ABO blood groups and the risk of venous thrombosis in patients with inherited thrombophilia

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Background. Although having a non-O blood type is now regarded as a risk factor for venous thromboembolism, the strength of this association is poorly defined, as is its interaction with inherited thrombophilia.

Materials and methods. The prevalence of non-O blood group and inherited thrombophilia (deficiencies of natural anticoagulants, factor V Leiden and prothrombin G20210A mutation) was assessed in a series of 712 consecutive patients with proximal deep vein thrombosis of the lower limbs who were referred to our Institution between 2004 and 2010, and in 712 age- and gender-matched healthy volunteers. Odds ratios (OR) of deep vein thrombosis and their 95% confidence intervals (CI) were computed for non-O group and thrombophilia, both separately and in combination.

Results. A non-O blood group was present in 492 cases and 358 controls (OR 2.21; 95% CI, 1.78 to 2.75). A thrombophilic abnormality was present in 237 cases and 105 controls (OR 2.82; 2.18 to 3.66). The combination of non-O group and thrombophilia was present in 152 cases and 51 controls (OR 7.06; 4.85 to 10.28).

Discussion. Having a non-O blood group is associated with an increased risk of proximal deep vein thrombosisof the lower limbs with or without pulmonary embolism. The addition of inherited thrombophilia increases the thrombotic risk conferred by non-O group alone by almost 3-fold.

Keywords: ABO blood groups, venous thrombosis, inherited thrombophilia.

Introduction

According to the results of recent studies[1-6], having a non-O blood type is now regarded as a risk factor for venous thromboembolism (VTE). However, the strength of this association is poorly defined, as is its interaction with inherited thrombophilia. Indeed, the effects of the combination of blood type with the factor V Leiden (FVL) or the prothrombin G20210A mutation (PTM) have been addressed in few studies[7-11], and the interaction with deficiencies of natural anticoagulants (antithrombin [AT], protein C [PC] and protein S [PS]) have never been investigated. In a retrospective case-control study we sought to confirm the association of non-O blood groups with deep venous thrombosis (DVT) of the lower limbs, to assess its strength and to investigate the impact of thrombophilia on this association.

Patients and methods

Patients

All consenting patients referred to the 2nd division of Internal Medicine of Padua University Hospital between January 2004 and December 2010 with a first episode of proximal DVT, as confirmed by ultrasonography, with or without clinical manifestations of pulmonary embolism, were eligible for inclusion in this study, provided that blood and plasma had been properly collected and stored (i.e. collected either prior to the beginning of anticoagulant treatment or at least 3 months after its withdrawal, and stored/frozen at −80 °C). Patients with recurrent VTE were excluded, as were those with primary pulmonary embolism (i.e. without clinical manifestations of DVT). DVT was categorised as secondary to risk factors in the case of active cancer, recent (less than 3 months) trauma or surgery, pregnancy, puerperium, ongoing hormonal treatment or medical diseases requiring immobilisation (for at least 7 days). All other DVT were regarded as unprovoked.

Controls

Consenting healthy volunteers, referred in the same study period to the blood bank, matched for age (±3 years) and sex with the study cases, for whom whole blood and plasma had been collected and stored, formed the control population for cases aged less than 60 years old. These subjects were randomly selected by a computer from the database of the blood bank. For cases over 60 years old,

consenting healthy friends matched for age (±3 years) and sex with the study cases qualified as controls.

Determination of blood type and thrombophilia

Patients and controls were screened for the main markers of inherited thrombophilia (AT, PC and PS deficiencies, FVL and PTM) and their ABO blood group was genotyped. AT, PC and PS levels and the presence or absence of FV Leiden and PTM were determined using methods described elsewhere[12].

Before their inclusion in the study, informed consent according to the Helsinki Declaration was obtained from each study subject.

Statistical analysis

Odds ratios (OR in matched case-control study) and their 95% confidence intervals (CI) were computed for non-O group and thrombophilia, both separately and combined. The analysis was repeated in patients with unprovoked and provoked DVT. Additional analyses concerned the non-O subgroups and the various components of thrombophilia. An odds ratio was considered to be statistically significant when the lower limit of the 95% confidence interval was greater than 1.0. Analyses were performed using the SPSS statistical (package for Windows 17.0 software; Chicago, Illinois, USA).

Results

Out of 950 eligible patients, 238 were excluded because of a history of past VTE (n =48), clinical presentation with primary pulmonary embolism (n =76), unavailability of blood or plasma (n =102), or refusal of informed consent (n =12). Thus, 712 patients qualified as study cases for the current investigation. Out of 1,005 eligible healthy volunteers, 712 were matched for age and sex with the study cases and thus qualified as the study controls. The main demographic and clinical characteristics of the study patients and controls are shown in Table I, which reports the main risk factors for thrombosis in cases, and the prevalence of blood groups and thrombophilia in both study arms. The prevalence of blood groups in the control population reproduces the pattern expected in the Italian population[13].

A non-O blood group was present in 492 cases and 358 controls (OR 2.21; 95% CI, 1.78 to 2.75). A thrombophilic abnormality was present in 237 cases and 105 controls (OR 2.82; 95% CI, 2.18 to 3.66). The combination of non-O group and thrombophilia was present in 152 cases and 51 controls, leading to an odds ratio of 7.06 (95% CI, 4.85 to 10.28).

The odds ratios for a variety of other combinations are presented in Tables II and III.

Table I - Main demographic and clinical characteristics of the study population.

	Cases (N=712)	Controls (N=712)
Age (median, range)	58.2 (26-83)	58.0 (25-82)
Male sex, N. (%)	372 (52.2)	372 (52.2)
Risk factors for DVT		
- recent trauma or surgery	198 (27.8)	---
- hormonal treatment, pregnancy or puerperium	27 (3.8)	---
- medical diseases	49 (6.9)	---
- active cancer	77 (10.8)	---
- unprovoked	361 (50.7)	---
Thrombophilia	237 (33.2)	105 (14.7)
- factor V Leiden	132 (55.6)	71 (67.6)
- prothrombin mutation	78 (32.9)	22 (20.9)
- protein C deficiency	15 (6.3)	10 (9.5)
- protein S deficiency	7 (2.9)	1 (1)
- antithrombin deficiency	5 (2.3)	1 (1)
Blood group		
- O	220 (30.9)	354 (49.7)
- A	335 (47.0)	219 (30.7)
- B	115 (16.2)	98 (13.8)
- AB	42 (5.9)	41 (5.8)

Legend Numbers in parentheses indicate percentages unless otherwise stated.

Table II - Prevalence of blood groups in the study cases and controls (OR and 95% CI).

	Cases (n=712)	Controls (n=712)	OR (95% CI)
O	220 (30.9)	354 (49.7)	1*
Non-O	492 (69.1)	358 (50.3)	2.21 (1.78-2.75)
A	335 (47.0)	219 (30.7)	2.46 (1.94-3.13)
B	115 (16.2)	98 (13.8)	1.89 (1.37-2.59)
AB	42 (5.9)	41 (5.8)	1.65 (1.05-2.62)
O without thrombophilia	135 (18.9)	320 (44.9)	1*
O and thrombophilia	85 (11.9)	34 (4.8)	5.93 (3.79-9.25)
Non-O without thrombophilia	340 (47.8)	307 (43.1)	2.63 (2.04-3.38)
Non-O and thrombophilia	152 (21.4)	51 (7.2)	7.06 (4.85-10.28)

Legend *Reference category. Numbers in parentheses indicate percentages.

Table III - Prevalence of blood groups in various combinations with thrombophilic abnormalities in the study cases and controls (OR and 95% CI).

	Cases (n=712)	Controls (n=712)	OR (95% CI)
O without FVL	177 (24.8)	328 (46.1)	1*
O and FVL	43 (6.0)	26 (3.7)	3.06 (1.82-5.16)
Non-O without FVL	403 (56.6)	313 (44.0)	2.39 (1.89-3.02)
Non-O and FVL	89 (12.6)	45 (6.2)	3.67 (2.45-5.48)
O without PTM	189 (26.5)	339 (47.6)	1*
O and PTM	31 (4.3)	15 (2.1)	3.71 (1.95-7.04)
Non-O without PTM	445 (62.5)	349 (49.0)	2.29 (1.82-2.87)
Non-O and PTM	47 (6.7)	9 (1.3)	9.37 (4.49-10.5)
O without deficiencies of AT, PC, PS	209 (29.5)	349 (49.1)	1*
O and deficiencies of AT, PT, PS	11 (1.5)	5 (0.7)	3.67 (1.26-10.7)
Non-O without deficiencies of AT, PC, PS	476 (66.8)	351 (49.3)	2.26 (1.82-2.82)
Non-O and deficiencies of AT, PC, PS	16 (2.2)	7 (0.9)	3.82 (1.54-9.43)

Legend *Reference category. Numbers in parentheses indicate percentages.

Discussion

In this large case-control study, having a non-O blood group increased the risk of DVT by 2.2 times over that in subject with group O, an increase comparable to that (2.8) observed in carriers over non-carriers of inherited thrombophilia. Interestingly, the risk of DVT conferred by the association of non-O blood group with thrombophilia was approximately 7 times higher than that observed in non-thrombophilic patients with blood group O, with 95% confidence intervals ranging between 5 and 10. Our results are consistent with findings obtained in recent investigations[3-6]. They suggest that having a non-O blood group confers an increased likelihood of developing a thrombotic episode, and that this risk is particularly high in thrombophilic subjects, irrespective of the specific type of non-O blood group and the type of inherited thrombophilia. The unexpectedly high risk of DVT observed in carriers of PTM who were also carriers of non-O blood group is probably a chance finding, as the prothrombotic risk conferred by this abnormality is generally lower than that conferred by FVL and deficiencies of natural anticoagulants[14], and the 95% confidence intervals around the odds ratio clearly overlap those observed for the other thrombophilic abnormalities.

The mechanism by which non-O blood group increases thrombotic risk is virtually unknown. Recently, higher levels of factor VIII:C and von Willebrand factor have been described in subjects with non-O blood groups than in those with O blood group[15,16], but these findings are unlikely to account by themselves for the marked difference in the thrombotic risk between carriers of non-O and O blood groups observed by us and consistently shown across all investigations dealing with this issue[17].

The potential limitations of our study include its retrospective nature, the exclusion of patients with recurrent VTE and those with primary pulmonary embolism, and the heterogeneity of the controls. However, cases were retrieved from a large cohort of patients who had been consecutively recruited at our study centre for a number of scientific purposes[18]. Patients with primary pulmonary embolism and those with recurrent VTE were excluded because they had not been consecutively recruited. The exclusion of these patients is unlikely to have biased the interpretation of the association of non-O blood groups with venous thrombosis. The heterogeneity of controls (identified among blood donors up to the age of 60 and from among healthy volunteers over the age of 60) was due to the well-known exclusion of older people from the list of blood donors.

What are the clinical implications of our findings? Conceptually, assessing the contribution of blood group has the potential to provide caregivers with an instrument that may be of help for identifying individuals at higher risk of VTE. However, knowledge of the blood group is unlikely to change the management of patients with VTE, because of the high prevalence of non-O blood subgroups and the low absolute incidence of thrombotic events occurring in these individuals. However, as the combination of thrombophilia with non-O blood group increases the thrombotic risk conferred by thrombophilia alone by almost 3-fold, determining blood group in only the subjects who have already been identified as carriers of thrombophilia may be worthwhile. This is especially true for those individuals who face circumstantial risk factors. For example, the awareness of this association could assist physicians in deciding whether to prescribe hormonal treatment, whether to implement prophylaxis

in conditions for which guidelines offer weak or no recommendations, whether to prolong prophylaxis beyond the period spent in hospital in a variety of medical and surgical conditions at risk of thrombosis, whether to speed up diagnostic procedures in patients with symptoms of VTE, and whether to administer anticoagulants in these patients while awaiting the results of confirmatory tests.

In conclusion, our data show that having a non-O blood group is associated with an increased risk of VTE and that the addition of thrombophilia increases the thrombotic risk conferred by non-O group alone by almost 3-fold. This simple information may help to identify groups of patients at high risk suitable for counselling, further testing or closer monitoring. Finally, this robust and easily assessable risk factor has the potential to be included -alone or in association with the determination of thrombophilia- as part of a more comprehensive risk assessment model for VTE.

The Authors declare no conflicts of interest.

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