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Haemostatic trends in HIV-infected individuals in Yaoundé, Cameroon: a pilot study

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Abstract

Bleeding disorders are haematological manifestations that are frequently observed during HIV infection. This study intends to describe the haemostatic trends in HIV-infected patients in Cameroon. This cross-sectional descriptive study was carried out at the haematology unit of the Yaoundé University Teaching Hospital from March to June 2012. It included consenting HIV-positive patients, aged 18 years and above, naive to antiretroviral treatment or not. The coagulation profile was measured with Stago reagents (Stago Diagnostics, Asnières sur Seine, France) using a chronometric technique on a semi-automate (Stago Diagnostics). Platelets count was estimated on a human count automate (Human diagnostic, Wiesbaden, Germany) by flow cytometry. A total of 139 HIV-infected patients were included in this study, out of which 106 were females (76.3%) against 33 (23.7%) males, giving a sex ratio of 0.3 (M/F). Mean age was 38.85 years (range 22–73 years) and median CD4 count was 353 cells/μl (Interquartile range 200–500 cells/μl).

Hyperfibrinogenaemia was the most frequent bleeding disorder in the studied population [40 of 139 (28.78%)], followed by low prothrombin time (PT) [22 of 139 (15.83%)], thrombocytopenia [19 of 139 (13.67%)], hypofibrinogenaemia [18 of 139 (12.95%)], prolonged activated partial thromboplastin time (7.91) and by thrombocytosis which was less frequent [6 of 139 (4.32%)].

Out of the six haemostatic disorders, only low PT was significantly associated with CD4 count ($P=0.02$). This study showed that bleeding disorders are very frequent in the HIV-infected patients studied. Low PT was significantly associated with CD4 count, hence it may be recommended to systematic screen for bleeding disorders in severe immune-depressed (CD4 < 200) HIV-infected patients.

Keywords

Africa; Cameroonian; disorders; haemostasis; HIV infection

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Conflicts of interest

There are no conflicts of interest.

Introduction

The HIV, which is responsible for the global AIDS pandemic, is more frequent in developing countries, where other endemic diseases already exist and represent public health problems. According to the World Health Organization, of the 34 million people infected by this virus in 2011, about two-thirds live in sub-Saharan Africa [1]. In Cameroon, the National AIDS Control Committee (NACC) estimated that 533 000 people lived with HIV in 2010, corresponding to a general prevalence of 5.1% [1,2]. The haematological manifestations frequently observed at every stage of HIV infection, from the primo infection to AIDS, are mainly anaemia, neutropenia, lymphopenia and thrombocytopenia [3]. Some authors reported abnormalities in haemostasis in the course of HIV infection, including Choi *et al.* [4] in Korea who reported a 2.4% prevalence of thrombocytopenia, Mannuci and Gringeri [5] in Italy who reported 5–15%, which is lower to that reported by Talom [6] in a study done in Mali in 2005. Toulon [7] in 1998 reported hyperfibrinogenaemia in the course of HIV infection, whereas Omoregie *et al.* [8] in Nigeria reported low prothrombin time (PT) and prolonged activated partial thromboplastin time (APTT) in HIV-infected individuals, and further proved that low PT was associated with very low CD4 counts. These abnormalities of haemostasis could lead to haemostatic disorders such as haemorrhage or thrombosis during HIV infection. Because of the almost inexistence of data and studies on haemostatic disorders in HIV infection in Central Africa, we hereby intend to set bases by describing haemostatic trends in people living with HIV in Cameroon.

Study design and methods

This cross-sectional descriptive study was carried out at the haematology unit of the Yaoundé University Teaching Hospital from March to June 2012. It included consenting HIV-infected patients, aged 18 years and above, on antiretroviral treatment or not. Those on anticoagulant or pro-coagulant treatment were excluded, and this study was approved by the Cameroon National Ethics Committee. Data collected from each participant included socio-demographic information, a past medical history of illnesses such as cancer, liver diseases, thrombosis, recent infections, immunological and virological evolution of HIV infection (last CD4 count and HIV viral load measurements) and treatment received [antiretroviral therapy (ART), aspirin, antivitamin K drugs, heparin and nonsteroid anti-inflammatory drugs], as well as a history of recent blood transfusions. From each participant, two samples of 5 ml of blood were collected into a tri-sodium citrate and ethylene diamine tetraacetate-containing tubes for coagulation screen (PT, APTT and plasma fibrinogen levels) and for platelets count, respectively. Coagulation profile was measured with Stago reagents (Stago Diagnostics, Asnières sur Seine, France) using a chronometric technique on an semi-automate (Start 4) from the same company, whereas platelets count was estimated on a Human count automate (Human diagnostic, Wiesbaden, Germany) by flow cytometry, following the manufacturer's instructions. Before each measurement, both normal and pathologic system controls were used to ensure the quality of results. Results were interpreted as normal values when PT=10–14 s, APTT=±7 s of the control value, platelet counts =150–450×10⁹/l, fibrinogen levels=2–4 g/l and CD4 counts=500–1000 cells/μl.

Immune depression was considered as severe, moderate or mild when CD4 count values were less than <200 cells/ μ l, 200–349 cells/ μ l or 350–499 cells/ μ l, respectively.

Data was analysed with STATA 11.0 statistical package (Stata Corporation, College Station, Texas, USA). Association between categorical variables (sex, age group, CD4 category and ART) and haemostatic parameters (platelet count, fibrinogen, PT and APTT) in contingency tables was tested by the Fisher's exact test and significance was set at the level of 0.05 (two sided).

Results

A total of 139 HIV-infected patients were included in this study, out of which 106 were females (76.3%) and 33 (23.7%) were males, giving a sex ratio of 0.3 (M/F). The mean age of the study population was 38.85 years (range 22–73 years). The 30–40 year age group was the most represented [57 of 139 (41%)]. A total of 6 out of 139 (4.3%) patients of the study population showed clinical signs of gum bleeds, epistaxis and a deep venous thrombosis. The median CD4 count was 353 cells/ μ l (interquartile range: 200–500 cells/ μ l). A total of 39 out of 139 (23.7%) patients were classified as having severe immunodepression, 34 of 139 (24.5%) as having moderate immunodepression and 33 of 139 (23.7%) as having mild immunodepression. A normal CD4 count was observed in 34 of 139 (24.5%) of the participants, and 5 of 139 (3.6%) were newly diagnosed who were not yet screened for CD4 count. In total, 29 out of 139 (20.9%) participants were treatment naive.

Out of the six bleeding abnormalities noted in the study population, hyperfibrinogenaemia was the most frequent [40 of 139 (28.8%), 95% confidence interval (CI) 21.42–37.06%], followed by low PT [22 of 139 (15.8%), 95% CI 10.20–22.98%], thrombocytopenia [19 of 139 (13.7%), 95% CI 8.43–20.52%], hypofibrinogenaemia [18 of 139 (12.9%), 95% CI 7.86–19.69%], prolonged APTT [11 of 139 (7.9%), 95% CI 4.02–13.72%] and thrombocytosis which was less frequent [6 of 139 (4.3%), 95% CI 1.60–9.16%] (Table 1). The association of independent factors with the bleeding disorders was analysed by the Fisher's exact test. Platelet count, fibrinogen and APTT were not associated with sex, age group, CD4 category or ART. Only CD4 count was found to be significantly ($P=0.02$) associated with low PT.

Discussion

The aim of this study was to establish the haemostatic trends of HIV-infected individuals in Cameroon.

Hyperfibrinogenaemia was observed in 28.8% of the patients. This finding is in accord with the several studies and confirms the existence of hyperfibrinogenaemia and an elevated C-reactive protein (CRP) during HIV infection [9]. This can be explained by the inflammatory reaction induced by the cytokines which are synthesised during HIV infection. This acute and permanent inflammatory state leads to the elevation of inflammatory markers. Inflammatory markers such as fibrinogen are considered by many authors as a risk factor for cardiovascular diseases, both in HIV-infected and in non-infected persons [10,11]. Hyperfibrinogenaemia was the most frequent of all the disorders, even though fibrinogen level showed no association with immunodepression. However, Toulon [7] reported a

correlation between hyperfibrinogenaemia and CD4 decrease, similarly to the findings of Omoregie *et al.* and Jason *et al.* [11,12]. Hyperfibrinogenaemia was more frequent in treatment-naïve patients (33.3%) than in those on ART (27.5%). It is possible that hyperfibrinogenaemia occurring during HIV infection could be associated with prothrombotic state, but its effects are limited by the antiretroviral treatment.

Hypofibrinogenaemia was observed in 12.9% of the study population, even though it has not been described by other authors in the course of HIV infection. This result may be explained by the liver's incapacity to fulfill its synthesis function, particularly the synthesis of inflammatory markers, in the case of severe immunodepression. Another possibility to explain this resides in one limitation of our study of not screening for hepatic C virus, hepatic B virus and other hepatic viruses co-infections which are not only very frequent in our setting, but also known to be strong contributors to liver damage. Drug toxicity is also a hypothesis, and further studies are necessary to elucidate the different causes of hypofibrinogenaemia in HIV infection.

A total of 15.8% of patients had low PT. This result could be explained by a potential co-infection with a hepatic virus or any liver disease in general. Indeed, from a study done by Toulon [7] in France, low PT was not found in HIV-positive patients without any liver disease. Low PT was significantly associated with CD4 count ($P=0.02$), and 30.3% of patients having low PT were severely immunodepressed. This high frequency of low PT associated with severe immunodepression was also observed by Omoregie *et al.* [8] in 2009. With the significant association of low PT with severe immunodepression, the hypothesis of a liver dysfunction which leads to its incapacity to ensure its synthesis function during severe immunodepression is reinforced. In case of a co-infection with a hepatic virus, the severe immunodepression can be an open access to its replication, resulting in the destruction of hepatocytes.

Thrombocytopenia was observed in 13.7% of the patients. It has been described during HIV infection and may occur through various mechanisms such as bone marrow destruction induced by viral toxicity, by ART or by immunological factors. In Cameroon, Mbanya *et al.* [13] in 2002 identified HIV as a cause of thrombocytopenia.

We reported prolonged APTT in 7.9% of our study population. This was also reported by Toulon [7] amongst people living with HIV. This abnormality may be due to the presence of circulating anticoagulants, which vary between 8 and 70% depending on the study. Taillan *et al.* [14], in a study with 157 HIV-positive patients, reported that 84 patients (53.5%) had circulating anticoagulants with or without opportunistic infections. Even though prolonged APTT was not significantly associated with CD4 count, one of its highest frequencies (15.1%) was observed amongst patients who had severe immunodepression. Omoregie *et al.* [8] also observed this high frequency amongst people with severe immunodepression.

Thrombocytosis had the lowest frequency amongst all the abnormalities related to haemostasis (4.3% in the study population) and could be because of the bone marrow regeneration. There was no association between thrombocytosis and the immunodepression status, or the type of antiretroviral treatment.

Conclusion

This study was limited first of all by the sample size, which is not adequate to draw conclusions at the national level, and by the nonscreening of hepatitis B and C co-infections which are very common in our setting, and are responsible for liver dysfunction, thus hindering some of our observations. Taking into account these limits, we concluded that haemostatic abnormalities are frequent in the HIV-infected patients studied, with hyperfibrinogenaemia, low PT and thrombocytopenia being the most frequent, and thrombocytosis the less frequent. Low PT was significantly associated with immunodepression. Hence, it may be recommended that systematic screening for parameters be introduced in severely immunodepressed people living with HIV.

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Table 1

Frequency (percentage) of haemostatic disorders and median CD4 counts in 139 HIV-infected patients

Haemostatic disorders	Frequency (percentage)	95% CI	Median CD4/ μ l (IQR)
Hyperfibrinogenaemia	40 (28.8)	21.42–37.06	346 (229–497)
Hypofibrinogenaemia	18 (12.9)	7.86–19.69	191 (111–374)
Thrombocytopenia	19 (13.7)	8.43–20.52	252 (141–563)
Thrombocytosis	6 (4.3)	1.60–9.16	368 (241–497)
Low PT	22 (15.8)	10.20–22.98	211 (141–522)
Prolonged APTT	11 (7.9)	4.02–13.72	201 (106–304)
Total	139 (100)	–	353 (200–500)

APTT, activated partial thromboplastin time; IQR, interquartile range; CI, confidence interval; PT, prothombin time.