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Original Article

Inherited thrombophilia in unprovoked venous thromboembolism: Is non 'O' blood group an additional culprit in Indian patients?

Ujjwal Dimri^a, T. Chatterjee^{b,*}, R.S. Mallhi^c, J. Philip^d,
N. Kushwaha^e

^a Officer in Charge, Blood Bank, Armed Forces Transfusion Centre, Delhi Cantt, India

^b Brigadier In Charge (Adm), Army Hospital (Research & Referral), New Delhi, India

^c Professor, Department of Immunohaematology & Blood Transfusion, Armed Forces Medical College, Pune 411040, India

^d Commanding Officer, Eastern Command Transfusion Centre, Kolkata, India

^e Assistant Professor, Department of Immunohaematology & Blood Transfusion, Armed Forces Medical College, Pune 411040, India

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ABSTRACT

Background: Venous thromboembolism (VTE) is a known situation of considerable mortality and morbidity and occurs due to the convergence of multiple acquired and genetic risk factors.

Methods: In this study, we have comprehensively analyzed the effect of ABO blood groups and inherited thrombophilia factors [Protein C (PC), Protein S (PS), Antithrombin III (AT III), Activated Protein C Resistance (APCR) and Homocysteine (Hcy)] on 150 unprovoked VTE patients, comparing with normal healthy controls. ABO phenotyping was done using gel cards and thrombophilia workup done using standard kits on coagulation autoanalyzer.

Results: Non O blood group was significantly more frequent among cases than controls (77.3% vs. 62.7%) and had higher odds of VTE (OR = 2.03, 95%CI: 1.22–3.37).

Positivity for at least one marker of thrombophilia was more in cases (40%) than controls (16%), and led to significantly higher odds (OR = 3.5, 95%CI: 2.03–6.04) of VTE. Deficiency of PS was the commonest thrombophilia abnormality.

Combination of non O group with positivity for thrombophilia markers was also more among cases (OR = 5.67, 95%CI: 2.76–11.65). Highest odds of VTE in cases were associated with non O group in combination with increased Homocystein (OR = 10.8, 95%CI: 2.27–51.5).

Conclusion: The study results show non O blood group and positivity for factors of inherited thrombophilia in cases impart higher odds of VTE individually. Also combination of both non O blood group and positivity for factors of inherited thrombophilia in cases further

* Corresponding author.

E-mail address: ctathagat@hotmail.com (T. Chatterjee).

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increases the odds of VTE. This awareness could assist physicians in identifying those at higher risk of VTE and tailor-made the thromboprophylaxis accordingly.

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Introduction

Venous thromboembolism (VTE) is a dreaded clinical condition and is till date not fully understood. According to latest studies, VTE incidence in Indian population ranges from 14.9% to as high as 54% among hospitalized patients, and up to 17.6 VTE episodes per 10,000 admissions.¹

The most well-known genetic risk factors for VTE are prothrombin G20210A mutation (PTM), deficiencies of natural anticoagulants like antithrombin III (ATIII) and protein C(PC), protein S (PS) and the factor V Leiden (FVL).^{2,3} According to the reports, the frequency of deficiency of natural anticoagulants among Indian VTE patients ranges between 15 and 33%.^{4,5} Higher risks of VTE has also been found with non O blood group patients (ranging from 1.8 to 2.5-fold).⁶ However, relatively few studies have dwelled into the association of ABO groups and its interaction with inherited thrombophilia in VTE, especially in Indian patients.^{7,8} Also to the best of our knowledge, correlation of ABO blood group with inherited thrombophilia markers in VTE patients vis-à-vis that of normal healthy controls among Indian subjects has not been attempted till date.

We at our institute did a study to do the risk analysis of ABO blood groups with VTE episodes and to assess its association with inherited thrombophilia risk factors like ATIII, PC, PS, Homocysteine (Hcy) and Activated Protein C Resistance (APCR). APCR was used as a surrogate marker for FVL mutation as APCR has yielded sensitivity and specificity of up to 99.1% in detection of FVL mutation attributable VTE in various studies.⁹ Due to virtually nonexistence of PTM among Indian VTE patients, this parameter was not included in our study.^{4,10,11}

Material and methods

This study was conducted in the Department of Immunohaematology & Blood Transfusion (IH & BT) of a tertiary care hospital of Western India. Study included consecutive fresh cases of VTE (in age group 18–60), without identifiable acquired risk factors. Study period was of two years (July 2013–June 2015). Diagnosis of VTE was established using colour Doppler/high resolution spiral CT studies. Exclusion criteria included patients with acquired causes such as history of trauma/surgery, prolonged bed rest, smoking, pregnancy, use of oral contraceptives (OCPs), recurrent DVT, patients on oral anticoagulants, patients with lupus anticoagulant positivity, patients reporting within 12 weeks of onset, patients with liver disorders, recurrent VTE, lack of informed consent, patient age >60 years and lack of suitable age/sex matched control.

Consenting healthy volunteer donors reporting in the same study period to the blood bank, matched for sex and age ($\pm$ 3

years) with the cases, formed the control population. Institutional Ethical Committee's approval and informed consent from patients and controls was taken before carrying out the study.

Tests carried out on samples were: activated partial thromboplastin time (aPTT), Prothrombin time (PT), ABO grouping (Dia-Med ID Micro typing Gel System), PC (STACLOT PROTEIN C kit), ATIII (STACHROM AT III kit), APCR (STACLOT APC-R kit), PS (ASSERACHROM FREE PROTEIN S kit), and Hcy (Axis Hcy Enzyme immunoassay Kit). Samples for thrombophilia workup were collected only after 12 weeks from cessation of oral anticoagulant therapy. Normal reference value of tests used in our study is given in Table 1. The assays of PT, aPTT, PC, APCR and ATIII were done on a fully automated coagulation analyser i.e. STA COMPACT of Diagnostica Stago 9, rue des Frères Chusson, 92600 Asnieres (France). Free PS and Hcy results were read via ELISA reader.

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 20.0 for Windows) was used for statistical analysis. Odds ratios (OR in matched case–control study) and their 95% confidence intervals (CI) were computed for ABO blood group and thrombophilia markers, both separately and combined.

Results

In total 1040 VTE patients were referred to our dept during our study period. Majority of them were excluded because of the history of risk factors ($n = 838$, 80.6%). Patients with recurrent VTE were excluded because they had not been consecutively recruited.

Out of 202 (19.6%) cases of apparently unprovoked VTE, 28 patients could not be taken off of oral anticoagulation mandated for thrombophilia profile during our study period. Also 24 patients were lost to follow up. Thus remaining 150 consecutive consenting eligible patients and 150 matched controls were enrolled in our study. Majority of cases/controls were of male sex (81%) as compared to female sex (19%).

Table 1 – Normal values of the screening coagulation and thrombophilia tests.

Tests performed	Normal values
Prothrombin time	11–16 s
Activated partial thromboplastin time	30–40 s
Protein C	70–200%
Protein S	Male – 75–140% Female – 50–120%
Antithrombin III	80–120%
Activated Protein C Resistance	>120 s
Homocysteine	5–15 μ mol/L

Maximum cases of VTE were of deep vein thrombosis (DVT, $n = 87$), followed by cerebral venous thrombosis (CVT, $n = 52$) and pulmonary thromboembolism (PTE, $n = 11$).

Non O group was significantly higher among cases than controls i.e. 116 (77.3%) vs. 94 (62.7%), respectively with OR of 2.03 (95%CI: 1.22–3.37) (Table 2). Highest odds of VTE were in cases with AB blood group, an OR of 3.95 (95%CI: 1.69–9.27). Cases with 'A' blood group also had higher odds of VTE (OR = 1.741) but not statistically significant ($p = 0.11$).

Positivity for at least one marker of thrombophilia among cases ($n = 60$, 40%) was higher than the controls ($n = 24$, 16%) with an OR of 3.5 (95%CI: 2.03–6.04) (Table 3). Odds of VTE were further increased in cases that had positivity of more than one thrombophilia markers (OR = 5.25, CI: 1.69–16.34). We could not analyze the effect of combined positivity of more than one individual inherited thrombophilia marker (like PC + PS or PC + APCR) due to very low numbers in cases and control arms with dual positivity. Deficiency of PS ($n = 25$, 16.7%) was the most common thrombophilia marker amongst the cases and controls (Table 4).

The combination of non O group with positivity for any of the thrombophilia markers was present in 51 cases and 18 controls, leading to an OR of 5.67 (95%CI: 2.76–11.65) (Table 5). In our study, highest odd of VTE was found in combination of non O group cases with elevated Hcy with OR of 10.8 (95%CI: 2.27–51.5) (Table 6). ATIII deficiency among study cases, neither individually nor in combination with non O group had any statistically significant higher odds of VTE (Tables 4 and 6).

Discussion

Among genetic risk factors for VTE, association of VTE and non O blood group is probably the most studied.¹² In a recently conducted meta-analysis, the DVT patients had significantly higher frequency of non-O blood group vis-à-vis that of healthy blood donors (70.6 vs. 53.9%; $p < 0.001$) with pooled OR of 2.09 (95%CI: 1.83–2.38; $p < 0.00001$).⁶ In our study also, non O group frequency was much higher among cases (77.3%) with OR of 2.03 (95%CI: 1.22–3.37) (Table 2). ABO blood group distribution among the controls (Table 2) was comparable with

blood donor population of the institute (unpublished data) and general population of the region.^{13–15}

A number of theories have been postulated as to how ABO blood groups alter the thrombotic or bleeding tendencies of a patient. The theory of altered levels of coagulation factor is one of them that also include deficiencies of natural anticoagulants. In Caucasian population, deficiency of PC, PS and ATIII among VTE patients have ranged from 5 to 10%, 5 to 10% and 2 to 5%, respectively.¹⁶ Studies in Indian VTE subjects have also reported a comparable prevalence of PC deficiency as 9.5–21.1%, PS deficiency as 6.5–19.0% and ATIII deficiency as 2.6–6.4%.^{5,17,18} In these Indian studies, PC deficiency was the commonest. However, in our study, deficiency of PS was the commonest (16.7%) (Table 4). In our study APCR positivity was 9.33% ($n = 14$) amongst the VTE cases (Table 4) which is much lower than APCR/FVL positivity reported amongst western (64%) and Indian VTE subjects (12–12.5%).^{5,17–19}

In Caucasian population, positivity of these thrombophilia markers in patients confer them quite higher relative risk of VTE than in general population.²⁰ These values range from a relative risk of 2–5 for deficiency of ATIII to as high of 40–50 for APCR.³ Cases with thrombophilia abnormality had significantly higher odds of VTE in our study also (OR = 3.5, 95%CI: 2.03–6.04; $p < 0.05$) (Table 3).

Elevated levels of Hcy have also been found to confer an increased risk of VTE (2–4 times the normal person's risk).²¹ Incidence of hyperhomocysteinemia in Caucasian population has been estimated to be just 5–7%.^{21,22} In contrast, a higher incidence (52–84%) of hyperhomocysteinemia has been reported among Indian population.²³ In our study, hyperhomocysteinemia was present in 10.67% of cases and 2.67% of controls with an OR of 4.35 (95%CI: 1.42–13.36) (Table 4). Hyperhomocysteinemia is considered a thrombophilic disorder with mixed aetiology i.e. both genetic and acquired (deficiency of vitamin B12, folic acid, vegetarian diet). The preponderance of vegetarian diet amongst Indians could be ascribed to the deficiency of Hcy lowering B vitamins, which in turn leads to hyperhomocysteinemia.²³ However, vitamin B12 or folic acid levels were not done in our study as they were not part of the thrombophilia profile protocol.

Our study results showed that even though non O group and positivity for thrombophilia markers individually consti-

Table 2 – ABO blood group distribution of cases and controls along with odds ratio (OR).

ABO blood group	Cases (%)	Controls (%)	Odds ratio (CI)	p value
O	34 (22.7)	56 (37.3)	–	Reference
A	37 (24.7)	35 (23.3)	1.74 (0.93–3.27)	0.111
B	55 (36.6)	49 (32.7)	1.85 (1.04–3.28)	0.043
AB	24 (16.0)	10 (6.7)	3.95 (1.69–9.27)	0.001
Total Non O	116 (77.3)	94 (62.7)	2.03 (1.22–3.37)	0.008

Table 3 – Cumulative thrombophilia markers positivity amongst the cases and controls along with ORs.

With/without thrombophilia	Cases N (%)	Controls N (%)	OR (CI; p)
Without thrombophilia	90 (60)	126 (84)	1 (reference)
With thrombophilia	60 (40)	24 (16)	3.5 (2.03–6.04; 0.000)
With more than one thrombophilia	15 (10)	4 (2.7)	5.25 (1.69–16.3; 0.003)

Table 4 – Positivity of individual thrombophilia markers amongst VTE cases and normal controls along with ORs.

Thrombophilia marker	Cases		Controls		OR (CI; p)
	N	%	N	%	
Without PC	128	85.3	142	94.7	1 (reference)
With PC	22	14.7	8	5.3	3.05 (1.31–7.09; 0.01)
Without PS	125	83.3	140	93.3	1 (reference)
With PS	25	16.7	10	6.7	2.8 (1.29–6.06; 0.01)
Without ATIII	143	95.3	147	98	1 (reference)
With ATIII	7	4.7	3	2	2.39 (0.61–9.45; 0.34)
Without APCR	136	90.7	145	96.7	1 (reference)
With APCR	14	9.3	5	3.3	2.98 (1.05–8.51; 0.05)
Without Hcy	134	89.3	146	97.3	1 (reference)
With Hcy	16	10.7	4	2.7	4.35 (1.42–13.36; 0.009)

tuted a risk factor, the presence of both of them together in cases further raised the odds of VTE (OR = 5.67, CI: 2.76–11.65) (Table 5). It may be noticed that the odds of VTE conferred by combination of non O blood group and thrombophilia abnormality together (OR = 5.67) is more than double the odds

conferred by presence of non O blood group individually (OR = 2.03), and more than 1.5 times the odds conferred by the individual positivity of a single thrombophilia abnormality (OR = 3.5). These results point towards a synergistic association of non O blood group and thrombophilia abnormalities in development of VTE and are in consonance with the result of most of the similar studies.^{7,8,24}

Positive association of combination of non O blood group with APCR positivity and deficiencies of PC, PS leading to higher odds of VTE has been explained by the higher levels of factor VIII in non O group individuals.²⁵ However even in the absence of FVL, decreased responsiveness to APC with high FVIII levels has been observed.²⁶ Further in cases with deficiencies of PC or PS in non O group individuals, the higher levels of factor VIII may overwhelm the neutralizing capacity of already deficient PC and PS in plasma – leading to a prolonged procoagulable state.

One relatively novel association of elevated levels of Hcy and non O blood group having much higher odds of VTE in combination (OR = 10.8) vis-à-vis isolated Hcy (OR = 4.35) or non O group (OR = 2.03) has come out of our study (Tables 6, 5 and 2 respectively). Our result could be a chance finding also,

Table 5 – Association of ABO blood groups and thrombophilia markers in cases and controls.

Association with O and non O blood group	Cases (n)	Controls (n)	OR (CI; p)
O without thrombophilia	25	50	1 (reference)
O with thrombophilia	9	6	3.0 (0.96–9.37; 0.08)
Non O without thrombophilia	65	76	1.71 (0.96–3.07; 0.08)
Non O with thrombophilia	51	18	5.67 (2.76–11.65; 0.000)
A without thrombophilia	24	28	1.71 (0.8–3.7; 0.2)
A with thrombophilia	13	7	3.71 (1.2–12.3; 0.02)
B without thrombophilia	28	40	1.43 (0.7–2.9; 0.42)
B with thrombophilia	27	9	6.0 (2.3–16.5; 0.0001)
AB without thrombophilia	13	8	3.25 (1.2–10.2; 0.03)
AB with thrombophilia	11	2	11.0 (2.2–53.4; 0.001)

Table 6 – ORs of VTE observed for association of O and non O blood groups with presence or absence of individual markers of thrombophilia.

Association with O and non O blood group	Cases (n)	Controls (n)	OR (CI; p)
O without PC	32	55	1 (reference)
O with PC	2	1	Not significant (p = 0.554)
Non O without PC	96	87	1.89 (1.12–3.20; 0.019)
Non O with PC	20	7	4.91 (1.87–12.89; 0.001)
O without PS	32	55	1 (reference)
O with PS	2	1	Not significant (p = 0.554)
Non O without PS	93	85	1.88 (1.11–3.18; 0.019)
Non O with PS	23	9	4.39 (1.81–10.65; 0.001)
O without ATIII	32	55	1 (reference)
O with ATIII	2	1	Not significant (p = 0.554)
Non O without ATIII	111	92	2.07 (1.24–3.47; 0.007)
Non O with ATIII	5	2	Not significant (p = 0.108)
O without APCR	31	54	1 (reference)
O with APCR	3	2	Not significant (p = 0.362)
Non O without APCR	105	91	2.01 (1.19–3.39; 0.009)
Non O with APCR	11	3	6.39 (1.65–24.66; 0.007)
O without HCY	30	54	1 (reference)
O with HCY	4	2	Not significant (p = 0.194)
Non O without HCY	104	92	2.04 (1.20–3.44; 0.009)
Non O with HCY	12	2	10.80 (2.26–51.50; 0.001)

as there is a very large range of 95%CI (2.27–51.5). However, similar results were obtained by Jukic et al. in Croatian population.⁷ Thus, it may be possible that some unknown mechanism could be at large, regarding interaction of Hcy and ABO blood group and would most probably require genetic or metabolomics studies.

In our study there was an alarmingly high prevalence of 16% of positivity for any one marker of inherited thrombophilia amongst the controls (Table 3), as against the published literature. As there is a paucity of Indian studies evaluating the role of inherited thrombophilia markers in VTE development vis-à-vis in normal controls,^{4,27,28} it may theoretically be possible that the Indian population has a higher prevalence of inherited thrombophilia than its western counterparts. However, it is also admitted that such a deduction would entail large scale population based study in which the prohibitive cost of thrombophilia testing may prove as deterrent in current Indian setup. More Indian studies studying this aspect may come up once the thrombophilia testing becomes more economically feasible. In our study, this summing up of all the controls with positivity of any one marker of inherited thrombophilia was done for the statistical analysis. However, if the prevalence of positivity for individual markers of inherited thrombophilia is taken into account separately (Table 4), these results are in consonance with published literature.^{5,7,37}

There is paucity of Indian studies linking ABO blood groups and VTE in Indian patients that had calculated the odds of VTE for non-O blood type between cases and controls. In our setup, the presence of blood transfusion services and a dedicated special coagulation lab under one roof afforded us this opportunity.

At present, assessments and tests to evaluate patient population at risk of VTE does not include determination of ABO blood grouping. However there may be a higher population attributable risk of blood type for VTE if one considers higher frequency of non O blood group in comparison to markers of inherited thrombophilia among general population.²⁹ Thus instead of universal screening, the addition of ABO grouping to identify those in need of thromboprophylaxis may be fruitful, both in isolation and in combination with other routine thrombophilia testing.

Limitations to our study include the retrospective nature of all case control studies, exclusion of recurrent VTE patients and estimation of vWF levels. Future studies on Indian subjects can be directed to address these factors also. Similarly further exploration in form of larger prospective and molecular genetic studies are also warranted to study the interaction of ABO blood group, in order to settle these issues.

Conclusion

To conclude our study results show that presence of non O group or positivity of inherited thrombophilia markers among Indian patients conferred higher odds of development of VTE. Non O blood group and inherited thrombophilia in combination had a synergistic effect on each other leading to higher odds of development of VTE, in comparison to isolated positivity of each. We believe that this awareness could assist

physicians in our setup in identifying those individuals at higher risk of VTE and tailor-made the thromboprophylaxis accordingly.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study

Conflicts of interest

The authors have none to declare.

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