Non-O blood group: an important genetic risk factor for venous thromboembolism

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Since its first description in the 1960s[1], a number of studies have documented that the ABO blood group has a profound influence on haemostasis, as it is a major determinant of plasma levels of von Willebrand factor (VWF)[2-6]. Overall, approximately 70% of the variation in plasma levels of VWF/factor VIII is determined genetically, with 30% of this genetic variation being due to the ABO blood group of an individual[2]. Notably, VWF levels are approximately 25% higher in individuals who have a blood group other than O[7].

It is not, therefore, surprising that many investigators have studied the possible clinical implications of this biological interaction, i.e. whether the ABO blood group could influence the risk of developing bleeding or arterial/venous thrombosis. Several studies have analysed whether the different ABO blood groups are associated with different risks of developing venous thromboembolism (VTE). Wautrecht and colleagues retrospectively analysed the phenotypic blood group distribution among ambulatory patients with a diagnosis of deep vein thrombosis of the lower limbs over a period of 14 years[8]. The blood group was known for 369 of these patients and the frequencies of the various groups was compared with those in 49,373 asymptomatic Belgian blood donors. The frequency of non-O blood group in patients with deep vein thrombosis was significantly higher than that in the healthy blood donors (70.6% *vs* 53.9%; p <0.001). To further clarify the interplay of ABO blood group, VWF, and factor VIII in the pathogenesis of VTE, Koster and colleagues performed a population-based case-control study of 301 consecutive patients with a first, objectively diagnosed episode of VTE and 301 healthy, matched controls[9]. Blood group O was confirmed to be less represented among VTE patients than among controls (25% *vs* 43%), and group O subjects had lower concentrations of both factor VIII and VWF as compared to those of non-O individuals. Overall, the matched, unadjusted odds ratio (OR) for VTE in individuals with non-O blood groups *vs* O blood group individuals was 2.0 (95% CI, 1.4-2.9). After adjustment for factor VIII and VWF levels, the risk of VTE among non-O blood group carriers remained significantly higher than that among individuals with O blood group (OR 1.5; 95% CI, 1.0-2.2). Similarly, Tirado and colleagues investigated the role of factor VIII, VWF and ABO blood group on thrombotic risk in a case-control study (250 patients with VTE and 250 unrelated controls)[10]. The frequency of group O was more frequent in controls than in patients with VTE (44% *vs* 23%), while that of group A was higher in VTE patients than in controls (59% *vs* 41%). The risk of thrombosis was, therefore, higher in non-O *vs* O blood group individuals both when expressed as a crude odds ratio (2.6; 95% CI, 1.8-3.8) and after adjustment for levels of factor VIII and VWF (OR 1.7; 95% CI, 1.1-2.6). The levels of both factor VIII and VWF were higher in non-O group individuals and the relative risk attributed to VWF was strongly dependent on blood group as it disappeared after adjusting for the ABO groups. In 2007 Ohira and colleagues performed a nested, case-control study (Longitudinal Investigation of Thromboembolism Etiology [LITE] Study) that included 492 participants who subsequently developed VTE and 1,008 participants who remained free of VTE[11]. After analysis of blood group genotypes, they also observed a significantly higher risk of VTE among non-O blood type carriers than among those with O-blood type (age-adjusted OR 1.64; 95% CI, 1.32-2.05), which decreased but remained statistically significant after further adjustment for sex, race, body mass index, diabetes mellitus and factor VIII levels (OR: 1.31; 95% CI, 1.02-1.68). The risk was increased in non-O blood type individuals who were also carriers of factor V Leiden (OR 6.77; 95% CI, 3.65-12.6).

Recently, Wu and colleagues performed a systematic review and meta-analysis on the association between ABO blood group and vascular disease[12]. The 21 studies included in the VTE analysis yielded a pooled odds ratio of 1.79 (95% CI, 1.56-2.05) for non-O compared to group O individuals and this odds ratio was even higher when the analysis was restricted to subjects who also carried the factor V Leiden defect: pooled OR of 3.88 (95% CI 2.51-6.00). In three studies in which blood group genotyping was performed, the combination of $A_1A_1/A_1B/BB$ gave an odds ratio of 2.44 (95% CI 1.79-3.33), while the odds ratio for $A_1O/BO/A_2B$ was 2.11 (95% CI 1.66-2.68), suggesting that the risk was related to O(H) antigen expression.

These results are in line with those published in this issue of Blood Transfusion by Spiezia and colleagues[13]. In this retrospective case-control study conducted on a large number of Italian patients with deep vein thrombosis and controls (712 cases and 712 controls), the authors found that having a non-O blood group increased the risk of DVT by 2.2 times over that of individuals with group O. A greater increase in the VTE risk (up to 7 times) was observed when an inherited thrombophilic condition (factor V Leiden, prothrombin G20210A mutation, antithrombin, protein C and protein S deficiencies) was associated with non-O blood group as compared with non-thrombophilic group-O carriers. The data presented by Spiezia and colleagues are impressive and given the high prevalence of non-O blood group in the general population, this appears to be one of the most important genetic risk factors for venous thrombosis. Like other inherited thrombophilic factors (i.e., factor V Leiden and prothrombin G20210A mutation), non-O blood group is responsible for a moderate increase in the risk of VTE[14], and, accordingly the authors recommend ABO blood group analysis in thrombohilic individuals in order to complete their thrombotic risk profile assessment.

The decision of whether to test for thrombophilia in patients with venous thromboembolism is controversial[15] but the study by Spiezia *et al.* suggests that if the decision is made to test, determination of the ABO blood group should be added to the standard screening for inherited thrombophilia.

The Authors declare no conflicts of interest.

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