J Thromb Thrombolysis (2006) 21: 279–284
DOI 10.1007/s11239-006-6556-7

Non-catheter associated venous thrombosis in hemophilia A and B. A critical review of all reported cases

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Abstract All reported cases of non-catheter induced venous thrombosis in patients with hemophilia A or B have been carefully evaluated. A total of 27 cases were reported,12 patients with hemophilia A and 15 patients with hemophilia B. The age of patients varied between 9 and 67 years. There were 10 cases of deep vein thrombosis, 8 patients with pulmonary embolism accompanied or not by deep vein thrombosis, 5 cases of superficial vein thrombosis. In addition, there were 3 cases of thrombosis in unusual sites (1 retinal central vein thrombosis and 2 portal vein thrombosis). Finally, in one case, venous thrombosis was multiple. There was a fatality in a hemophilia B patient with pulmonary embolism.

The most frequent risk or triggering factor in hemophilia A was the administration of Feiba or rFVIIa concentrates in patients with inhibitors. Surgery together with Prothrombin Complex concentrates was the most frequent cause in hemophilia B patients. Congenital associated prothrombotic risk factors were present in two patients.

No or very few therapeutic procedures were initiated in these patients but for a suspension or reduction of concentrates infusion. In a few instances low molecular weight heparin was given for a few days. The frequent association of venous thrombosis with infusion of concentrates indicates the need for a careful evaluation of patients about to receive such therapy.

Keywords Hemophilia A · Hemophilia B · Pulmonary embolism · Venous thrombosis

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Introduction

*T*he occasional presence of thrombotic and/or atherothrombotic lesions in congenital bleeding disorders has received considerable attention in recent years [1–5]. It was widely thought, understandably, that the reason for the occurrence of such events in patients with a hypocoagulable state could cast some light on the pathogenesis of thrombosis and/or atherosclerosis.

In-dwelling catheter thrombosis is a frequent complication in normal subjects and also in haemophilia patients [6,7]. This seems to indicate that, in given circumstances, even a clotting defect, often a severe one, cannot prevent venous thrombosis to occur if mechanical devices irritate the venous endothelium.

Non-catheter related venous thrombosis have been occasionally described in patients with major congenital coagul ation disorders and also in hemophilia [8–11].

No systematic study has been carried out on the subject. Therefore no precise data on the triggering factors which may play a role in causing those thrombosis are available.

The present report aims at eliminating that void in an attempt to find, from a careful evaluation of the available literature, which associated or triggering factors, if any, could account for the thrombotic manifestations in congenital bleeders.

Patients and methods

All patients with hemophilia A and hemophilia B reported to have had at least a venous thrombosis were included in the study. Catheter associated thrombosis were excluded since the pathogenesis of thrombosis in this case appears clear and expected.

Diagnostic criteria for the inclusion of patients were the commonly accepted procedures. Only cases with objectively documented venous thrombosis were taken into consideration. Sonography, CT, MRI, perfusion/ventilatory scintiscan, spiral CT, phlebography were properly evaluated in accordance with the type of venous thrombosis.

Patients were subdivided in cases of severe, moderate or mild hemophilia according to the level of FVIII (<1%; 1–5% and 5–20% respectively). Patients with hemophilia and inhibitor were also included. Hemophilia patients who had also other congenital or acquired prothrombotic conditions were included together with a description of the associated defect.

Age, entity of the defect and type of venous thrombotic event: superficial vein thrombosis (SVT), deep vein thrombosis (DVT), thrombosis in unusual site (UST), and pulmonary embolism (PE), were recorded. Therapeutic procedures followed and outcome were obtained whenever possible.

A thorough search was carried out by means of repeated Pub-Med or Medline systems using appropriate and pertinent key words. Papers and observations from personal files gathered during the past 35 years were also included. Original papers were obtained through the assistance of the University of Padua Pinali library and through the service of Acta Med, Sorengo, Switzerland.

Results

The overall review of the literature has yielded data on 12 patients with hemophilia A who developed venous thrombosis. In most cases these were patients with severe hemophilia A (FVIII level $\leq$ 1% of normal). In two instances, they were cases of mild hemophilia A.

Fifteen patients with hemophilia B were reported to have had venous thrombosis. In this case too the majority of patients were cases with a severe form.

Altogether 27 patients with these two congenital disorders and venous thrombosis were found reported in the literature (Tables 1 and 2). These patients came from at least 9 different Countries.

For 6 of these patients the Country of origin is not specified. The type of venous thrombosis were: 10 DVT, 8 pulmonary embolism with or without DVT, 5 superficial venous thrombosis (SVT) and 3 thrombosis in unusual sites (1 retinal central vein thrombosis, 2 portal vein thrombosis). In one patient thrombotic manifestations were multiple (Table 3). The age of patients varied between 9 and 67 years.

In hemophilia A patients, the most frequent risk factor was the administration of Feiba or rFVIIa for inhibitors. Surgery and FVIII concentrate were present only in one case. Two patients had associated congenital prothrombotic condition at the heterozygote level, namely Prot. C deficiency and FV Leiden. In hemophilia B patients, the administration of pro-

Table 1 Venous thrombosis reported in hemophlia A patients

Authors	Year	Age	Type of defect	Site of thrombosis	Risk factors	Additional comments
Girolami et al.	1972	42	Moderate	SVT (basilic vein)	None	
Sartori et al.	1991	53	Severe	Portal vein	Post hepatitis C, liver cirrhosis	
Ritchie et al.	1992	67	Severe	DVT	Orthopedic surgery, FVIII conc.	During FVIII conc
Opanasenko et al.	1997	n.r	n.r.	PE	n.r.	Pulmonary artery thrombosis
Escuriola Ettingshausen et al.	1999	14	Severe	Portal vein	Het. FV Leiden, FVIII conc.	During infusion of FVIII conc. Heparin treatment
Stewart et al.	2000	40	Severe	DVT	Duplication of femoral vein	
Santagostino et al.	2001	n.r.	n.r.	SVT (site n.r)	rFVIIa infusion for inhibitors	
Rosenfeld et al.	2002	22	Severe	PE	Feiba + rFVIIa conc. for inhibitors	Sequential therapy for 12 days
Van der Planken et al.	2002	38	Severe	DVT	rFVII/a concentrates for inhibitors	Infection, antifibrinolytics
de Gaetano Donati et al.	2002	63	Mild	SVT (great saphena vein)	Prot. C deficiency (type n.r.) anticardiolipin antibodies	HIV positive
Dargaud et al.	2003	37	Severe	DVT	None	HIV positive, hepatitis C
Hg et al.	2003	28	Severe	DVT	FIX + rFVIIa conc. for inhibitors	Thrombosis detected 9 days after last rFVIIa conc.

Abbreviations: SVT = superficial vein thrombosis; DVT = deep vein thrombosis; PE = pulmonary embolism; n.r. = not reported.

Table 2 Venous thrombosis described in hemophlia B patients

Authors	Year	Age	Type of defect	Site of thrombosis	Risk factors	Additional comments
Kasper et al.	1973	n.r.	n.r.	SVT	Surgery, PCC	Types of surgery unspecified
		n.r.	n.r.	SVT	Surgery, PCC	Same
		n.r.	n.r.	DVT	Surgery, PCC	Same
		n.r.	n.r.	PE	Surgery, PCC	Same, fatal
		n.r.	n.r.	DVT, PE	Surgery, PCC	Surgery unspecified
		n.r.	n.r.	DVT	Surgery, PCC	Same
Istvan et al.	1982	n.r.	severe	PE	Feiba for inhibitors	
Lusher	1991	40	n.r.	DVT	PCC	After 4, 3000U doses
		64	moderate	PE	FIX conc.	7 days after last infusion
		9	moderate	DVT	FIX conc.	
		27	severe	PE	FIX conc. + surgery for femur fracture	On 6th postoperative day
		30	severe	DVT	FIX con.	Controlateral leg DVT
Schiemann et al.	1999	14	severe	Central retinal vein	CMV infection, AIDS	
Pruthi et al.	2000	nr	severe	DVT+PE	Hip fracture surgery. Het. FV Leiden	On high purity FIX concentrates (~4500 Units/day). Treated with LMWH
Douvas et al.	2004	n.r.	severe	Superior vena cava DVT (arm) Intracerebral sinus	FIX conc.	Conc. administered via central line

Note: abbreviations have the same meaning as in Table 1. PCC = Prothrombin Complex Concentrate; LMWH = low molecular weight heparin.

Table 3 Type of venous thrombosis seen in hemophilia A, hemophilia B together with pertinent risk factors. More than one risk factor was present in same cases

Type of venous thrombosis	No. of cases	Congenital risk factors	Acquired risk factors	Additional comments
DVT	**9**	None	1)Surgery in two 2)Malformation in one 3) FVIII conc. in one 4) Act. products conc. in three 5) PCC conc. in two 6) FIX conc. in two 7)Orthopedic surgery in one 8)None in one	HIV infection in one
DVT + PE	3	Het. FV Leiden in one	Orthopedic surgery; surgery	Type of surgery unspecified in 2 cases
PE	5	None	1)Activated product conc. in one 2)FIX conc. in one 3)Surgery in three	
SVT	6	Prot. C deficiency in one	1)Anticardiolipin antibodies in one 2)rFVIIa infusion in one 3)PCC in three 4)None in one	No catheter
Portal vein	2	Het. FV Leiden in one	Liver cirrhosis in one	
Multiple	1	None	Factor IX conc.	
Other	1	None	None	Central retinal vein, HIV infection

More than one associated risk factor was present in some patients.

thrombin complex concentrate (PCC) or FIX concentrates for surgery was present in 8 cases. In 5 cases only concentrate administration was reported (1 Feiba; 4 FIX concentrates). One patient with hemophilia B had FV Leiden at the heterozygous level.

There was a fatality in a hemophilia B patient with pulmonary embolism.

Few therapeutic procedures were instituted in these patients (Table 4). In most cases, only an interruption of factors VIII or IX concentrate was necessary. In a few instances heparin, usually LMWH, was also administrated for a few days together with a reduction of the amount of concentrates being given.

Discussion

Venous thrombosis seems rare in patient with hemophilia A and hemophilia B, but not exceptional.

12 patients with hemophilia A, and 15 patients with hemophilia B were reported to have had a venous thrombotic phenomenon [8–25].

Due to the known ratio between hemophilia A and hemophilia B, namely about 6 to 1, it could have been expected that patients with hemophilia B and thrombosis appeared less frequent by comparison with hemophilia A patients. In reality from the data of the literature the opposite is true, the frequency being much higher in hemophilia B.

In this regard it is interesting to remember that Kasper had noticed 6 venous thrombosis after 13 surgical operations in patients with hemophilia B whereas she failed to find any after 72 procedures in hemophilia A [17]. The discrepancy was attributed to the use of PCC in the former as compared to FVIII concentrates in the latter.

The patients reported to have venous thrombosis came from at least 9 different countries with a total population of about 730 million people (Table 5) [26]. Some of the cases reported by Lusher JM cannot be allocated to any country [25]. If one takes into account the expected hemophilic population in the same countries (1:10.000 people), reaches a value of about 73000 patients. The prevalence of venous thrombosis is therefore 1 out of about 27000 patients. In the normal male population is about 1/1000 or 2000 per year.

The overall prevalence of venous thrombosis in patients appears therefore much lower than that found in the general population. Since a thrombotic phenomenon in a patient with a congenital coagulation disorder is always of interest it is conceivable that the reported cases refer in reality to all patients observed to have this clinical manifestation. The significance of this low prevalence is due to the fact a plasmatic defect seems protective against venous thrombosis. This conclusion is in agreement with several studies [27,28].

It has to be observed that some of these hemophilia patients with venous thrombosis had associated risk factors. The associate risk factors were varied, both congenital but mainly acquired.

Table 4 Therapeutic procedures followed in some of the patients reported. In other cases no data are supplied as to management

Authors	Type of thrombosis	Anticoag.	UH	LMWH	Coumadin	Bleeding	Local measures	Comments
Girolami et al.	SVT	No	No	No	No	No	Yes	
De Gaetano Donati et al.	SVT	Yes	No	Yes	No	No	n.r.	
Stewart et al.	DVT	Yes	No	Yes	No	No	No	Together with FVIII conc.
Dargaud et al.	DVT	Yes	Yes	No	No	No	No	Some
Douvas et al.	DVT	Yes	No	Yes	No	Yes	No	Excessive bleeding
Lusher et al.	DVT	Yes	No	Yes	No	No	No	Together with FVIII conc.
Pruthi et al.	DVT	Yes	No	Yes	No	No	No	
Van der Planken et al.	DVT	No	No	No	No	No	No	
Rosenfeld et al.	DVT + PE	Yes	No	Yes	No	No	No	
Sartori et al.	Unusual site	Yes	No	No	Yes	No	No	
Escuriola Ettingshausen et al.	Unusual site	Yes	No	Yes	No	No	No	Reduction of FVIII conc. during LMWH

Note: abbreviations have the same meaning as in Table 1.

Table 5 Estimated prevalence of reported cases of venous thrombosis in the hemophilia population by Country

Country	Population (millions)	Approximate number of hemophilia patients	No of reported cases	Comments
France	59	5,900	1	
Canada	31	3,100	1	
Belgium	10	1,000	1	
U.K.	59	5,900	1	
Italy	58	5,800	4	
USA	288	28,800	15	For 6 cases country of origin not reported
Germany	82	8,200	2	
Singapore	4	400	1	
Russia	145	14,500	1	
Total	736	73,000	27	

The most frequent causative effect was the administration of factor concentrates, usually activated products (Feiba or rFVIIa), but also plain factor VIII or FIX concentrates, used for the management of inhibitors. Elevated levels of FVIII or FIX may be associated with thrombosis. The thrombogenic activity of activated factors concentrates is known [25,29,30]. It was thought in the past that rFVIIa concentrates might be less thrombogenic as compared to old products as Feiba [31]. This may not be the case. The impression was only due to the fact that rFVIIa concentrates were introduced in the management of hemophilia with inhibitors more recently as compared to Feiba. As it use became more widespread, patients with thrombosis started appearing [31].

Polymorphisms have been found in association with hemophilias. This is not surprising since polymorphisms are present in about 3–6% of the general population. It is conceivable that the same prevalence is also present in hemophilia. It was also speculated that the association of hemophilia A with one of these polymorphisms, usually FV Leiden, could modify the clinical picture, namely decreasing its severity. Subsequently this was not confirmed [32].

It has been suggested that atherosclerosis and/or arterial thrombosis is more frequent in these patients as compared to venous thrombosis [27]. However the role played by coagulation changes in the pathogenesis of atherosclerosis is still unsettled [27,33,34].

Thrombosis, both venous and arterial, has been often observed in immunoincompetent patients due to HIV infection. However only one of these patients was HIV positive in spite of the known fact that infection is frequent among hemophiliacs. The pathogenesis of thrombosis in HIV patients is complex since several coagulation or non-coagulation related risk factors have been claimed to be involved [35].

The present observations are evidence of the fact that venous thrombosis may occur in hemophiliacs even in absence of HIV infection.

However, since most of the cases of venous thrombotic manifestation occurred during or after substitution therapy

with PCC or similar products, it is advisable to exercise a careful control of patients undergoing such therapy.

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