; 2) hyperacute stroke and the follow-up examination 16–18 months after it (median of 17.3 months; 95% CI 16.4–18.3); 3) IS confirmed by neuroimaging; PV diagnosed according to WHO criteria (TOAST subtype: stroke of other determined etiology [21]); 4) cytoreductive therapy for PV (hydroxyurea or IFN-α in combination with antiplatelet drugs, such as aspirin) before stroke; 5) erythrocytapheresis in all patients with PV (2–6 sessions a year).

The studied cohort of patients was dominated by women (64% in group I and 67% in group II). Diabetics and smokers were less prevalent in the man group; dyslipidemia was diagnosed in 25% of patients with isolated IS and only in 3% of main group patients.

Physical examination included general and neurological health assessments with the NIHSS scale, the Barthel index (on admission) and the modified Rankin scale (1.5 years after stroke). The following laboratory tests were performed:

1) complete blood count on a MEK-7222 analyzer (Nihon Kohden; Japan);

2) evaluation of erythrocyte rheology (aggregation amplitude Amp, a.u.); time to rouleaux formation (Tf, s) and time to 3D aggregation (Ts, s); aggregation index (AI, a.u.); complete disaggregation rate (ϒ-dis, a.u.), which represents the force needed to break up RBC aggregates and deform RBC (DImax, a.u.). The measurements were conducted using a laser-assisted RBC aggregometer (LORRCA, Mechatronics; Netherlands);

3) evaluation of hemostasis and endothelial function (ATP-, adrenaline-induced platelet aggregation (ATP-Adr-PA, %) and ristocetin cofactor test, which measures the functional activity of von Willebrand factor (RCA-VWF, %); the tests were done using an aggregometer (Biola; Russia) and RENAM reagent kits (RENAM; Russia). Besides, we measured fibrinogen concentration (FG, g/L), activated partial thromboplastin time (APTT, s), prothrombin time (s; test results were expressed as the international normalized ratio INR), D-dimer levels (ng/ml), activity of protein C (PC, %), protein S (PS, %), von Willebrand factor (A – VWF, %), plasma coagulation factors V, VII, VIII, XII (%), antithrombin III (AT III, %), plasminogen (PLG, %), alpha2-antiplasmin (PL-IN, %), and von Willebrand factor antigen (VWF, %). The tests were performed using an ACL Elite Pro automatic hemostasis analyzer (Instrumentation Laboratory; USA) and reagents by IL (USA) and RENAM (Russia);

4) measurements of cytokines, inflammation, endothelial function and angiogenesis markers, including vascular endothelial growth factor A (VEGF-A, pg/ml), fibroblast growth factor β (FGFβ, pg/ml), transforming growth factor β (TGFβ1, pg/ml), tissue plasminogen activator (t-PA, ng/ml), plasminogen activator inhibitor (PAI-1, ng/ml), tissue factor (TF, pg/ml), metalloproteinase ADAMTS-13 (μg/ml), soluble thrombomodulin (sTM, ng/ml), soluble intercellular adhesion molecules sICAM and sVCAM, thrombin-activated fibrinolysis inhibitor (TAFI, %), tumor necrosis factor α (TNFα, pg/ml), interleukins IL1β and IL6 (pg/ml), endothelin-1 (pg/ml), and nitrogen oxide (NO, μmol/l). The measurements were conducted ELISA assays and regent kits by eBioscience Bender MedSystems (Austria), Technoclone (Austria), Cloud Clone Corparation (USA, China), R&D Systems (USA, China), Cayman Ataxia (India), Vector-Best (Russia), and Sekisui Diagnostics (American Diagnostica; USA);

5) molecular tests for the V617F mutation in the JAK2 gene; the tests were conducted using assays by GenoTechnology, Russia, and a Real-time DT-Lite PCR thermal cycler (DNA-Technology; Russia).

Statistical analysis was carried out in IBMSPSS 23.0 and R 3.4.3 (IBM Company; USA). Descriptive statistics for categorial data are provided below as frequencies and proportions (%). For normally distributed quantitative data, the results are presented as a mean value (M) and a standard deviation (SD). For non-normal distribution, medians (Md), upper and lower quartiles (Q 25%–75%) were used. For group comparisons, the Kruskal–Wallis test was applied followed by the Mann–Whitney U test for pairwise comparison. Associations between the studied variables were measured using Pearson's correlation analysis. Risks were assessed with the chi square test, contingency tables and OR. Principal component analysis of the correlation matrix was employed for factor extraction, considering weights >1 and the variable loading.

RESULTS

On admission, the neurological picture in both groups was almost the same; mean NIHSS scores were 12 (5.0; 20.0) and 13 points (5.0; 20.0), respectively.

Severe neurological deficit was observed in 16 stroke patients with PV (24%); in patients without PV it was significantly less frequent (11 patients, or 19%). Moderate neurological deficit was observed in 33 patients with PV (50%) and 36 patients without PV (61%), which is significantly more often. Mild deficits manifested as mild sensory disturbances were present in 17 patients with PV (26%) and 12 patients without PV (20%). Barthel index values did not differ significantly between the groups, equaling 70 (59; 76) in group I and 72 (62; 75) in group II.

Pyramidal syndrome was the main neurological symptom of IS in most study participants, presenting as marked hemiparesis or hemiplegia with sensory disturbances in 27% and 29% of patients in groups I and II, respectively.

Speech impairments (total, sensory, motor, or mixed aphasias) and cortical dysarthria were almost equally observed in both groups, affecting 45 (66%) patients in the main group and 38 (60%) patients in the control group. No significant differences were detected between the groups in terms of major neurological symptoms in the acute phase of CVD.

Neurological deficit dynamics were analyzed over the 1.5-year period from the end of the acute IS phase to the follow-up examination. We found that by the time of the follow-up examination, the frequencies of motor, sensory and speech impairments had decreased by 14, 20 and 25%, respectively; patients reported no reduction in the frequency of headaches and only slight improvement in the asthenic syndrome. According to the modified Rankin scale, functional recovery profiles 16–18 months after IS were good (0–1 points) in 18 patients (27%), satisfactory (2–3 points) in 26 patients (38%) and poor (4–5 points) in 24 patients (35%).

Complete blood counts and blood rheology tests performed in the acute phase of IS exposed significantly elevated platelets (613 vs. 271×10^9/L), RBC count (5.8 vs. 3.8×10^{12}/L), WBC count (12.6 vs. 8.7×10^9/L), hemoglobin (174 vs. 119 g/L), and hematocrit (49.5 vs. 38.7%) in patients with PV; their ESR was low (5 vs. 23 mm/h) and all studied morphological and functional erythrocyte characteristics were much worse than in patients without PV. In patients with PV vs. without PV, the aggregation index and the aggregation amplitude (12.8 and 9.3 a.u., respectively; p = 0.003), as well as the complete disaggregation rate, which reflects the density of erythrocyte aggregates (570 and 224 a.u.; p = 0.000), were significantly increased in the setting of reduced erythrocyte deformability (0.34 and 0.41 a.u., respectively; p = 0.000). We also found that cytokines, FGFβ (735.5 vs. 497.1 pg/ml), VEGF-A (1,257.6 vs. 568.4 pg/ml), $TGF\beta_1$ (1,824 vs. 710 pg/ml; p = 0.000), and angiogenesis markers were significantly elevated in patients with PV.

Hemostasis profiles of patients with IS with or without pre-existing PV are compared in Fig.1.

In comparison with patients without PV, individuals with PV had higher concentrations of fibrinogen, p-thrombomodulin, increased TAFI, TF and coagulation factor VII activities, lower concentrations and decreased activity of VWF, ATIII and ADAMTS-13. In the comparison group, coagulation factor VIII exhibited higher activity and D-dimers were also higher, whereas PLG and tPA were decreased and PAI-1 was elevated.

In order to analyze the effect of JAK2 V617F allele burden on the thrombogenic potential in the hyperacute phase of IS, we performed dimensionality reduction through factor analysis and identified factors with at least moderate loading (JAK2 V617F allele burden was assumed to be the leading variable with the highest loading). We identified 10 laboratory parameters having the strongest association with JAK2 V617F allele burden (Table 1).

High JAK2 V617F allele burden had the most pronounced effect on the reduction in erythrocyte deformability and the increase in coagulation factor VII activity. High JAK2 V617F allele burden was associated with the activation of pathologic angiogenesis mediated by VEGF-A and TGFβ1, high platelet count co-occurring with changes in platelet aggregation properties and endothelial dysfunction.

During the follow-up examination (16–18 months after stroke), we estimated the frequency of thrombotic and hemorrhagic complications developed over this period (Table 2).

The number of thrombotic, hemorrhagic and mixed complications in the main group was higher than in the comparison group; one of the key elements in potentiating thrombotic complications in patients with PV (manifested predominantly as recurrent CVD) was JAK2 V617F allele burden (Table 3).

The odds ratio for recurrent ischemic CVD in the long-term period based on JAK2 V617F allele burden in the hyperacute

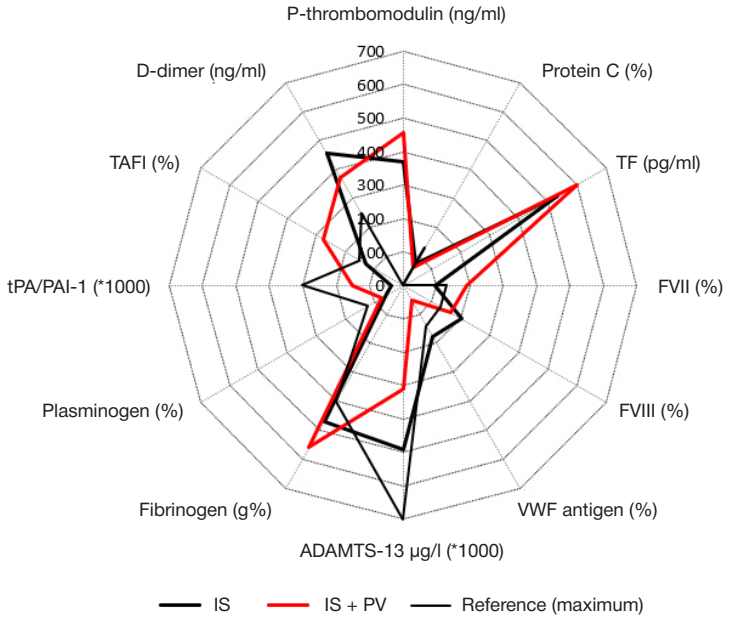

Fig. 1. Hemostasis profiles of patients in the hyperacute IS stage. ADAMTS-13 and fibrinogen concentrations and the tPA/PAI-1 ratio are shown concisely to fit into the overall hemostasis profile picture

Table 1. A correlation matrix showing effects of JAK2 V617F allele burden on the laboratory parameters in patients with PV in the hyperacute stroke phase

	Tested parameters	Component
	JAK2 V617F allele burden	0.722
1	RBC deformability (Dlmax), a.u.	0.492
2	Factor VII, %	0.464
3	VEGF-A, pg/ml	0.425
4	ADAMTS-13, μg/ml	0.412
5	TGF-β_1, pg/ml	0.398
6	ATP-PA, %	0.367
7	Platelet count (10^9/L)	0.354
8	WBC count (10^9/L)	0.341
9	VWF activity, %	0.323
10	t-PA, ng/ml	0.318

stroke phase with a threshold value of 48% was 2.9 times (95% CI 2.0–3.3).

Among the hemorheological risk factors for recurrent thrombotic complications in the long-term poststroke period were a decline in the complete RBC disaggregation rate (yDis) from 570 to 498 a.u. (p = 0.017), elevation of endothelin-1 concentrations from 4.6 to 5.2 pg/ml and elevation of adhesion molecules concentration (sVCAM-1 (p = 0.008) and sICAM-1 (p = 0.007)). Increasing microcirculation disturbances might have caused or resulted in pronounced inflammatory response reflected in heightened IL6 levels (from 13.5 ± 0.69 pg/ml to 15.2 ± 0.7 pg/ml (p = 0.034).

Almost no differences were observed between the hyperacute stroke phase and the long-term poststroke period in terms of hemostasis profiles of our patients (Fig. 2).

DISCUSSION

Hemostatic homeostasis is regulated by the balance of thrombogenic and antithrombogenic factors. If the balance is shifted towards secretion of procoagulation molecules, thrombosis develops. Therefore, it is important to identify causes, conditions and drivers of first-time and recurrent thrombosis in the affected patients., or, in other words, to timely detect pre-thrombosis or the so-called thrombotic preparedness [21], which combines clinical signs of pre-thrombosis and laboratory markers of thrombogenic potential. Reinforced by persisting factors of thrombotic risk and high likelihood of such risk, thrombotic preparedness can present as recurrent CVD and variously localized thrombosis.

According to Virchow's triad, changes of blood flow characteristics that can potentially trigger thrombotic complications are among the underlying causes of thrombosis.

It is noteworthy that prior or after stroke, patients with PV were receiving specific cytoreductive therapy (hydroxyurea or IFNα). On the one hand, cytoreductive therapy is an additional risk factor for IS and thrombotic complications in this cohort of patients. On the other hand, given that no significant differences were observed in the effect of cytoreductive therapy on the studied parameters, we can link changes in the studied laboratory parameters to the course and sequalae of IS in patients with pre-existing PV.

Blood counts were significantly elevated in patients going through the hyperacute phase of IS; RBC function and morphology were significantly compromised, which was associated with changes in membrane plasticity, substantial reduction in RBC deformability and increased RBC aggregates.

In general, the hyperacute phase of IS was characterized by multiple signs of vascular wall damage and endotheliopathy accompanied by formation of a prothrombotic endothelial

Table 2. Thrombotic and hemorrhagic complications in patients detected on the follow-up examination 16–18 months after IS

Groups / Complications	IS + PV (n = 68)	IS (n = 59)
Thrombotic complications (n)	28	18
– ischemic CVD	16	10
– venous thrombosis of lower extremities	12	8
– Pulmonary embolism	0	0
ГHemorrhagic syndrome (n)	20	n/a
– nasal, gingival, subcutaneous, hemorrhoidal bleedings	18	n/a
– gastrointestinal bleeding	2	1
Mixed thrombotic and hemorrhagic complications	7	0

Note: n/a — data not available.

Table 3. Coefficients of JAK2 V617F allele burden correlation with long-term thrombotic complications

	Pearson's correlation coefficient
All thrombotic complications, of them:	0.236 ($p < 0.05$)
– ischemic CVD	0.241 ($p < 0.05$)
– venous thrombosis of lower extremities	0.124
– mixed thrombotic and hemorrhagic complications	0.116

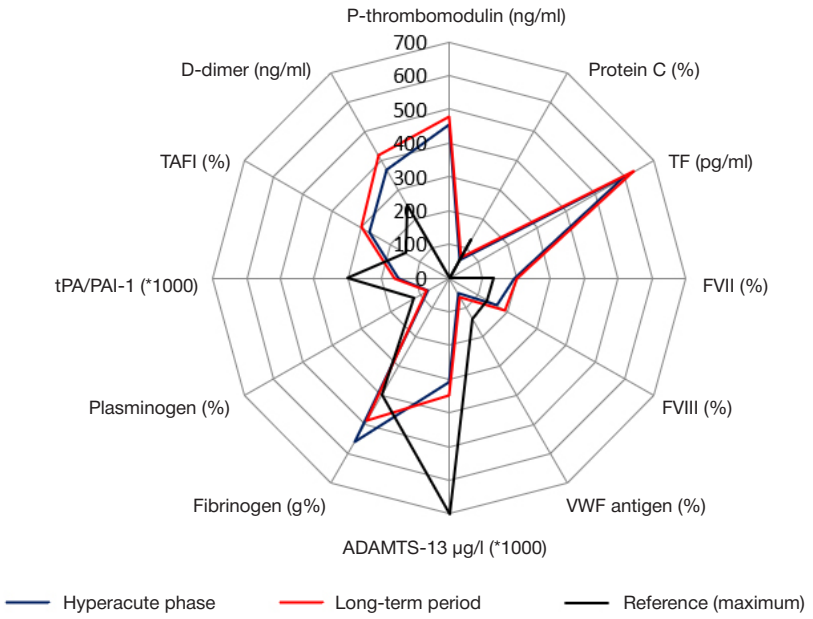

Fig. 2. Hemostasis profiles of main group patients in the hyperacute IS phase and in the long-term stroke period

phenotype. This is indicated by the fact that in both groups of patients with IS, suppressed protein C activity was not compensated by thrombomodulin, which is normally bound to the endothelial cell membrane and is nearly absent in the bloodstream. Its presence in the bloodstream signals significant damage to endothelial cells.

The thrombogenic potential of patients with IS and pe-existing PV greatly depended on the tissue factor and coagulation factor VII, whereas for patients with IS the balance between vWF, coagulation factor VIII and ADAMTS-13 were more important contributors to IS. Nevertheless, inflammatory response can be regarded as an initiator of increased thrombogenic potential specifically in comorbid patients, as suggested by lower activity of antithrombin III and higher concentrations of fibrinogen, studied cytokines and growth factors. Besides, hypothetically, inflammation might have been promoted by a combination of factors typical to a myeloproliferative process: the presence of neutrophil extracellular traps (NET), circulating free DNA, etc. [22]. Therefore, higher levels of tissue factor and coagulation factor VII in patients with IS and pre-existing PV should be interpreted as secondary signs of endotheliopathy.

Fibrinolysis is traditionally seen as a compensatory mechanism for such condition; I our study, fibrinolytic activity was markedly depressed in both groups, which was manifested as reduced plasminogen reserve, tPA deficit and prevailing activity of fibrinolysis inhibitors. In patients with IS and pre-existing PV, excess generation of thrombin resulting from inflammation also suppressed fibrinolysis through a pronounced increase in TAFI activity.

JAK2 V617F allele burden is a substantial contributor to the development of thrombotic complications (predominantly recurrent CVD). Higher burden is associated with decreased RBC functional properties, activation of pathologic angiogenesis, increased platelet count, and changes in platelet functional properties in combination with endothelial dysfunction.

Our findings show that the hematologic disorder was the main driver of the thrombogenic potential in patients with IS and pre-existing PV. Being a risk factor for thrombosis per se, myeloproliferation was sufficient to trigger thrombotic complications in spite of antithrombotic and cytoreductive therapy received by the patients. Over the 1.5-year followup, pronounced endotheliopathy and the intensity of hemocoagulatory and fibrinolytic activities in patients with IS and pre-existing PV did not undergo any significant changes, and increased systemic thrombogenic activity did not attenuate. Considering that arterial or venous thrombosis is a life-threatening situation, it is essential to refine diagnostic and therapeutic methods for vascular ischemia and to prevent the recurrence of vascular events. These facts necessitate 1) further research into the pathogenesis of increased thrombogenic potential/ thrombosis in MPN; 2) changes in diagnostic algorithms and standard antithrombotic regimens, including the adoption of personalized approaches to treatment and hemostasis monitoring.

CONCLUSIONS

Our findings suggest that the cumulative effect of all the factors contributing to high thrombogenic potential in patients with IS and pre-existing PV overpower the effect of antiplatelet therapy. This happens due to the persistence of almost all prothrombogenic conditions promoted by inflammation and manifesting as disturbances in blood rheology, endotheliopathy, thrombinemia and depressed fibrinolysis. This corroborates the postulates about the need for individually tailored and well-reasoned long-term antiplatelet therapy and prophylaxis of recurrent vascular events.

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