



Prevalence and Clinical Aspects of Hemophilia in the Western Region of Cameroon

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Authors' contributions

This work was carried out in collaboration among all authors. Author RDMT carried out the collection, the experimental phase, interpreted the data and made a major contribution in the writing of this manuscript. Authors ON, GBKT and ET supervised and contributed to the interpretation of the data, the statistical analysis and the writing of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Hemophilia is a constitutional defect in blood clotting related to a clotting factor deficiency. Its remains a major public health problem, mainly due to ignorance of the disease, limited screening capacities and access to treatment in sub-Saharan Africa and particularly in Cameroon. It causes heavy bleeding in the absence of adequate management. Few reports are available about the disease in countries with limited resources. This study assess the occurrence of hemophilia in the Western region of Cameroon and clinical aspects with the aim of raising public awareness of the disease.

Methods: A cross-sectional and descriptive study was carried out over a period of 04 months in 5 departments of the Western region of Cameroon, in particular Mifi, Ndé, Bamboutos, Haut Nkam and Menoua. The individuals were selected in their houses on the basis of clinical arguments, i.e. bleeding from the gums, traumatic wounds, hematomas. The blood samples taken from the latter were analyzed in the hemostasis laboratory of the Regional Hospital of Bafoussam. The epidemiological characteristics of hemophiliacs identified and suspects hemophiliacs were analyzed. The results obtained were analysed using statistical software R version 4.1.1.

Results: Out of 5995 people selected, 13 (0.22%) cases of hemophilia were identified, 09 confirmed cases and 04 new cases. The mean age of the patients was 14.85 years old (1.5-49). The disease

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was discovered mainly during circumcision in the months following birth (9/13, 69.23%), and by bleeding of the gums (9/13, 69.23%). Clinical signs were pain of the joints (46%), hematoma and swelling of the joints (38%). Platelets counts and prothrombin rate were normal in all. However, a prolonged Cephalin + Activator Time was found; it was corrected by supplying normal control plasma.

Conclusion: Hemophilia is a pathology little known for the general public. For this, with the help of public authorities, continuing education sessions must be set up to raise awareness among the population in order to limit the transmission of the disease and to eradicate this scourge which constitutes a real public health problem.

Keywords: Hemophilia; cephalin time + activator; prothrombin rate; platelet count; Cameroon.

1. INTRODUCTION

Hemophilia is a constitutional defect in blood clotting related to a clotting factor deficiency. It is a recessive inherited disease linked to the X chromosome, and therefore mainly affects only boys [1,2]. It involves a decrease or even a total deficit in factor VIII (hemophilia A) or factor IX (hemophilia B) in coagulation, which leads to a coagulation disorder. The main signs are so-called internalized clinical manifestations, mainly muscular and articular, bleeding (hemarthrosis, subcutaneous hematoma), but also hematuria and rare hemorrhages of the Central Nervous System (CNS) [1]. Globally, according to World Health Organisation, there are more than 400,000 people with hemophilia, but only 20% of them are diagnosed and have access to treatment [3,4]. It almost exclusively affects boys, and is estimated at around 1 in 5,000 male births for hemophilia A and 1 in 25,000 male births for hemophilia B [5,6].

The lack of awareness of hemophilia has been documented, making it one of the "rare" diseases. There are approximately 6,000 hemophiliac patients, half of whom have severe hemophilia in France [7]. It is mainly expressed in boys, but also affects around girls in France. There is a good correlation between the intensity of the anti-hemophilic factor deficiency and the clinical severity of the disease [8]. Severe hemophilia: Factors VIII or IX: <1%, moderate hemophilia due to factors VIII or IX (1 to 5%), minor hemophilia linked to factors VIII or IX: (6 to 35%) [7].

Hemophilia A affects less than one in 10,000 people, or about 2,500 Canadians. Hemophilia B is even less common, affecting only about one in 150,000 people, or nearly 500 Canadians [7,9]. Hemophilia remains a worrying issue, owing to the ignorance of the disease by the clinician practitioners, the high cost of its care, the lack

of hematologists and appropriated laboratories and tools of diagnosis of the disease in sub-Saharan Africa [7]. The number of people living with hemophilia was estimated at 1,800; 100 only being registered in Cameroon in 2014, [10].

Hemophilia could be classified as neglected disease, although population with abnormal and prolonged bleeding from unknown causes and deaths from unexplained hemorrhagic causes are encountered in Cameroon. Yet no data on hemophilia are available, as the disease is suspected by abnormally increased occurrence of ecchymoses in early childhood, spontaneous hemorrhages, particularly in joints or soft tissues, and excessive post-traumatic bleeding or bleeding during surgical procedures [5,11,12]. Few reports are available about the disease in countries with limited resources. The study assess the prevalence and clinical aspects of hemophilia in families residing in western region of Cameroon and bring new solutions to remedy this scourge.

2. METHODS

2.1 Study Sites and Populations

Our study was carried out on the population residing in the departments of the West Cameroon region: Mifi; Ndé, Bamoutos, Menoua. Haut Nkam. The size of our study population was obtained from the arithmetic formula $N = z^2 \times p(1-p) / m^2$ which gave us a size of 385 families; but we work on a set of 2000 families. The study population consisted of boys of all ages belonging to these families and presenting bleeding suggesting hemophilia. A total of 5995 boys belonging to these families were included. Female patients were not included, as well as those who refused to participate in the study and those absent during our stay in the homes. Patients who consumed

anticoagulant drugs such as heparin, antivitamin K and aspirin were excluded from the study.

2.2 Samples and Data Collection

This descriptive cross-sectional study carried out in 05 departments of the Western Cameroon Region: Mifi, Ndé, Menoua, Bamboutos and Haut Nkam, in 04 months from February 03, 2019 to May 30, 2019.

The study population consisted of men living in the study area. Recruitment was carried out by random method according to the route method, i.e. not having an exhaustive list of families in the village. The first household was drawn by lot, then the second was selected according to the route method until the number of participants to be included in each village is reached. All men living with families in the study area were included regardless of their age. People using drugs and the observation of a coagulation defect were excluded. People with a history of heavy and suspected bleeding were identified using a questionnaire; those who agreed to participate in the study signed the informed consent and were included.

Sampling were performed on included males using a Vacutenaire system. 05 mL of venous blood was collected in tubes containing 3.2% citrate anticoagulant. The samples were conditioned in a cold accumulator and transported to the Hematology Laboratories at the Bafoussam Regional Hospital and the Teaching Hospital of the Université des Montagnes i.e. Les Cliniques Universitaires des Montagnes. All blood coagulated were excluded.

2.3 Laboratory Analysis

Collected blood samples were centrifuged at 2500 rpm to obtain a plasma poor in platelets. All the biological analyzes carried out followed standard protocols. They were first carried out using the SOCIMED model AG04 coagulometer whose chronometric measurement principle is based on the use of ARM meaning to measure the speed of the magnetic ball in order to calculate the coagulation time. This machine allowed us to perform the coagulation tests. A 19 parameter MINDRAY BC-2800 Automated Hematology System was used to perform the platelet count.

Cephalin + Activator Time was first performed on blood plasmas. Cephalin + Activator times > 40

seconds was considered prolonged; comparison with the control value, or a ratio > 1.2 compared to the control were done. Cephalin + Activator Time Correction Test was then performed, in order to control the performance of the result of the prolonged Cephalin + Activator Times obtained after addition of normal control plasma. Subsequently, Prothrombin rate was obtained; plasmas with a ratio > 1.2 compared to the control were considered to be lengthened. And finally, we performed a platelet count; a rate of 150,000-400,000 / mL was considered normal.

2.4 Data Analysis

Data were recorded in a Microsoft Excel 2013 spreadsheet and analyzed using StatView software. Description of data were expressed in percentages and means. The prevalence of hemophilia in the Western region of Cameroon was calculated by relating the number of hemophilia cases to the study population. The proportion of families with hemophilia was calculated by dividing the number of families with at least one case of hemophilia to the total number of families included in this study. The 95% confidence interval for each parameter was calculated whenever necessary.

3. RESULTS

Two thousand (2000) families were visited, having an average of 5 siblings \pm 0.11, with 3 males \pm 0.054 (the father included). A total of 5995 boys \pm 0.054 (including the father) were identified. The data was collected in 05 departments of the West Cameroon region where we interviewed 500 (25%) families in the department of Ndé and Mifi, 350 in Menoua and Haut Nkam (18%) and 300 (15%) families in the Bamboutos. In total, 1,500 (25%) boys were identified in the families surveyed in the departments of Ndé and Mifi, 1,048 in those of Menoua and Haut Nkam (18%), and 900 (15%) in Bamboutos.

In sum, 13 cases of hemophilia have been identified, including 5 (38%) in Menoua, 4 (31%) in Bamboutos, 3 (23%) in Haut Nkam and 1 (8%) in Mifi.

3.1 Sociodemographic Characteristics of the Studied Population

The mean age of the study population was 13.55 and standard deviation (σ) = 11.87. The majority of our population had only a primary education

level (91.89 %) and came from a rural area (77%). Seventeen (17) (0.85%) families out of 2000 (0.85%) had at least one case of abnormal bleeding. In these families, a total of 28 boys (0.47 %) had a history of abnormal bleeding, joint swelling (05/28, 17.9%), joint pain (06/28, 21.4%); hematomas (10/28, 37.71%), bleeding during circumcisions (24/28, 85.7%), and gingivorrhagia (09/28, 32%) were signs of bleeding discovered by the included individuals or their family members.

3.2 Circumstances of Discovery of Suspected Hemophilia Bleeding

Our results showed that 17 families out of 2000 (0.85%) had at least one case of abnormal bleeding historically. In these families, a total of 28 boys (including fathers) had a history of abnormal bleeding, with a prevalence of 0.47%.

The circumstances in which bleeding occurred in the patient or family members, in order of frequency, were: joint swelling 05 of 28 cases (17.9%); joint pain 06 cases out of 28 (21.4%); hematomas 10 out of 28 cases (37.71%); bleeding during circumcisions 24 out of 28 cases (85.7%); gingivorrhagia 09 cases or 32%.

3.3 Prevalence of Confirmed Hemophilia Cases

The hemostasis exploration tests carried out on the 28 people with a history of abnormal bleeding confirmed 13 cases of hemophilia in 09 families, for an overall prevalence of hemophilia of 0.22% (13/5995) and a proportion of hemophilic families of 0.45% (28/5995).

The majority of hemophilia patients (53.85%) had a primary education level. The vast majority of the hemophilic population (76.92%) comes from rural areas (Table 1).

There was a predominance of hemophilia cases in the Department of Menoua with 5 cases (38%) including 4 new suspected cases, followed by the Department of Bamboutos with 4 cases (31%) for a total of 13 cases of hemophilia encountered during the study (4 suspected cases, particularly in the department of Menoua); for a prevalence of 0.22% compared to this total study population. In addition, no case of hemophilia has been identified in the department of Ndé. The mean age of the subjects with hemophilia was 14.85; with standard deviation σ , 12.92 (Table 1).

Table 1. Sociodemographic characteristics of the population

Age group (Years old)	Male population n (%)	History of bleeding n (%)	Confirmed hemophilia n (%)
Total	5995 (100%)	28 (100%)	13(100%)
0 - 4	1071 (17.86)	5 (17,86)	3 (23.08)
5 - 9	1499 (25)	7 (25)	3 (23.08)
10 - 14	1285 (21.44)	6 (21.43)	2 (15.38)
15 - 19	1283 (21.40)	6 (21.43)	2 (15.38)
>20	857 (14.30)	4 (14,28)	3 (23.08)
Average of ages	M = 13.55 σ =11.87	M =12.35 ; σ =10.74	M =14.85 σ =12.92
Level of education	Male population n (%)	History of bleeding n (%)	Confirmed hemophilia n (%)
Unschooling	428 (7.14)	3 (10.71)	3 (23.08)
Primary	5509 (91.89)	22 (78.57)	7 (53.85)
Secondary	55 (0.92)	2 (7.14)	2 (15.38)
Superior	3 (0.05)	1 (3.58)	1 (7.69)
Origin	Male population n (%)	History of bleeding n (%)	Confirmed hemophilia (%)
Rural	4611 (77)	21 (75)	10 (76.92)
Urban	1384 (23)	7 (25)	3 (23.08)

For Table 1, the numbers = n and frequency in parentheses in %; σ = Standard deviation, M= moyenne

Table 2. Platelet values and prothrombin rate ((Quick time (s))

Platelets per mm ³	n=28	(%)
<150000	0	0
150000 - 250000	19	67.86
250001 - 350000	8	28.57
>350000	1	3.57
Quick time (s)	n=28	(%)
<11	0	0
11 - 13	10	35.71
14 - 18	18	64.29
>20	0	0

NB: Prothrombin Rate= Quick Time in percent (%) and σ = standard deviation

Table 3. TCA (hemostasis test) and corrections results

TCA values (s)	n=13	(%)	Correction 50/50 n=13	Correction 75/25 n=13
<51	0	0	5	8
51 - 60	2	15.38	3	0
61 - 70	2	15.38	2	5
71 - 80	2	15.38	3	0
81 - 90	3	23.09	0	0
91 - 100	1	7.69	0	0
>100	3	23.08	0	0

3.4 Laboratory Results of Hemostasis Exploration

Ours findings showed that no patient presented with a platelet count <150,000/ mm³ and a Prothrombin Rate (Quick time) <11 s. Patients have normal platelet values (Table 2) and a normal Prothrombin Rate. Our results shows the distribution of the TCA results of the patients obtained following the biological analyzes, as well as the values obtained after correction (or mixing test) by adding the normal control plasma: first after mixing 50 % diseased plasma and 50% control plasma, followed by mixing 75% control plasma and 25% diseased plasma (Table 3).

There is a predominance of hemophilia cases with a Prothrombin Rate ranging from 81 to 90 seconds and a Prothrombin Rate > 100 seconds with a size of 3 in each case for a frequency of 23.08%. It is also observed an average TCA of 83.54 seconds and standard deviation σ = 18.40. After 50/50 correction, 5 individuals are observed with an TCA <51 seconds and yet no individual with an TCA> 80 seconds for a general average of TCA of 57.46 seconds and standard deviation σ = 13.91. Furthermore, after correction to 75/25, 8 cases of TCA <51 seconds are observed. However, no case of TCA> 70 seconds, this for an average of TCA in this case of 52.62 seconds and a standard deviation σ = 12.23 (Table 3). We

noted that no subject presented with a platelet count <150,000 / mm³ and a Prothrombin Rate or Quick time <11 s. Subjects have normal platelet values and a normal Prothrombin Rate. The distribution of the TCA results of the subjects obtained following the biological analyzes, as well as the values obtained after correction (or mixing test) by adding the normal control plasma: first after mixing 50 % diseased plasma and 50% control plasma, followed by mixing 75% control plasma and 25% diseased plasma (Table 3).

3.5 Clinical Presentation of Confirmed Hemophilia

Joint pain was the most common functional sign (46%) complaining by hemophilic males, while clinical signs found in hemophilic population were mostly swelling of the joints (38%) and hematoma (25%). Hematomas were the most frequent clinical signs (25%). Bleeding of the gum was also observed 69.23% (9/13). The main circumstances of discoveries of the disease were circumcision in the months following birth 69.23% (9/13) and bleeding from the gums 69.23% (9/13).

Abnormal bleeding following circumcision reported in subjects from non-hemophilic families were the results of poor surgical

practice; they were cured subsequently with appropriate medications in local hospitals.

3.6 Attitude and Practical Knowledge of Hemophilia Subjects

Only the families of the confirmed hemophiliac subjects had heard of hemophilia (9/17). Almost all of the patients with hemophilia in sick families consumed clotting factors only after trauma because of the difficulty of accessing treatment.

There were subjects from families with hemophilia who abstained from performing circumcision because of a history of death of the first children from heavy bleeding, that is to say 3 of 13 hemophiliacs or 23%.

Of the 9 families of hemophiliacs 8 were already known as families of hemophilia and were being followed; while 1 family had 4 boys (ages: 1 year 3 months, 3 years, 4 years and 9 years) who presented heavy and suspicious bleeding but did not know their status and were detected during this investigation. These 04 boys from the family who were unaware of their hemophilia status had to undergo circumcisions and presented heavy and prolonged bleeding, forcing the family to return to the hospital for treatment aimed at stopping the bleeding.

4. DISCUSSION

This study aimed at establishing the occurrence of hemophilia in the Western Cameroon region and some clinical characteristics of patients. Thirteen (13) cases of hemophilia out of 5995 people selected (0.22%) have been detected with a mean age of 14.85 (1.5-49). Previous studies in Cameroon, Ivory Coast, Senegal and South Africa also found a similar age [5,8,10,13,14]. The young age is usually the period of diagnosis of the disease. Moreover being a life-threatening disease in cases of high coagulation factor deficiency, most patients die and do not reach advanced ages [2].

The main report circumstances were bleeding during circumcision in the months following birth (69%), and traumatic wounds in the childhood. In 2017, Padaro et al. in Togo also found circumcision as the first circumstances of discovery of hemophilia [13]. However, the mean age of patients at diagnosis was higher than the age of onset of abnormal bleeding, suggesting the delay of subjects to attend the; which suggests that patients do not immediately go to a

hospitals, or the defect of the technical capacities of laboratories for an accurate diagnosis. Joint pain was the most common functional sign (46%); in contrary clinical signs were, joint swelling (38%). The study conducted in Togo by Padaro et al. in 2017 also showed that joint pain was the most common functional sign, and joint swelling was the most clinical sign [13]. Moreover, Catherine Lambert et al. report heavy bleeding after tooth extractions (4.9%), menorrhagia (31%), and surgery (4.9%) [12].

One third (1/3) of hemophiliac families presented with at least one hemophiliac brother; two thirds (2/3) of them had a familial history of hemophilia in the family represented by other relatives suggesting the detection of new cases of hemophilia in the last generation. Deaths were observed in families mainly during the ascendant generation during which grandparents performed traditional male circumcisions and observed deaths from unexplained causes. This information suggests that the hemophilia had long been ignored, thus considered as a "now-a-days disease". All cases of hemophilia reported in this study were male, owing to its recessive sex-related transmissibility, thus being rare in African women [10,13,15,16]. However, women carrying the abnormal gene may have a mild or moderate factor VIII or IX deficiency and may suffer from bleeding disorders, particularly gynecological or obstetric [16]. During the study, individuals with hemophilia were recruited from urban and rural areas of the 5 departments of the Western region. All presented with bleeding disorders.

The level of education of hemophiliac subjects reveals that 77% have a primary or secondary level. Any difference is not pointed out from children of the same age group in the general population [13,17,18]. Tayou et al. in 2014 showed a level of education between primary and secondary level. A family antecedents of hemophilia was common (up to 66% of cases) as in Senegal and in the study by Tayou et al. During the present study, male circumcision was the main diagnostic circumstance, followed by mucosal bleeding. Haemarthrosis and joint complications have been found in almost all patients as well as in studies conducted in other African countries (Ivory Coast, Western Cape, Senegal and South Africa) [10,13,17,18]. Biological analyzes carried out using the SOCIMED model AG04 coagulometer whose chronometric measurement principle is based on the use of ARM meaning to measure the speed

of the magnetic ball in order to calculate the coagulation time.

The main biological performed tests in this study the platelet count, the Prothrombin rate, the Cephalin + Activator Time and the Cephalin + Activator Time correction test. All patients listed had normal platelet counts and prothrombin levels; however, they exhibited a prolonged Cephalin + Activator Time which was corrected by supplying normal control plasma. Padaro et al. 2017 in Lomé, Togo also reported a normal Bleeding Time and Prothrombin rate as well as a prolonged Cephalin + Activator Time which corrected after adding normal control plasma. This can be explained by the fact that the TCA explores the intrinsic pathway of coagulation, including factors VIII, IX, XI and XII. The presence of the hemorrhagic syndrome characteristic of hemophilia allows us to rule out a factor XII deficiency. Moreover, the correction of coagulation after addition of normal control plasma leads us to conclude to factor VIII or IX [10,19] deficiency. This observation was also made by Johnny Mahlangu et al. in 2018 who report an extension of the Cephalin Time + activator.

At the end of the hemostasis tests, 13 cases (0.22% of our total study population) of hemophilia cases were identified; we have newly tracked 4 new cases. Most of cases came from Menoua 38% (including these 4 newly tracked), Bamboutos (31%), and Haut Nkam (3 cases); only 1 case were detected in the Mifi Department, while no case of hemophilia has been identified in the department of Ndé. This could be due to our small study population in Ndé and the short period of the study that prevent identification of more. Ignorance of hemophilia is high (80%) of the study population, owing to the traditional habits of the population to consult traditional practioners bleeding being perceived as of mysticism instead of consulting clinical practioners in hospitals who could educate them on hemophilia, the low financial conditions of the families and the lack of health insurance schemes in our country.

5. CONCLUSION

It appears that hemophilia is a reality in our country and in particular in the 05 departments of the Western region of Cameroon, with 0.22% found in this study which was conducted within a 04 months period. Sensitization and education of the population are mandatory. They would allow

to rise the index of suspicion of the disease and encourage genetic counseling and hemostatic tests in family and in prenuptial period in Cameroon.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

ETHICAL APPROVAL AND CONSENT

The study ethical clearance was obtained from the Institutional Ethics and Research Committee Board, Université des Montagnes, Authorization No. 2019/145 / UdM / PR / CIE. The study received local authorisation from 15 villages in 05 Departments of the Western Region including Mifi, Ndé, Menoua, Bamboutos and Haut Nkam in rural and urban areas. Before starting our study, an information letter on the objectives and progress of the investigation was given to each of participants. All eligible participants had given their free and informed consent and assent with signature of the participants. The confidentiality of the research results was respected by using a unique identification code for each participant.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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