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Study of JAK2V617F gene allele burden in polycythemia vera

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Objective: In recent years, it became necessary to identify a new clinical form of polycythemia vera – latent polycythemia vera (LPV). Considering the significant role of the JAK2V617F gene in the pathogenesis of LPV, we investigated the relationship between the allele burden of the JAK2V617F gene and clinical and laboratory parameters of the disease.

Case report: Patient G.N., at the age of 64, complained of pain in the legs, itching during bathing, weakness, headaches. He had been ill for several years. He suffered from glaucoma, as a result of which he acquired blindness. For a long period paresthesias, erythromelalgia and a gradual impairment of movement in the lower extremities had been observed. The patient was observed by a neurologist with a diagnosis of sensory neuropathy. Recently pain in the legs intensified and there were difficulties in walking. Due to changes in the hemogram, the patient was sent for a consultation to a hematologist. During examination, hyperemia on the face, traces of scratching were visible on the skin. On palpation, the spleen was enlarged by 1.5 cm. In laboratory analysis in the hemogram Hb-185 g/L, RBC-6.96 $\times 10^{12}$/L, Ht-58.5%, WBC-13.4 $\times 10^{9}$/L, PLT-471 $\times 10^{9}$/L. Taking into account the clinical and laboratory data, the patient underwent trepanobiopsy and molecular genetic analysis for the JAK2V617F mutation. As a result of histological examination of the trepanobioptate, three-branch proliferation in the bone marrow was revealed. The allele burden of the JAK2V617F gene was 79.5%. The patient was diagnosed with PV. After phlebotomy 4 times at a dose of 500 ml + LDA, the patient's condition improved, the pain in the legs disappeared, and independent movement without the help resumed. Control parameters of the hemogram: Hb-131q/L, RBC-4.5 $\times 10^{12}$/L, Ht-40%, WBC-9.69 $\times 10^{9}$/L, PLT-394 $\times 10^{9}$/L.

Methodology: The data of 193 patients were analyzed: hemogram parameters, allele burden of the JAK2V617F gene, analysis of the risk groups of patients were carried out. The WHO classification of 2008 and 2016, the prognosis of the risk of thrombohemorrhagic complications (TC) according to the Marchioli scale was used.

Results: Out of 193 patients, 127 were with classic polycythemia vera (CPV), and 66 were with LPV. The age of the patients (M ± m) with CPV was 57.01 ± 1.1 years, with LPV – 55.03 ± 1.6 years ($p > 0.05$). 97% of patients had the mutation of JAK2V617F gene. Laboratory parameters of patients with CPV and LPV were compared (M ± m): hemoglobin – 182.66 ± 2.1 g/L and 157.97 ± 2.2 g/L ($p < 0.05$), hematocrit – 71.85 ± 1.4% and 63.5 ± 1.8% ($p < 0.05$), erythrocytes – 6.18 ± 0.1 $\times 10^{12}$/L and 5.46 ± 0.1 $\times 10^{12}$/L ($p < 0.05$), platelets – 526.85 ± 30.9 $\times 10^{9}$/L and 429.3 ± 34.7 $\times 10^{9}$/L ($p < 0.05$), leukocytes 11.92 ± 0.6 $\times 10^{9}$/L and 10.79 ± 0.7 $\times 10^{9}$/L ($p > 0.05$), allele burden of the JAK2V617F gene – 55.0 ± 6.4% and 27.0 ± 6.9% ($p < 0.05$). Allele burden was divided into quartiles. In CPV 21.78% of patients belonged to the 1st, 20.16% to the 2nd, 18.55% to the 3rd, 39.51% to the 4th quartile. In LPV – 20% of patients belonged to the 1st, 80% to the 2nd quartile, in the 3rd and 4th quartiles there were no patients. In CPV the highest leukocyte count was in the 4th quartile. In LPV patients with an allele burden of the JAK2V617F gene above 40% had higher leukocyte and platelet counts, while the allele burden did not exceed 50%. We did not find any more relationship between allele burden and other hemogram parameters in patients with CPV and LPV. TC risk groups in CPV-low – 56.34%, intermediate – 38.03%, high – 5.63%, in LPV- low – 51.3%, intermediate –16.2%, high – 32.5%. In the analysis of JAK2V617F gene allele burden in the 1st and 2nd quartiles, no differences were found between the risk groups of LPV patients.

Conclusion: Out of PV patients 65.8% were with CPV, and 34.2% with LPV. In LPV the allele burden was lower than in CPV and did not exceed 50%. In CPV and LPV more than 51% of patients were at low risk of TC. CPV patients with JAK2V617F allele burden >75% had higher leukocyte count. LPV patients with JAK2V617F allele burden >40% had higher leukocyte and platelet counts.

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COAGULATION DISEASES

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Clinical and anamnestic signs of hypercoagulation in patients with β-thalassemia

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Objective: Hypercoagulation in β-thalassemia patients is known to manifest as arterial and/or venous thrombotic complications. Along with the clinical assessment of thrombotic complications (TC), it is also important to study latent (masked) hypercoagulation (LH) hypercoagulable state (HS) in patients with β-thalassemia. HS assessment is possible based on the analysis of various clinical symptoms and patient history.

Case report: In the National Centers of Hematology and Transfusiology, we studied 315 women aged 18–40 years: 130 with β-thalassemia Major (TM), 95 with β-thalassemia intermedia (TI), 60 with β-thalassemia minor (Tm), 30 blood donors (BD).

Methodology: The data were analyzed retrospectively and as a result of our survey on the increased thrombotic tendency. Statistics: data input system MS Excel, data processing using the program Statistics 6.

Results: In 10.0 ± 2.6% of TM patients and in 14.7 ± 3.6% of TI patients, various TCs were revealed: arterial thrombosis, venous thrombosis, chronic venous insufficiency (varicose nodes of the lower extremities, telangiectasia, trophic ulcer, venous eczema, swelling of the feet and lower legs). Such complications was not detected in patients with Tm and in the control group. Out of 60 splenectomized patients with

TM, arterial thrombosis was observed in 2 (3.3%) patients, venous thrombosis in 3 (5.0%) patients, and signs of chronic venous insufficiency in 4 (6.7%) patients. Out of 70 non-splenectomized patients with TM, venous thrombosis was observed in 1 (1.4%) patient, and signs of chronic venous insufficiency in 3 (4.3%) patients. Of the 40 splenectomized TI patients, arterial thrombosis was observed in 2 (5.0%), venous thrombosis in 3 (7.5%), and signs of chronic venous insufficiency in 4 (10%). Of 55 non-splenectomized TI patients, venous thrombosis was observed in 2 (3.6%), and signs of chronic venous insufficiency in 3 (5.4%). Assessment of thrombotic tendency was conducted among non-splenectomized patients. HS (the total score for the PTT questionnaire >30) was detected in 36.0 ± 6.8% of TM patients and 40.0 ± 7.7% of TI patients. In patients with TI and in BD, increased thrombotic tendency was not detected (the sum of the scores for the PTT questionnaire is <30).

Conclusion: TCs detected in patients with homozygous β-thalassemia was more common in patients with TI compared with patients with TM ($p \geq 0.05$). In patients, cases of venous thrombosis were detected 2 times more often than arterial thrombosis ($p \geq 0.05$). Chronic venous insufficiency was detected identically in patients with TM and TI. TCs was observed more often in splenectomized patients with TM and TI compared with non-splenectomized patients ($p \geq 0.05$). It was established that some patients with β-thalassemia who did not have clinical thrombotic complications had prethrombotic state. A study of clinical and anamnestic risk factors revealed a tendency to HS in 1/3 of patients with β-thalassemia. Based on the results of the survey, the risk factors (predictors) of HS were determined. The tendency to form blood clots in patients with anemia was associated with two groups of clinical and anamnestic symptoms: “comorbidity” and “chronic stress conditions”.

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Factor XIII deficiency case with posttravmatic subcutaneous bleeding

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Objective: Factor XIII deficiency; is a rare hereditary bleeding disorder caused by heterogeneous mutations that can lead to life-threatening bleeding. Hereditary factor XIII deficiency's inheritance is autosomal recessive and its incidence is about 1–3/1,000,000. The form of bleeding can be seen in a wide spectrum, from life-threatening bleeding (such as intracranial bleeding) to skin bleeding. Umbilical cord hemorrhage and soft tissue hematoma is the most common and often first symptom of factor XIII deficiency (1). Lifelong bleeding diathesis can be seen in hereditary FXIII deficiency. Especially subcutaneous bleeding (57%), delayed umbilical cord bleeding (56%), muscle hematoma (49%), postoperative bleeding (40%), intracerebral bleeding (34%) and recurrent abortion can be seen. Bleeding after trauma or surgery (12–36 h) is pathognomonic in factor XIII deficiency. (2) Diagnosis of factor XIII deficiency is difficult due to its rarity. Because standard clotting screening tests including prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), platelet count or bleeding time are normal; therefore, specific factor XIII assays are required. For all these reasons, factor XIII deficiency remains one of the least diagnosed rare bleeding disorders (1).

Case report: 34-year-old male patient applied to the emergency department due to the swelling that developed after hitting his right arm on the door. He stated that he had a history of factor 13 deficiency. Fracture or fissure line was not observed in the patient's physical examination and direct radiography. Bleeding observed in skin and subcutaneous region. In the anamnesis, the patient stated that he had a history of skin-subcutaneous bleeding and hematoma after trauma. In hospital records, it was observed that he had posttraumatic intramuscular hematoma two times in the last 5 years (the largest is 75 mm × 25 mm × 40 mm). In these hematomas treatment; there was no need for factor XIII concentrate, it was regressed with fresh frosen plasma replacement. In the laboratory tests performed in emergency department; leukocyte value 12,370/μL, neutrophil 6720/μL, hemoglobin 16.7 g/dL, platelet 315,000, PT: 9.12 s, aPTT 23.2 s, INR 1.02 was detected. Fresh frozen plasma was replaced at a dose of 15 mL/kg. The patient, who did not have any additional systemic problem, was discharged by recommending polyclinic control.

Conclusion: Hereditary factor XIII deficiency is an autosomal recessive bleeding disorder with a serious course (4). Unlike other hereditary hemostatic protein deficiencies, clotting tests and platelet function tests are normal in factor XIII deficiency. For this reason, specific factor XIII assays should be performed and the factor XIII level should be checked. The basis of treatment is replacement of the missing factor with plasma, cryoprecipitate and FXIII concentrates (2). However, in cases where there is a serious decrease in factor XIII levels, prophylaxis strategies with factor XIII concentrate can be applied to minimize bleeding events (5). In cases with recurrent delayed bleeding after trauma, factor XIII deficiency should be considered if the clotting profile is normal (2).

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