POLYCYTHEMIA VERA SYNDROME-AS A PROTROMBOTHIC STATE

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POLYCYTHEMIA VERA SYNDROME-AS A PROTROMBOTHIC STATE (Abstract): **The aim** of our study was to investigate whether the disorder of coagulation and fibrinolysis factors are mechanisms that contribute to the prothrombotic state in patients with polycythemia vera (PV) syndrome with or without cardiovascular disease (CVD), in order to identify the patients having high risk for thrombotic events. **Material and methods:** The study comprises 20 patients divided in 2 groups: 10 patients with PV syndrome (PV) and 10 pacients with PV and cardiovascular diseases associated (PV+CVD). The patients were tested by determining three factors of coagulation profile: protein S, free fraction (PS), antithrombin III (AT III) and Protein C (PC). **Results:** The level of the three parameters were found significantly modified in the both groups ($p<0.05$); comparing the results between the two groups of patients, in the second group (PV+CVD) the level of the parameters were significantly lower than in the first group (PV). **Conclusions:** In PV syndrome the risk for thrombosis is also due to the changes in coagulation factors. Patients with associated cardiovascular disease, present a more severe risk for trombothic events, so regarding the disorder of coagulation factors, this represent a major mechanism implicated in the etiology of thrombosis in these categories of patients. **Keywords:** THROMBOSIS, POLYCYTHEMIA VERA, PROTEIN S

Polycythemia vera (PV) is a clonal disorder arising in a multipotent hematopoietic progenitor cell that causes the accumulation of morphologically normal red cells, white cells, platelets, and their progenitors in the absence of a definable stimulus and to the exclusion of nonclonal hematopoiesis (1. 2). Described for the first time in 1892, polycythemia vera is not a new disease and while uncommon, with an incidence of at least 2 per 100,000 (3). Multiple factors are likely to contribute to the pathogenesis of thrombosis, including increased cell mass, possibly platelet number, activation of platelets and leukocytes and their interaction to form platelet leucocyte aggregates, in addition to prothrombotic circulating and endothelial factors. Endothelial activation may also have been due to elevated levels of vascular endothelial growth factor, which has also been reported to be elevated in PV (4. 5. 6). Activated leukocytes (neutrophils and monocytes) promote coagulation by release of granule contents, formation of aggregates with platelets. Subsequent effects include plate-

let leukocyte aggregates playing a pathogenic role in triggering monocyte tissue factor expression as well as superoxide anion and inflammatory cytokine release causing endothelial activation and damage. Besides the procoagulants mechanisms, the thrombotic risk is also amplified by the association of the other risk factors for thrombosis represented by advanced age, history of thrombotic vascular diseases, repeated phlebotomies, hypercholesterolemia and smoking (7, 8).

MATERIAL AND METHODS

The study comprises 20 adult patients, diagnosed according to Polycytemia Vera Study Group criteria, divided in 2 groups: 10 patients with PV syndrome (PV) and 10 pacients with PV with CVD associated (PV+CVD). Patients' age ranged from 61 to 80 years, significantly higher in the PV+CVD group ($p<0.05$). The old of the disease ranged from 1 to 4 years, significantly higher in the PV+CVD group ($p<0.01$).The patients were tested by determining three factors of coagulation profile: Protein S (PS), Antithrombin III (AT III) and Protein C.

RESULTS AND DISCUSSIONS

Protein S, Ag (PS): In the studied groups, the mean values of PS not significantly differ between genders, but in males from PV group, the mean values of PS are significantly lower than those observed in the PV+CVD group ($p<0.05$). In both studied group, it was observed a direct correlation between PS values and the patients' age; low values of PS were recorded in 66% of elderly patients from PV group and in 85% of elderly patients from PV+CVD group.

We have been observed a direct strong correlation between PS values and the age of the disease, both in the PV group ($r=0.76$) and in the PV+CVD group ($r=0.88$).

On the studied groups, comparing PS values, we have been observed the following characteristics:

- PS had the most homogeneous individual values in the PV+CVD group (12.15 CV%);
- in PV+CVD group, all of the patients had the PS values below normal limit (65%), significantly more cases compared with PV group (just 14 cases over limt) ($\chi^2=4.60$; GL=1; $p=0.027$);
- the mean values of PS are statistically significantly lower in PV+CVD group compared with PV group ($t=5.54$; GL=38; $p<0.001$). (fig. 1, 2, 3).

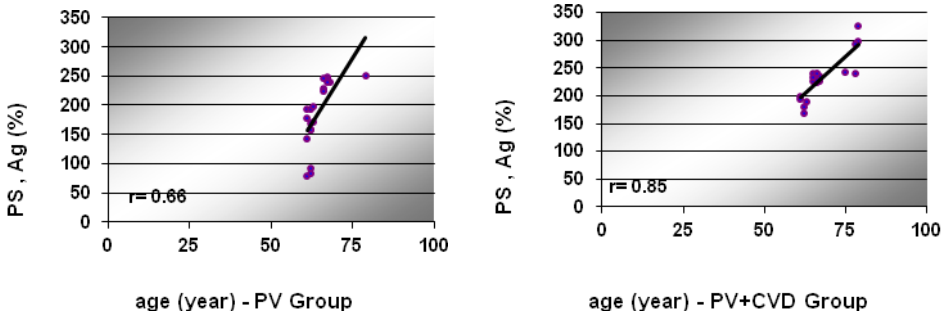


Fig. 1. Correlations between PS, Ag values and patients' age

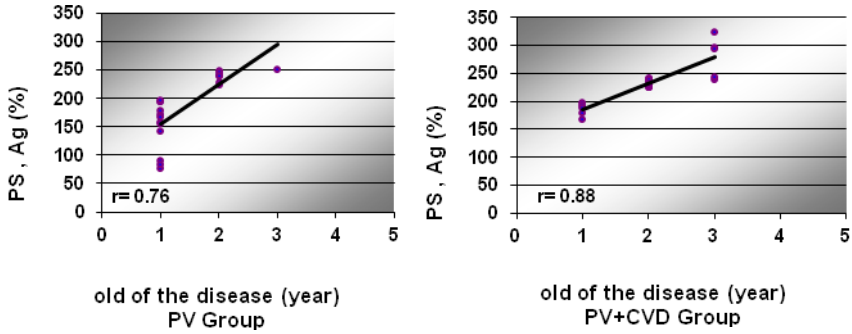


Fig. 2. Correlations between PS, Ag values and the old of the disease

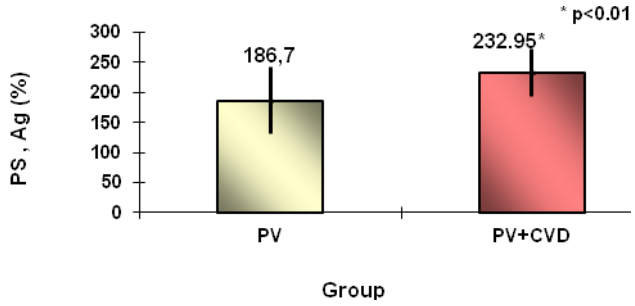


Fig. 3. The mean values of PS, Ag in the studied groups

Antithrombin III, Ag (AT III): On the studied groups, the mean values of AT III did not significantly differ between genders. On both studied groups, it was observed a direct correlation between AT III values and the patients' age; low values of AT III were recorded in 85% of elderly patients from PV group and in 89% of elderly patients from PV+CVD group.

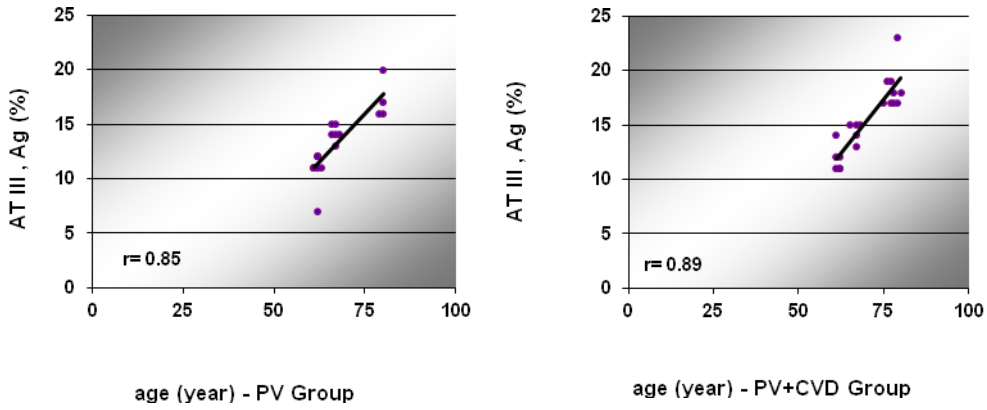


Fig. 4. Correlations between AT III, Ag values and patients' age

It was observed a direct strong correlation between AT III values and the age of the disease, both in the PV group (r=0.92) and in the PV+CVD group (r=0.89).

On the studied groups, comparing AT III values, we have been observed the following characteristics:

- the AT III individual values have a large dispersion, but the most homogeneous individual values was found in the PV+CVD group (12.66 CV%);
- we found the AT III levels below normal limits (65%) in all of the 20 patients from PV+CVD group and in 19 patients from PV group, without registering a significant statistically differences between these groups (χ^2=1.03; GL=1; p=0.311);
- the mean values of AT III are significantly lower in PV+CVD group compared with PV group (t=2.78; GL=38; p<0.05) (fig. 4, 5, 6).

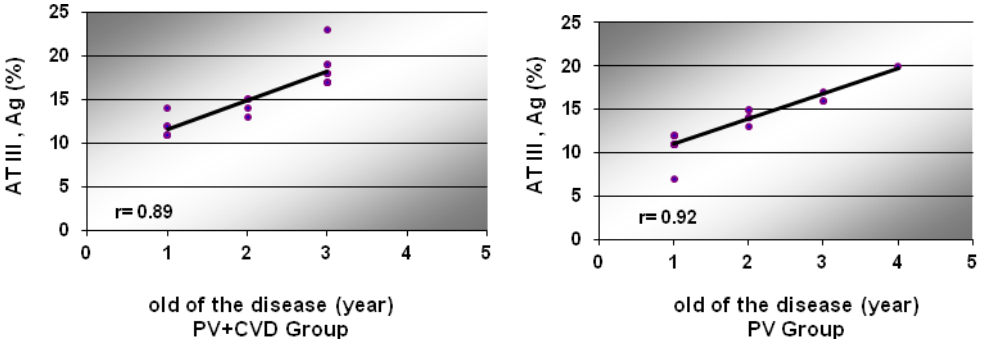


Fig. 5. Correlations between AT III, Ag values and the old of the disease

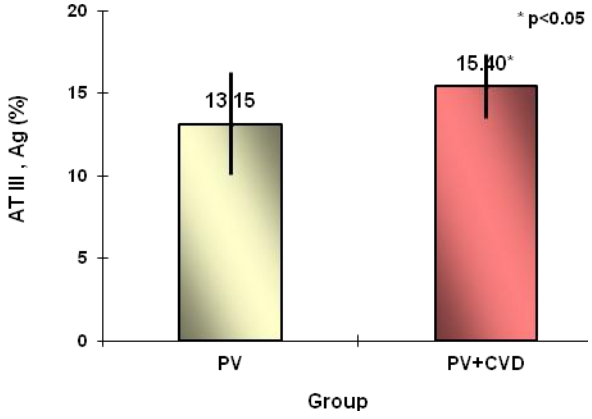


Fig. 6. The mean values of AT III, Ag in the studied groups

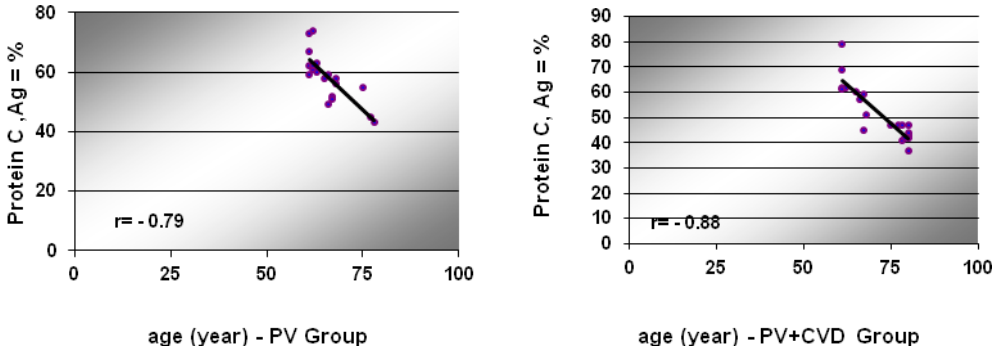
Protein C, Ag (PC): In the PV group, the mean values of protein C, Ag differ significantly between genders (p<0.05); in the PV+CVD group, in women, the values of this parameter are significantly lower compared with the values observed in women, from PV group (p<0.05). In both studied groups, it was observed an indirect

correlation between protein C values and the patients' age; low values of protein C were recorded in 79% of elderly patients from PV group and in 88% of elderly patients from PV+CVD group.

We also have been observed a strong indirect correlation between protein C values and the old of the disease, in both, in the PV group (r=0.84) and in the PV+CVD group (r=0.89).

On the studied groups, comparing protein C values, we have been observed the following characteristics:

- The variation of individual protein C, Ag values are large, but the most homogeneous series of values were found in PV+CVD group (14.49 CV%);
- We found the protein C, Ag level below normal limit (65%), in 18 patients from PV+CVD group and in 17 patients from PV group, without registering significant statistically differences between these groups (χ^2=0.23; GL=1; p=0.633);
- The mean values of protein C are significantly lower on PV+CVD group compared with PV group (t=2.42; GL=38; p<0.05) (fig. 7, 8, 9).



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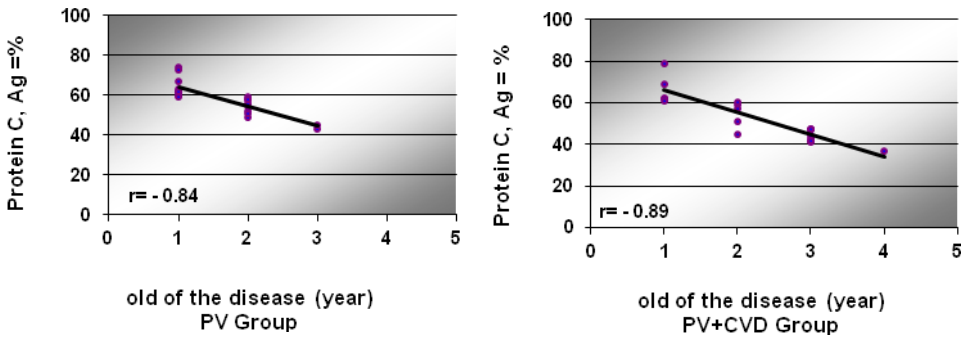

Fig. 8. Correlations between Protein C, Ag values and the old of the disease

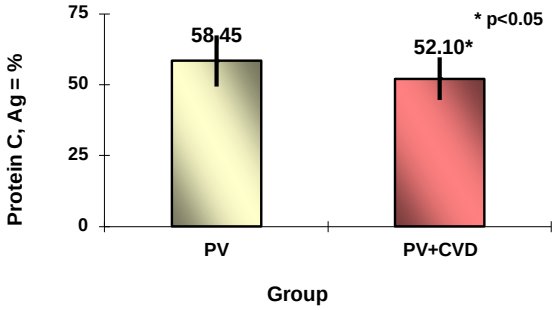

Fig. 9. The mean values of Protein C, Ag in the studied groups

DISCUSSION

Thrombosis and bleedings are the major causes of morbidity and mortality in PV. Large vessel arterial thrombosis in PV involves the cerebral, coronary and peripheral arterial circulations, while microcirculatory disturbances may cause erythromelalgia and digital ischemia. This hypercoagulable state in the group of patients with PV, could in part be explained by the known hypercoagulable condition associated with malignancy, by increases in white blood cells (WBC) count, but polymorphonuclear (PMN) enzyme involvement is possible. Activated PMN release reactive oxygen species and intracellular proteases, which can act on the endothelial cells and platelets and may modify the hemostatic balance toward a prothrombotic state. Endothelial activation may also have been due to elevated levels of vascular endothelial growth factor, which has also been reported to be elevated in PV (9). Leukocyte elastase and cathepsin G can induce detachment or lysis of endothelial cells and can modify endothelial cell functions involved in thromboregulation-that prevent thrombin-induced prostacyclin production, induce plasminogen activator inhibitor release and proteolyze endothelial surface components such as thrombo-modulin (10). Furthermore, the potential thrombogenic effects of PMN-derived proteases include the direct potent platelet activation elicited by cathepsin G. Elastase can directly proteolyze and inactivate natural inhibitors of blood coagulation, including protein C, protein S, tissue factor pathway inhibitor, antithrombin, and heparin cofactor II. This inactivation may contribute to local progression of coagulation reactions at the inflammation sites (11).

CONCLUSIONS

In PV syndrome the risk for thrombosis is also due to the changes in coagulation factors. Patients with associated cardiovascular disease, present a more severe risk for trombothic events, so regarding the disorder of coagulation factors, these represent a major mechanism implicated in the etiology of thrombosis in these category of patients. We may hypothesize that hypercoagulable state associated with malignancy, increases in WBC count, endothelial dysfunction, and reduced levels of physiologic anticoagulants (antithrombin III, proteins C and S) and decreased fibrinolytic activity that in part may be secondary to increased plasma levels of plasminogen activator inhibitor could explain, the pathogenesis of the thrombo-philic state in PV.

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NEWS

SERUM REACTIVITY TO *DEMODEX*-ASSOCIATED *BACILLUS OLERONIUS* PROTEINS IN ROSACEA PATIENTS

There is increasing evidence that suggests the role of *Bacillus oleronius*, isolated from within *Demodex folliculorum* mite in the induction of rosacea. A group of researchers tried to determine the correlation between the level of sebum and the density of *D. folliculorum* and the serum reactivity to the 62 and 83 kDa proteins of *B. oleronius* in patients with erythematotelangiectatic rosacea. Serum reactivity to *B. oleronius* proteins was detected in 82.6% of the rosacea patients compared to 26.9% of controls. In this group of patients, the level of sebum was lower and the density of *Demodex* populations on their faces was statistically higher than in controls, suggesting a potential role for this bacterium in the aetiology of rosacea (Jarmuda S, McMahon F, Zaba R *et al*. Correlation between serum reactivity to Demodex-associated Bacillus oleronius proteins, and altered sebum levels and Demodex populations in erythematotelangiectatic rosacea patients. *J Med Microbiol*. 2014; 63(Pt 2):258-62. doi: 10.1099/jmm.0.065136-0).

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