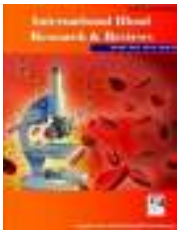

International Blood Research & Reviews
2(6): 289-298, 2014, Article no. IBRR.2014.6.004

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Higher Ratio of Arterial vs Venous Thrombosis in Hemophilia A as Compared with Von Willebrand Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Author AG wrote the final paper. Author VD gathered and analyzed the cases and made the calculations. Authors EC and LS wrote the first draft of the paper. Author FF overviewed the selections of the cases. All authors have approved the final manuscript.

Original Research Article

Received 28th April 2014
Accepted 28th June 2014
Published 15th July 2014

ABSTRACT

Objectives: to investigate the ratio between arterial and venous thrombosis in patients with Hemophilia A or B in comparison with that of patients with von Willebrand Disease.
Methods: analysis of a time unlimited survey of the literature together with an evaluation of personal records. Thrombotic events had to be proven by objective methods. Acquired forms were excluded. 222 patients were found to meet the inclusion criteria, 131 patients with Hemophilia A or B and 91 patients with von Willebrand Disease.
Results: The ratios between arterial and venous thrombosis resulted to be 3.75, 1.12, 2.54 and 1.75, for Hemophilia A, Hemophilia B, combined Hemophilia A and B and von Willebrand Disease, respectively. The difference between Hemophilia A and von Willebrand Disease was statistically significant.
Conclusions: The plasmatic defect present in the Hemophilias, especially in Hemophilia A, seems to protect more from venous rather than from arterial thrombosis. This pattern is less evident for von Willebrand Disease. The clinical significance and the pathogenetic implications of these findings are discussed.

Keywords: Hemophilia; von Willebrand Disease; thrombosis; arterial; venous.

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1. INTRODUCTION

The occurrence of either an arterial or a venous thrombosis in congenital bleeding disorders has drawn considerable attention in recent years. It has been clearly demonstrated by now that clotting defects are unable to protect fully from thrombosis. This regards both the most frequent clotting disorders such as the Hemophilias and von Willebrand Disease (vWD) and also the rare coagulation disorders, mainly FVII deficiency [1-6].

Little is known about the comparative prevalence existing among the different clotting disorders.

Recently it was shown that venous thrombosis is comparatively more frequent in FVII deficiency as compared to the Hemophilias whereas, for arterial thrombosis, the reversal may be true [7].

It was also shown that the ratios between arterial versus venous thrombosis was different in Hemophilia A as compared to Hemophilia B [8]. Finally it was demonstrated that no difference exists in the sporadic thrombotic events seen in the clotting defects of the contact phase of blood coagulation [9].

These studies have cast further light in the pathogenesis of a thrombotic event in congenital bleeding or non bleeding coagulation disorders.

The purpose of the present study was to investigate the ratios between arterial versus venous thrombosis in Hemophilia A and Hemophilia B in comparison with that seen in von Willebrand disease.

2. PATIENTS AND METHODS

Patients with Hemophilia A, Hemophilia B and vWD studied in Padua during the years 1972-2010 were reevaluated for the occurrence of thrombotic events.

A time-unlimited Pub Med search was carried out using several pertinent keywords including the medical subject headings (MeSH) proposed by Pub Med. The Detail Tabs shown by Pub Med were also examined in every instance. The search was carried out on Sept. 2013 and again on Jan. 2014. Original papers were then obtained with the cooperation of The Pinali Medical Library of our University. Cross-checking of the references listed at the end of the single papers was also carried out to avoid omissions.

Inclusion criteria were: an established diagnosis of Hemophilia A, Hemophilia B or von Willebrand disease together with a compatible hereditary pattern.

All cases of Hemophilia A or B, mild, moderate or severe were included providing the above mentioned criteria were met. Similarly, all types of vWD were included providing they met the inclusion criteria.

Acquired forms of Hemophilia due to the presence of autoimmune inhibitors or acquired forms of vWD due to aortic disease, aortic prosthesis or to other causes were excluded.

The myocardial infarction (MI) and the acute coronary syndromes (NSTEMI and unstableangina) had to be proven by objective means (abnormal EKG, increased troponin levels, coronary angiography studies). Cases of stable angina or effort angina were excluded even if coronary arteries abnormalities were documented by coronary angiography. Ischemic stroke had to be proven by CAT, MRI or angiography. Hemorrhagic strokes were excluded.

Venous thromboembolism had also to be proven by objective means. Sonography or venography were needed for peripheral vein occlusions; spiral CAT and/or ventilatory/perfusory scintiscan for pulmonary embolism (PE). Cerebral sinuses occlusions had to be demonstrated by Angio CAT, Angio MRI or arteriography. Portal system occlusions had to be demonstrated by sonography, CAT or MRI. Cases with catheter related venous thrombosis were excluded.

The presence of common risk factor for thrombosis were recorded whenever available. These were: old age, hypertension, hypercholesterolemia, smoking, diabetes, obesity for arterial thrombosis and trauma, obesity, old age, congenital thrombophilia, immobilization and oral contraceptives for venous thrombosis.

Statistical analysis of the significance among the different ratios between arterial vs venous thrombosis was carried out according to Chi squared test [10].

3. RESULTS

The total number of Hemophilia A, Hemophilia B and vWD patients who presented a thrombotic event is 222 (Table 1). References pertaining to these patients have already been supplied in part in previous papers in 2005 and 2006 [1,2,11,12]. Only the cases reported after those dates have been taken into account and referenced in the present paper together with a few reports which had been originally omitted for lack of information. However, the data and calculations here presented and discussed refer to the entire pool of patients.

Table 1. Reported cases of arterial or venous thrombosis in the Hemophilias and in vWD. The figure includes the six cases studied in Padua

Condition	Arterial	Venous	Total
Hemophilia A	75	20	95
Hemophilia B	19	17	36
vWD	58	33	91
Total	152	70	222

3.1 Arterial Occlusions

Personal records revealed two cases of acute coronary syndrome (two patients with Hemophilia A, one with a M.I. and the other with unstable angina) [1]. Furthermore two patients with type I v WD showed a M.I. or unstable angina [13]. There were no ischemic strokes or peripheral arteries occlusions.

The survey of the literature yielded 92 additional patients with Hemophilia A or B and an arterial occlusion for a total of 94 [14-30]. 85 of these patients with Hemophilia A or B had an acute coronary syndrome while 7 had an ischemic stroke. No peripheral artery thrombosis

was described. As far as vWD is concerned, 56 additional patients were found for a total of 58 [5,31-42]. 48 of these patients had M.I. or another acute coronary syndrome whereas 8patients had an ischemic stroke. Again, no isolated peripheral artery occlusion was noted (Table 2).

Table 2. Cases and types of arterial occlusion seen in Hemophilias and vWDisease. The table includes the four cases seen in Padua

Condition	M.I.	Ischemicstroke	Peripheralarteries	Comments
Hemophilia A	69	6	0	M.I. includes all cases
Hemophilia B	18	1	0	of acute coronary
vWDisease	50	8	0	syndromes

3.2 Venous Occlusions

Personal records revealed the presence of two patients with Hemophilia A, one with a superficial vein thrombosis of the arm and the other with a portal system vein thrombosis [2]. Venous thrombosis was described in 35 additional patients with the Hemophilias (18 for Hemophilia A and 17 for Hemophilia B) bringing the total to 37 patients (Table 1) [2,4,8,43-46]. Altogether, among the Hemophilia patients there were 20 cases of deep vein thrombosis (DVT) with or without pulmonary embolism (PE); 5 patients with isolated PE; 3 cases with portal system vein thrombosis; 8 cases with superficial vein thrombosis (SVT) and 1 case with cerebral sinuses thrombosis (Table 3).

Table 3. Cases and types of venous thrombosis seen in the Hemophilias and in vWD. The two patients seen in Padua are included.

Condition	DVT	Isolated P.E.	Cerebralsinuses thrombosis	Portal system thrombosis	Superficialveins thrombosis	Comments
Hemophilia A	9 a)	2	1	3	5	a) It includes cases with PE b) It includes a case of central retinal vein thrombosis
Hemophilia B	11 a)	3	0	0	3	
vWDisease	17 a)	8	2 b)	2	4	

None of our patients with vWD presented with a venous thrombosis. The number of patients with vWD and venous thrombosis found in the literature were 33. For vWD the breakdown figures were the following: DVT with or without PE, 17 cases; isolated PE, 8 patients; cerebral sinuses thrombosis, 2 cases; portal system occlusions, 2 patients and 4 cases of SVT (Table 3) [4,12,47-50].

The Arterial Thrombosis vs Venous Thrombosis ratios were 3.75, 1.12, 2.54 and 1.75 for Hemophilia A, Hemophilia B, combined Hemophilia A and B, and vWD, respectively (Table 4). The difference between the value for Hemophilia A and that for vWD was statistically significant.

Risk factors were present in 71 out of 85 patients with Hemophilia and in 28 out of 58 patients with Vwd and arterial thrombosis.

Table 4. Ratios between Arterial vs Venous thrombosis in the Hemophilias and in vWD

Condition	Arterialthrombosis	Venousthrombosis	Ratios	pvalue vs vWD
Hemophilia A	7	20	3.75	p< 0.01
Hemophilia B	19	17	1.12	n.s.
vWDisease	58	33	1.75	/

As far as venousthrombosis are concerned, risk factors were present in 30 out of 34 patients with Hemophilia and in 26 cases out of 33 patients with vWD.

There were no major difference in the distribution of risk factors but for the fact that replacement therapy was more frequent among Hemophiliacs as compared with patients with vWD. Furthermore papers dealing with vWD failed often to mention the presence or absence of risk factors [13]. Finally, in this comparison the gender differences involving patients with vWD vs those with Hemophilia have to be also taken into consideration.

4. DISCUSSION

Arterial and venous thrombosis have different predisposing factors.

Attempts to indicate a common pathogenetic mechanism have failed to materialize.

The study of the ratios between arterial and venous thrombosis occurring in congenital bleeding disorders, may supply useful information in this regard. This has been already investigated for Hemophilia A vs Hemophilia B and for the Hemophilias as a whole versus FVII deficiency [7,8]. The results have indicated that FVII deficiency is more protective from arterial occlusion than from venous thrombosis whereas the opposite is true for the Hemophilias, especially for Hemophilia A. No data are available for the comparison between Hemophilia A or Hemophilia B and von Willebrand Disease.

The presence of a greater ratio in the incidence of arterial vs venous thrombosis in patients with Hemophilia A in comparison with those with vWD has great clinical and scientific implications.

Hemophilia A and vW Disease have in common, despite a different hereditary pattern, a variable degree of FVIII deficiency. However von Willebrand Factor (vWF) is normal in Hemophilia A patients whereas it is defective in vWD. The absence or abnormality of vWF seen in patients with vWD is responsible for the second major difference existing between the two conditions, namely the behaviour of the bleeding time which is prolonged in vWD but normal in the Hemophilias. It seems that the protection afforded by the clotting defect of Hemophilia patients is more evident towards venous thrombosis as compared to atherosclerosis and atherothrombosis.

The discrepancy seems to involve mainly Hemophilia A patients since it is less evident for Hemophilia B. The reasons of this discrepant behaviour between the two Hemophilias probably rests on the different type of defect, similar to vWD defect in Hemophilia A and quite different in Hemophilia B. Factor IX, deficient in Hemophilia B, is structurally similar to

FVII since both are vitamin K dependent factors [51]. It is interesting to note in this regard that FVII deficiency is the only congenital clotting defect in which venous thrombosis are comparatively more frequent than arterial thrombosis [7,52].

As far as von Willebrand Disease is concerned, the degree of protection is still greater for venous thrombosis but it is not as pronounced as that of Hemophilia A, being similar to that of Hemophilia B. In one study the incidence of venous thrombosis has been maintained to be similar to that of the general population of the larger Detroit area (39). However the majority of studies, in agreement with our personal observations, indicate that venous thrombosis is rare in patients with vWD [4,49,53,54].

This type of studies have limitations in the sense that they are constructed on the analysis of indirect observations and conclusions coming from different authors and different countries. However they allow the possibility to cast some light on the fascinating event of a thrombus formation in patients with bleeding disorders. Because of the rarity of the event there is no other way to gather at least some orientative information on the subject. The approach has been proficuous since several assumptions have been by now confirmed. The established facts may be summarized as follows: the Hemophilias and vWD do not protect fully from the occurrence of thrombosis.

Taken altogether, these observations indicate, in spite of the limitation due to the type of studies, that the protection against thrombotic events assured by coagulation defects is only partial and not absolute. Common risk factors, both for arterial or venous thrombosis, seem able to overcome the potential protection afforded by the congenital hypocoaugulability. The critical point at which the protective affect is overcome and the homeostatic balance altered is difficult to define and will certainly be the subject of future research. Furthermore it is becoming clear that the hypocoagulability induced by the clotting defects is not always the same but it may vary with the defect and it may even be influenced by conditions (diet, for example) present in different countries [5,6,13,39].

The systematic study of the thrombotic events, both arterial and venous, which occasionally occur in patients with congenital bleeding disorders is contributing to the understanding of the pathogenesis of thrombosis despite the coexistence of a hypocoagulable state. These studies may apply also to the mechanism whereby occasional thrombotic events occur even in patients on anticoagulant therapies.

5. CONCLUSION

The most important aspect of the paper is the demonstration that the ratio of arterial vs venous thrombosis may vary from one congenital bleeding condition to the other. Despite the limitation inherent in this type of studies, the information is relevant for the understanding of the role each congenitally deficient condition plays in the occurrence of an arterial or a venous thrombosis.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=576&id=28&aid=5331