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Bleeding Symptoms in Carriers of Hemophilia A and B

E. P. Mauser Bunschoten[1], J. C. van Houwelingen[2], E. J. M. Sjamsoedin Visser[1, 3], P. J. van Dijken[1, 3], A. J. Kok[1], and J. J. Sixma[4]

From the Van Creveld Clinic[1], Hemophilia Clinic, Medical Center "Berg en Bosch", Bilthoven, The Netherlands, the Department of Mathematical Statistics[2], State University, Utrecht, The Netherlands, the University Hospital for Children and Youth "Het Wilhelmina Kinderziekenhuis"[3], Utrecht, The Netherlands and the Department of Hematology[4], State University, Utrecht, The Netherlands

Key words

Hemophilia – Carrier – Bleeding symptoms

Summary

In order to investigate the bleeding tendency in clinically identified carriers of hemophilia, a self-administered questionnaire was held among 135 carriers of hemophilia A and B, 25 females with relatives with hemophilia and a matched group consisting of 60 females without relatives with hemophilia. Carriers of hemophilia appeared to suffer more often from bleeding than their relatives or the matched unrelated control group. A relation was seen between factor VIII:C or IX:C activity and the tendency to bleed. Obligatory carriers with normal factor VIII:C levels showed no bleeding tendency and were in this respect similar to a group of 25 females with relatives with hemophilia. This study shows that it is important to assay factor VIII:C or IX:C also in those women in whom the carrier status has already been established otherwise.

Introduction

Hemophilia A and B are inherited as X-linked recessive disorders. Mostly males are affected by the disease and females are carriers. As they have only one affected X-chromosome, factor VIII:C and IX:C activity levels of 50% of normal would be expected. However, a wide range of activity levels has been observed (1, 2, 3, 4, 5) due to lyonisation (6). In carriers of hemophilia A, a mean factor VIII:C level of 54% (range 22–116%) was found (3), while the mean factor VIII:C activity in a reference group of normal healthy females was 96% (range 44–136%). Factor VIII:C activity is less than 30% in 2% of hemophilia carriers (1). Within one family factor VIII:C levels in carriers are variable (4).

Because of the possibility of low levels of factor VIII:C or IX:C activity, one may expect a bleeding tendency in some carriers. The aim of the study was to investigate whether there is indeed a bleeding tendency in women who have been identified as carriers of hemophilia A and B and whether this is related to the factor VIII:C or IX:C activity.

Patients, Materials and Methods

Patient Groups and Controls

The investigation was performed by means of a questionnaire which was sent to 148 known carriers of hemophilia A and B. In the carrier group (A) response was obtained from 94 obligatory carriers and from 41 women closely related to hemophilia patients who were classified as carriers by laboratory assay as defined in the World Health Bulletin (7). Obligatory carriers were defined as: daughters of hemophilia patients, mothers with two or more sons with hemophilia, mothers with one affected son and a brother, grandfather or uncle (maternal) with hemophilia and mothers of one affected son and one or more daughters who are carrier. The first reference group (B) consisted of 29 females also closely related to hemophilia patients, but who were classified as *non-carriers* by laboratory assay (7). A second matched reference group (C) consisted of 68 females of the same age and social class as the carrier group. This matched group was composed by asking all carriers who responded to the questionnaire to send us one to five names of female friends of the same age, who had no relatives with hemophilia themselves. One friend per carrier was chosen as a referent.

All women who were identified as carriers on the basis of the laboratory assay had probabilities of carriership varying between 96 and 100% with two exceptions, one at 91% and one at 70%. All women identified as non-carriers on the basis of the laboratory assay had probability of carriership values of 1% and below, with two exceptions, one at 2% and one at 3% probability.

Laboratory Studies

Factor VIII coagulant activity was assayed in a one stage clotting time assay using the kaolin activated partial thromboplastin time (8). Factor IX coagulant was assayed according to Veltkamp et al. (9). Von Willebrand antigen was assayed according to Bouma et al. (10).

The carrier status for hemophilia A was determined as described by Bouma et al. (10) on the basis of the F VIII coagulant activity and von Willebrand antigen. The levels of F VIII and IX activity and von Willebrand antigen were the mean values obtained from blood collections at three separate occasions with at least one week interval. The results were averaged using the logarithm of the values. The F VIII:C or F IX:C activity were measured in 70 carriers and in all non-carriers.

Registration of Bleeding Symptoms

Binary questions (yes-or-no alternatives) were answered by the carriers, non-carriers and matched reference group by use of a self-administered questionnaire. A summary of the questions is given in Table 1.

Statistical Methods

Answers were analysed by Chi-square, McNemars test (11) and logistic regression analysis by means of the BMDPLR computer program (12).

Results

The total number of questionnaires sent and analysed and the response rate are given in Table 2. Of the carrier group, all questionnaires received could be analysed (94 obligatory carriers and 41 other carriers). Of the non-carrier group, four females turned out to be mother of one hemophilia patient. Because the laboratory tests were probably false negative in these cases, they were excluded from the study. Six females from the matched reference group were also eliminated because they appeared to have relatives with hemophilia.

Correspondence to: Dr. E. P. Mauser Bunschoten, Van Creveld Clinic, P.O. Box 401, 3720 AK Bilthoven, The Netherlands

Table 1 Summary of questions

- Are you a carrier?
- Level of Factor VIII:C or IX:C if known
- Tendency to bruising, nose bleeding
- Prolonged bleeding from small wounds
- Were there any tooth extractions performed?
  If yes, was there prolonged bleeding and did you receive blood or blood products.
- Have you ever been operated?
  If yes, was there prolonged bleeding and did you receive blood or blood products.
- Was a tonsillectomy performed?
  If yes, was there prolonged bleeding and did you receive blood or blood products.
- Did you give birth to a child?
  If yes, was there prolonged bleeding after delivery and did you receive blood or blood products.
- Do you think you are suffering from a greater blood loss during menstruation than other women?
- Do you use any analgetics?

N.B. 1: The questions about bleeding symptoms were asked as binary questions.
N.B. 2: A specimen of the questionnaire can be obtained from the authors on request.

Table 2 Number of questionnaires sent and analysed and the response rate

	Number sent	Number received	Number analysed	Response rate (%)
Carriers (A)	148	135	135	91.2
Non-carriers (B)	29	29	25*	100
Matched reference group (C)	68	66	60**	97.1

* 4 mothers of one hemophilia patient were excluded
** 6 were excluded because of relatives with hemophilia

In Table 3, the bleeding symptoms in the three groups are given and the p-value from a simple χ^2-test is presented (2 × 3 table). Compared to the other groups the carrier group has a significantly higher tendency to bruise ($p = 0.01$), shows prolonged bleeding from small wounds ($p = 0.02$) and prolonged bleeding after tooth extraction ($p = 0.001$), tonsillectomy ($p = 0.004$), operation ($p = 0.02$) and delivery ($p = 0.03$). With exception of tooth extraction, the significant differences are explained by the greater tendency to prolonged bleeding in the carrier group. The significant difference in tendency to bleed after tooth extraction can be explained by the fact that the matched reference group showed less prolonged bleeding than the carrier and non-carrier group.

Caution is needed in the interpretation of these significant results because other effects such as age may interfere (the non-carriers in group B are much younger). Therefore we compared the carriers with their matches by means of McNemars test for matched pairs. Results are given in Table 4. Also in this analysis, significant differences for prolonged bleeding from small wounds ($p = 0.04$), bleeding after tooth extraction ($p = 0.008$), operation ($p = 0.01$) and delivery ($p = 0.04$) were found. No significant difference of bleeding after tonsillectomy was found which may be due to the small number of matched pairs for this operation. The fact that there is no significant difference for the tendency to bruises can be explained by the relation between tendency to bruise and the ability to produce a match. Women who did not give a possible match had a significantly higher tendency to bruise.

In order to analyse the influence of factor VIII:C or IX:C activity, age etc. on bleeding tendency we used logistic regression analysis. Factor VIII:C or IX:C activity was assayed in 70 carriers and in all non-carriers of group B. It appeared that the factor VIII:C or IX:C activity was of significant influence on bleeding after tooth extraction, tonsillectomy, and operation, and that the difference between carriers and non-carriers was completely explained by the difference in factor VIII:C or IX:C activity. The results of the logistic regression analysis are given in Table 5. The confidence intervals for p (the probability of bleeding) at various factor VIII:C or IX:C levels for bleeding after tooth extraction, operation and tonsillectomy are presented in Figure 1a, b and c respectively.

In order to investigate the positive or negative influence of bleeding and the knowledge of being an obligatory carrier, we compared the bleeding tendency in obligatory carriers with normal factor VIII:C activity with the bleeding tendency in the non-carrier group (Table 6). Both groups showed little difference in tendency to bleed. A χ^2-test was not performed because the numbers in the first group were too low.

In Table 7, the absolute numbers of blood transfusions after tonsillectomy, operation and delivery are given. In the carrier

Table 3 Bleeding symptoms

	A carriers	B non-carriers	C reference group	χ^2-test
Number analysed	135	25	60	
Mean age in years	37.0	23.9	37.4	
Range of age in years	7–76	12–65	11–66	
Positive answers with regard to symptoms below**				
– tendency to bruise	37% (48/129)	24% (6/25)	17% (10/60)	p = 0.001
– long bleeding from small wounds	20% (24/120)	0% (0/19)	2% (1/48)	p = 0.002
– nose bleeding	8% (11/130)	12% (3/24)	5% (3/60)	n.s.*
– prolonged bleeding*** after tooth extraction	43% (46/107)	45% (5/11)	13% (6/46)	p = 0.001
– prolonged bleeding*** after tonsillectomy	45% (23/ 51)	11% (1/ 9)	11% (3/26)	p = 0.004
– prolonged bleeding*** after operation	30% (21/ 70)	11% (1/ 9)	6% (2/31)	p = 0.02
– prolonged bleeding*** after delivery	22% (21/ 97)	0% (0/ 8)	6% (3/47)	p = 0.03
– menorrhagia	31% (32/102)	10% (2/19)	23% (12/51)	n.s.
– use of analgetics	45% (57/126)	39% (9/23)	56% (33/58)	n.s.

Results were compared by Chi-square test:
* n.s. = not significant
** the percentage of positive answers is related to the total number of answers
*** as a percentage of positive answers

Table 4 Analysis of matched pairs by means of McNemars test

	Number of matched pairs	Significance
Tendency to bruise	57	n.s.*
Long bleeding from small wounds	44	p = 0.04
Nose bleeding	56	n.s.
Prolonged bleeding after:		
– tooth extraction	40	p = 0.008
– tonsillectomy	12	n.s.
– operation	22	p = 0.01
– delivery	42	p = 0.04
Menorrhagia	43	n.s.
Use of analgetics	55	n.s.

* n.s. = not significant

Table 5 Logistic regression of probability of bleeding on factor VIII:C or IX:C concentration (percentage). Model: $\ln(p/[1-p]) = a + b$ factor VIII:C or IX:C; p = probability of bleeding

	Number of patients involved	a	b	Significance of b (two-sided)
Bleeding after:				
– tooth extraction	74	0.999	−0.017	0.040
– tonsillectomy	45	2.584	−0.049	0.000
– operation	48	0.789	−0.022	0.066

Table 6 Bleeding symptoms in obligatory carriers with normal factor VIII:C or IX:C levels and non-carriers

	Obligatory carriers with normal FVIII/IX:C*	Non-carriers
Number analysed	17	25
Mean age in years	33.5	23.9
Range of age in years	12–66	12–65
Mean FVIII:C/IX:C	83.6%	98.5%
Range of FVIII:C/IX:C	60–177%	60–160%
Positive answers with regard to symptoms below**		
– tendency to bruise	41% (7/17)	24% (6/25)
– long bleeding from small wounds	6% (1/17)	0% (0/19)
– nose bleeding	12% (2/17)	12% (3/24)
– prolonged bleeding after***:		
– tooth extraction	18% (3/17)	45% (5/11)
– tonsillectomy	18% (2/11)	11% (1/ 9)
– operation	0% (0/ 9)	11% (1/ 9)
– delivery	15% (2/13)	0% (0/ 8)
– menorrhagia	29% (4/14)	11% (2/19)

* FVIII:C or IX:C = factor VIII:C or IX:C activity
** The percentage of positive answers is related to the total number of answers
*** as a percentage of positive answers of females who underwent tooth extraction, tonsillectomy, operation or delivery

group the number of blood transfusions is higher than in the two other groups.

Discussion

Prolonged bleeding in clinically identified hemophilia carriers was found after dental and surgical intervention, delivery, tonsillectomy, and from small wounds; there also seemed to be a tendency to increased bruising. The lack of difference in increased nose bleeding and menorrhagia may be due to the influence of local factors. By logistic regression analysis, we found that the tendency to bleed was completely explained by the plasma levels of factor VIII:C and IX:C. The relationship between factor VIII:C or IX:C activity and the probability of bleeding is shown in Figure 1. This figure should not be taken too absolutely, because the number of patients involved is small, but it gives an impression of the effect of factor VIII:C or IX:C activity on the bleeding tendency. Factor VIII:C levels may have been influenced by psychological and physical stress or by the use of oral anticonceptive drugs, but care was taken to minimize stress by taking three samples with at least weekly intervals. The considerably higher number of blood transfusions after tonsillectomy and specially after operation and delivery in patients with low F VIII:C is also an indication that there is indeed a bleeding tendency in the carrier group. Whether an individual is aware of her carrier status seems to have little influence, because the bleeding tendency in obligatory carriers with normal factor VIII:C or IX:C levels was similar to the bleeding tendency in the non-carrier group with relatives with hemophilia.

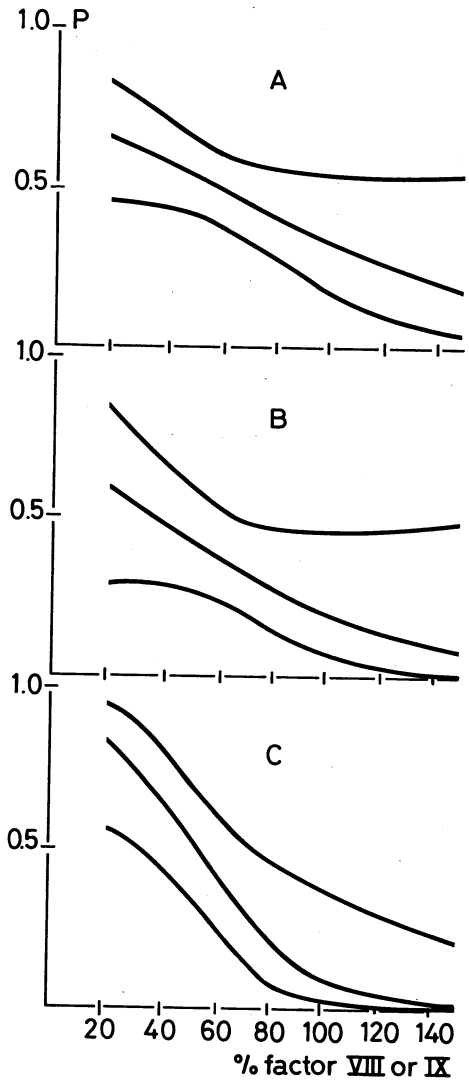

Fig. 1 Influence of factor VIII:C or IX:C activity on the probability (P) of bleeding (see Table 5). A. Bleeding after tooth extraction. B. Bleeding after operation. C. Bleeding after tonsillectomy

Table 7 Blood transfusion frequency in carriers, non-carriers and matched reference group after tonsillectomy, operation and delivery

	A carriers	B non-carriers	C matched reference group
Blood transfusion after tonsillectomy	4 (51)*	1 (9)	0 (26)
Blood transfusion after operation	10 (70)	0 (9)	0 (31)
Blood transfusion after delivery	7 (97)	0 (8)	0 (47)

* between brackets the number of women that had undergone the specified procedure

Our results agree well with those published before. Already since the 19th century, it is known that in carriers of hemophilia there is an increased tendency to bleed (13). Later on many case reports have confirmed the presence of increased bleeding in occasional carriers with low factor VIII:C or IX:C activity (4, 14, 15). In 1951 Merskey (16) published the results of a more systematic study of bleeding symptoms in 19 obligatory carriers and 12 mothers of one affected hemophilia son compared to a control group of 100 healthy females. The first group was more liable to hemorrhages especially after tooth extraction. Wahlberg (17) reported a comparable study of 29 carriers in which he found increased bleeding after delivery and operation and a tendency to nose bleeds. However, he did not find a bleeding tendency after tooth extraction. In our study the number of carriers investigated is much larger than has been published thus far. It is also the first time that bleeding tendency in carriers is compared to a matched reference group. Our study has practical consequences in dealing with female family members of hemophilia patients. As the bleeding tendency is related to the factor VIII:C or IX:C activity one should always measure clotting activity in carriers of hemophilia A and B even if they are obligatory carriers or when the carrier status has been established by means of restriction fragment length polymorphism (18, 19). When clotting activity is less than 50%, drugs interfering with platelet function should be avoided. In case of severe trauma, operation or tooth extraction, local hemostasis must be practised carefully. When clotting activity is less than 30%, it may be necessary to increase the factor VIII:C or IX:C level to at least 60% by using DDAVP or clotting products. Antifibrinolytic drugs can be useful in case of open bleeds. It is recommended to vaccinate carriers with a factor VIII:C or IX:C activity of less than 30% against hepatitis B in order to prevent post-transfusional infection (20, 21).

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