EDITORIAL

ABO blood group type and the risk of venous thromboembolism: the impact of interactions

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First observations on the association between ABO blood group type and the risk of venous thromboembolic events (VTE) date back to more than 50 years ago.[1] According to a large number of studies from the past few decades, the non-O blood type is considered a risk factor for VTE.[2] Despite the growing body of evidence generally supporting this statement, the picture today is not entirely clear. Pieces of the puzzle are lacking for the exact pathomechanism linking the non-O blood type with VTE risk. Moreover, effect modifiers, including interactions with other well-known inherited or acquired thrombophilia risk factors, are not fully understood. From a clinical point of view, evidence on the strength of ABO blood group type as a VTE risk factor is inconsistent and while in different populations (eg, in healthy populations, pregnant women, patients with cancer, ethnically different populations, etc) related evidence is still growing, the impact of the non-O blood type as a VTE risk factor is yet to be defined for the clinical practice.

Most studies are consistent that individuals with non-O blood type have higher levels of factor VIII (FVIII) and von Willebrand factor (VWF) than people with blood type O, and elevated levels of these factors contribute significantly to the observed increased risk of VTE.[2,3] In the plasma of non-O blood group individuals, the carbohydrate determinants of VWF have been indicated to provide protection against proteolysis by a disintegrin and metalloprotease with thrombospondin type 1 motif 13, resulting in a lower rate of VWF clearance and longer VWF half-life.[2] Specific N-linked glycosylation sites have also been shown to modulate the synthesis and secretion of VWF, representing another mechanism potentially leading to increased levels of VWF in non-O blood group individuals.[4] More recent findings suggest that interactions of the blood group O VWF with platelets might be reduced, indicating that VWF functional activity is also affected by blood type.[5] As VWF and FVIII circulate in a complex form, high levels of VWF lead to increased levels of FVIII. Some data support an independent association between FVIII levels, ABO blood group, and the risk of VTE, however, conflicting data have also been published and further results are awaited to extend the current hypotheses.[5,6] Altered levels of coagulation factors, however, are considered only one of the potential mechanisms by which ABO blood type may affect VTE risk. ABO(H) expression on platelet membrane receptors may influence their functional activities and contribute to an altered interaction with their ligands.[5] Genome-wide association studies have linked the ABO locus to serum levels of certain soluble adhesion molecules (eg, soluble intercellular adhesion molecule-1, tumor necrosis factor α) or soluble selectins (sEselectin, sPselectin), which have been recently in the focus of studies linking inflammation or cancer to thrombosis.[2]

It is clear that genetic and lifestyle factors may modify the association between ABO blood group and the VTE risk. As VTE is triggered by a combination of risks, the effect of ABO blood group might be of different strength in various populations. A supra-additive effect on VTE risk has been shown in a few studies when the non-O blood type is combined with inherited thrombophilia risk factors, including Factor V Leiden (FVL) mutation.[2,6] The exact relationship between ABO blood type and other inherited or acquired thrombophilia risks has been less investigated as yet.

In the meta-analysis published by Pomero et al[7] in this issue of *Polish Archives of Internal Medicine*, the authors sought to determine the extent of VTE risk increase in the case of simultaneous occurrence of FVL mutation or prothrombin 20210A allele polymorphism and non-O blood type. According to their study including 11 publications with more than 85 000 patients and controls, coexistence of non-O blood group with the presence of FVL mutation or prothrombin

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20210A allele polymorphism considerably augmented the risk of VTE. In non-O blood group type individuals who were carriers of the FVL mutation, the odds ratio (OR) was found to be 5.94 (95% CI, 5.33–6.61; P <0.01). This was considerably higher than the VTE risks calculated for only 1 of the 2 risk factors present. Equally, the patients with prothrombin 20210A allele and non-O blood group manifested a significantly augmented risk of VTE (OR, 4.01; 95% CI, 3.00–5.36; P = 0.01), although equivalent population attributable risk of VTE was considerably lower in these individuals than in those carrying FVL mutation (3.7% vs 21%, respectively). Thus, according to their findings, the coexistence of FVL mutation and non-O blood group type leads to an augmented risk of VTE that may have a clinical influence and drive therapeutic decisions, while the coexistence of prothrombin 20210A allele and the non-O blood group seems to play a less important role in VTE occurrence.

The strength of the above findings was further supported by the results of subgroup analyses. It has been known for a long time that the prevalence of FVL and prothrombin 20210A allele mutations, as well as blood type distributions vary greatly across continents and populations. According to a large body of data, VTE incidence rates are by 30% to 100% higher in the black than in the white Americans,[8] despite lower prevalence of FVL mutation and prothrombin G20210A polymorphism and higher percentage of blood type O in the black American population.[8,9] As genetic and lifestyle factors may concurrently modify the risk attributed to ABO blood type, a subgroup analysis of various ethnical backgrounds may lead to important findings. In the paper by Pomero et al,[7] the subgroup analysis including only studies conducted in European populations, yielded results similar to the overall analysis. The results were analogous also when the studies including only women were excluded from the analysis.

Given the morbidity and mortality of thrombotic disorders, continuous research on factors increasing VTE risk is necessary, including advances on the interactions of ABO blood type with genetic or acquired risk factors. It will be also an aim for the future to determine how the impact of these findings translates into clinical practice and whether ABO blood genotype should be considered when defining an exact thrombotic risk profile in certain individuals.

ARTICLE INFORMATION

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