Paediatrica Indonesiana

VOLUME 42 May - June • 2002 NUMBER 5-6

Original Article

Clinical characteristics of hemophilia A patients with hemarthrosis

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ABSTRACT

Background Hemarthrosis is the most frequent bleeding manifestation of severe hemophilia. Repeated hemarthrosis will cause chronic arthropathy, which results in a physical disability.

Objectives To obtain data of clinical characteristics of hemophilia-A patients with hemarthrosis (particularly chronic hemarthrosis) and to know the effect of on-demand therapy on joints of the patients.

Methods We evaluated 102 hemophilia A patients in Pediatric Hematology and Oncology Division, Cipto Mangunkusumo Hospital for 6 months beginning from March 2001.

Results The number of cases of chronic hemarthrosis was 22%, smaller than previous study (54%). Chronic hemarthrosis mostly occurred in hemophilia A patients who aged between 13-18 years, had severe hemophilia A and frequency of hemarthrosis more than 12 times a year, and also patients who did not receive adequate therapy. The joint which most frequently suffered from hemarthrosis were knee (26%), ankle (23%) and elbow (21%). The critical period for the first hemarthrosis was at the age of 2-12 years, and repeated hemarthrosis episodes commonly occurred at the age 6-18 years owing to the child's increasing physical activities.

Conclusion Hemarthrosis can be prevented and anticipated. It is important to notice the critical period when first hemarthrosis and repeated hemarthrosis occur. The certain joints like knee, ankle and elbow must be given more attention due to the risk of repeated hemarthrosis. **(Paediatr Indones 2002;42:101-105)**

Keywords: hemophilia A, hemarthrosis, clinical characteristics

Hemarthrosis is the most frequent bleeding manifestation of severe hemophilia; it occurs in around 85% of the patients.[1,2] Hemarthrosis may occur several times and if it is not managed adequately, it can cause chronic arthropathy and finally may disturb the growth and development of the patient.[1,3] The prevalence of hemophilia-A compared to hemophilia-B patients in Cipto Mangunkusumo Hospital is 13:1. Sixty-two percents of hemophilia-A patients belong to severe category, while moderate and mild hemophilia respectively consists of 24% and 14%. Fourteen percents of hemophilia-B patients are in severe category and 86% moderate.[4] Since most of the hemophiliacs are hemophilia-A and most of which are severe, hemarthrosis has become a serious problem for the patients.

Hemophiliacs, particularly the severe one should receive maintenance therapy of factor VIII or IX concentrates to prevent bleeding episode especially hemarthrosis.[3] Severe hemophiliacs in Sweden get maintenance therapy as a prophylaxis therapy beginning at the age of 1-2 years to prevent hemarthrosis.[5-7] Studies done in US, Europe, and Japan have indicated that maintenance therapy of factor VIII or IX concentrates have reduced hemarthrosis episodes and prevent joint damage.[8]

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Studies on hemarthrosis have shown a lot of progress in developed countries. However, in Indonesia especially in our department such a study has never been made. The aim of this study was to determine the clinical characteristics of hemophilia-A patients with hemarthrosis, number of hemarthrosis events of hemophilia-A, and the effects of on-demand therapy on joints of the patients. Attention was mainly focused on the hemophilia-A patients because the number is greater than that of hemophilia-B. Besides, the percentage of severe hemophilia-A patients is significantly high.

Methods

This was a descriptive, cross-sectional study carried out on all hemophilia-A patients treated in Pediatric Hematology and Oncology Division, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital within 6 months beginning from March 2001.

The inclusion criteria were: (1) Hemophilia-A patients with hemarthrosis treated in Pediatric Hematology and Oncology Division, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital. Diagnosis was made based on unusual bleeding manifestation, prolonged activated partial thromboplastin time, and thromboplastin generation test examination. (2) Patients who received factor VIII on-demand therapy. (3) Patients who had complete medical records. Patients receiving factor VIII maintenance therapy or prophylaxis were excluded. Subjects were recruited consecutively.

Factors VIII that was given only when hemarthrosis occurred was called on-demand therapy, factors VIII that was given 3 times a week regularly was called maintenance or prophylaxis therapy.[5-7] Acute hemarthrosis was defined when the joint was tense, hard, warm, and pain and there was soft tissue swelling from radiological examination. Subacute was defined when the joint was edematous with moderate restriction of joint movement and the radiological examination showed osteoporosis, epiphyses hypertrophy without narrowing of the cartilage space. Chronic was defined when the joint changed progressively to the last stage of arthropathy with contracture and the radiological examination showed disorganization of the joint, narrowing of the joint space and cartilage destruction, fibrous joint contracture, and loss of joint space.[2] Mild hemophilia is defined when the level of procoagulant activity of factor VIII was 6-30%, moderate 1-5% and severe when the level was less than 1%.[1,3]

Data of history, physical and radiological examinations were obtained from medical records including clinical characteristics, patient's age, age at the diagnosis of hemophilia-A, age at the first hemarthrosis, family history, hemophilia classification, annual hemarthrosis frequency, severity and distribution of hemarthrosis and also factor VIII therapy. The result of radiological examination was evaluated by a pediatric radiologist. Hemophilia classification was determined based on the level of factor VIII (study by Rahajuningsih and Gatot within 1999-2000). When data on the level of factor VIII was not available, classification was determined based on thromboplastin generation test (TGT) and the occurrence of spontaneous hemarthrosis. Data were then analyzed by SPSS 10.0 program for Windows.

Results

During the study period, 102 hemophilia-A patients were evaluated. Eighteen patients were excluded because they had never had hemarthrosis (n=14) and had incomplete medical record (n=4) so that only 84 hemophilia-A patients were recorded. The clinical characteristic data can be seen on **Table 1**.

Most of hemophilia-A patients with hemarthrosis were 6-12 years old (38%), 61% diagnosed at early age (0-1 year) and most patients had their first hemarthrosis at 6-12 years old (42%). Most patients had severe hemophilia-A (72%); 57% had positive family history, 42% experienced hemarthrosis 1-5 times a year, and 76% got adequate therapy. Chronic hemarthrosis were found in 18 patients (22%). The locations of hemarthrosis in 84 hemophilia-A patients can be seen on **Table 2**. The joints that most frequently suffered from hemarthrosis were knee (26%), ankle (23%), and elbow (21%).

Table 3 shows that chronic hemarthrosis often occurred in hemophilia-A patients who aged between 13-18 years (8/18) and the age group of 6-12

Table 1. Clinical characteristics of hemophilia A patients with hemarthrosis

Variables		n	%
Age (yr)	0 - 1	-	-
	2 - 5	12	14
	6 - 12	32	38
	13 - 18	31	37
	> 18	9	11
Age at the first diagnosis (yr)	0 - 1	51	61
	2 - 5	26	31
	6 - 12	7	8
	13 - 18	-	-
	> 18	-	-
Age at the first hemarthrosis (yr)	0 - 1	11	13
	2 - 5	34	40
	6 - 12	35	42
	13 - 18	4	5
	> 18	-	-
Hemarthrosis stadium	Acute	58	69
	Sub-acute	8	9
	Chronic	18	22
Annual hemarthrosis episode	1 - 5 times	35	42
	6 - 12 times	25	30
	> 12 times	24	28
Hemophilia classification	Mild	6	7
	Moderate	18	21
	Severe	60	72
Treatment	Adequate	64	76
	Inadequate	20	24

years (11/18) viewed from the age at the first hemarthrosis. It was also occurred in severe hemophilia-A patients (13/18), patients with hemarthrosis more than 12 times a year (12/18) and in patients with no adequate therapy (8/20).

Table 2. The locations of hemarthrosis in 84 hemophilia A patients*

Location	n	%
Knee	78	26
Ankle	71	23
Elbow	64	21
Finger	30	9
Wrist	22	7
Toe	21	6
Shoulder	17	5
Hip	10	3
Total	303	100

* 1 patient could have more than 1 joint suffered from hemarthrosis

Discussion

The study has certain limitations, including (1) Incomplete medical records data so it was based on parent's memory which might lead to bias. (2) Adequate therapy in this study was not in conformity with standard therapy. "Adequate" in this study meant optimal therapy according to the limitation of cost and facilities. (3) Classification of hemophilia in this study was not only based on factor VIII level but also on TGT examination and type of trauma preceding the hemarthrosis.

Most of the hemophilia-A patients in the series with hemarthrosis were teenagers between 6-12 years (38%) and 13-18 years (37%). It is said in the literature that the incidence of hemarthrosis is higher in the teenagers and decrease with age owing to an over-

Table 3. Details of clinical characteristics of hemophilia A patients with hemarthrosis based on hemarthrosis stadium

Variables	Characteristics	Hemarthrosis		
		Acute	Sub-acute	Chronic
Age (yr)	0 - 1	-	-	-
	2 - 5	12	-	-
	6 - 12	23	4	5
	13 - 18	20	3	8
	> 18	3	1	5
Age at the first hemarthrosis (yr)	0 - 1	10	-	1
	2 - 5	25	4	5
	6 - 12	20	4	11
	13 - 18	3	-	1
	> 18	-	-	-
Hemophilia classification	Mild	4	1	1
	Moderate	14	-	4
	Severe	40	7	13
Annual hemarthrosis episodes	1 - 5 times	28	2	5
	6 - 12 times	23	1	1
	> 12 times	7	5	12
Treatment	Adequate	49	5	10
	Inadequate	9	3	8

all modified activity, restricted joint activity and compensatory changes in hemostatic process.[2]

Diagnosis of hemophilia-A was mostly made at the age 0-1 year (61%). It is in conformity with the literature that hemophilia symptom is generally seen when the child begin to crawl, sit and walk.[9,10] Fifty-seven percents of patients have positive family history. This figure is different from the other reports that 80% of patients have had positive family history.[9,10] This difference is likely caused by the inaccuracy of the data obtained or it may result from the unavailability of carrier detection. When there is a hemophilia history in a family, factors VIII and IX should be examined so that the status of the child can be determined to facilitate further management.

In most cases first hemarthrosis occurs at 6-12 years of age (42%) and of 2-5 years of age (40%). Children at these age periods have increasing physical activities. At the age of 2-5 years, children begin to develop gross motoric skills and explore environments,[11] but on the other hand do not know how to take care of themselves properly. Children of 6-12 years of age have developed more intensive interaction with their friends of similar age in line with the development of their gross motoric skills.[11] As a result, games and other sports give them opportunity for getting hemarthrosis while they themselves do not fully realize the result of excessive activities.

It has initially been assumed that by giving factor VIII on-demand the number of chronic hemarthrosis events was large. This study has shown that chronic hemarthrosis only occurred in 18 patients (22%). In contrast study in Austria in 1973 showed 53 chronic hemarthrosis cases out of 97 patients (54%).[12] We have got no answer why with factor VIII on demand therapy the number of chronic hemarthrosis was so small compared to that reported in the literature. This number can be much minimized when the hemophilia patients, particularly the severe form are earlier given prophylaxis therapy (1-2 years),[5-7] or at least after the first episode of hemarthrosis.[13] Appropriate acute management and adequate therapy may prevent the disease to become chronic.

Most patients belong to severe hemophilia classification (72%). It is to be noted that in this study not all patients have had factor VIII level detection, and factor VIII examination was not done due to financial reason so that classification was made clinically based on the availability and type of trauma.

Hemarthrosis often occurs on the knee joint, elbow, and ankle. It results from the inability of diarthrodial joint which bears rolling and angle forming movement, voluntarily and involuntarily.[14] This study result is in conformity with literature.

The severity of hemarthrosis is influenced by factor VIII level, hemarthrosis episode, and patient's age.[2] This study showed that chronic hemarthrosis has mostly occurred in 13-18 years old patients, patients with severe hemophilia, and patients with hemarthrosis more than 12 times a year.

Chronic hemarthrosis more commonly occurred in the patients who have not got adequate therapy that out of 20 patients did not receive adequate therapy and 8 persons have experienced chronic hemarthrosis (40%). From 64 hemophilia-A patients who received adequate therapy only 10 have experienced chronic hemarthrosis (15%). It is similar to other studies. [5,12]

Chronic hemarthrosis occurs as a result of repeated and continuous intraarticular bleeding which causes damage of joint through various kinds of mechanism.[2] Hyperemic synovium may cause repeated bleeding so that the first hemarthrosis will predispose the next one. Repeated and continuous bleeding occurs on account of inadequate therapy so that factor VIII level can not reach the desired value to stop and prevent bleeding.[15,16]

This study has also indicated that hemarthrosis in the hemophiliacs is preventable. Diagnosis of hemophilia can be made at early age (0-1 year) when first time bleeding manifestation is seen. Examination of factor VIII level should be done promptly so that hemophilia-A classification can be established, because when a child has serious hemophilia, it is very possible that the child will get hemarthrosis.

The critical period for the first hemarthrosis in hemophilia-A patients is at the age of 2-12 years in accordance with the development of a child's gross motoric skills. It should be carefully perceived, so that the activities of a child at this age can be watched and directed. Protection of knee, ankle and elbow joints should be attentively done.

Repeated hemarthrosis episodes commonly occur at the age 6-18 years, owing to the child's in-

creasing activities. Apart from appropriate and adequate hemarthrosis handling, the child's activities should also be directed so that repeated hemarthrosis can be avoided to prevent chronic event.

The best prevention for the first hemarthrosis is prophylaxis therapy at early age (1-2 years),[5-7] or at least after the first hemarthrosis event to prevent repeated hemarthrosis so that chronic arthropathy can be prevented.[13] This is hard to apply due to the high cost. When prophylaxis therapy can not be given, any acute hemarthrosis should be properly and adequately managed even on demand, supported by other therapy such as physiotherapy.

In conclusion, it is important to give information to the parents of hemophilia children that hemarthrosis can be prevented and anticipated. They must pay attention on critical period when first hemarthrosis and repeated hemarthrosis occur. Activities in this period must be watched and directed without over protective behavior from the parents. The joints like knee, ankle and elbow must be given more attention due to the risk of repeated hemarthrosis.

We suggest carrying out further study (analytic study) to determine factors related to hemarthrosis stadium. The limitations of this study must be considered for the further study.

Acknowledgments

The authors would like to thanks Kemas Firman MD, for evaluating radiological findings. Thanks are also dedicated for staff of Hematology and Oncology Division of Pediatric Department of Dr. Cipto Mangunkusumo Hospital, Jakarta.

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