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Characteristics of Venous Thrombo–Embolic Disease in People with and without HIV infection in Yaounde: A Cross-sectional Study

Caractéristiques de la maladie veineuse thromboembolique associée au VIH à Yaoundé : une étude transversale.

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RÉSUMÉ

Introduction. La maladie veineuse thromboembolique (MVTE) est un problème de santé publique de par le monde et surtout dans les pays à faibles et moyens revenus. A ceci, s'ajoute le lourd fardeau que représente l'infection par le VIH. Nous avons peu de données locales sur les caractéristiques de la MVTE associée au VIH. L'étude avait pour but de combler ce vide. **Méthodologie**. Entre janvier 2013 et juillet 2017, nous avons réalisé une étude transversale dans trois hôpitaux de références de la ville de Yaoundé. Nous avons revu rétrospectivement les dossiers des patients admis pour la MVTE. Nous avons recueilli des données sur le profil sociodémographique, la présentation clinique, les résultats des scanner thoracique et le doppler veineux des membres inférieurs de la population d'étude. **Résultats.** Nous avons inclus 73 patients (dont 32 hommes) atteints de MVTE. Leur âge moyen était de 53,4 ± 16,9 ans. 15 (20,5%) patients avaient une association de VIH et de MVTE. Comparativement aux patients séronégatifs, les sujets séropositifs étaient plus jeunes (p <0,001), de sexe masculin (OR : 3,3, [IC 95%: 0,9 - 10,8]), avaient moins de facteurs de risque de MVTE (p = 0,007), une pression systolique plus faible (p = 0,04), une fréquence respiratoire plus élevée (p = 0,04), un indice de masse corporelle plus bas (p = 0,02) et une localisation tronculaire sur un scanner pulmonaire (p = 0,03). La syncope était plus fréquente chez les personnes vivant avec le VIH et l'embolie pulmonaire (OR : 8,7, [IC à 95%: 0,7 - 104,2]). L'évolution à l'hôpital était favorable chez 64 (87,7%) patients. Des complications sont survenues chez 13 patients (17,8%). Les hémorragies (38,7%) et les infections nosocomiales (38,7%) étaient les complications les plus fréquentes. **Conclusion**. À Yaoundé, un patient atteint de MVTE sur cinq est infecté par le VIH. Par rapport aux séronégatives, les personnes séropositives sont moins âgées, ont moins ou une absence de facteurs de risque classiques de MVTE et une modification fréquente des paramètres hémodynamiques et anthropométriques. Par ailleurs, les localisations proximales semblent plus fréquentes. Il n'y a pas de différence significative dans la présentation clinique de la MVTE dans les deux groupes.

ABSTRACT

Background. Venous thromboembolic disease (VTE) is a public health problem worldwide, with a high burden in low-income settings. This is associated with a high burden of HIV infection. Local data on the characteristics of VTE associated with HIV are lacking. The aim of the study was to fill this gap. **Methods.** Between January 2013 and July 2017, we carried out a cross-sectional study in three hospitals in Yaounde. We retrospectively reviewed patients' records admitted for VTE. We collected data on socio-demography, clinical presentation, venous Doppler/pulmonary CT scan, and outcome. **Results.** We included 73 (32 males) patients with VTE. Their mean age was 53.4 ± 16.9 years. 15 (20.5%) patients had both HIV and VTE. Compared to HIV negative patients, those with HIV were younger (p<0.001), more likely to be males (OR: 3.3, [95% CI: 0.9 – 10.8]), had fewer risk factors for VTE (p=0.007), had lower systolic pressure (p=0.04), higher respiratory rate (p=0.04), lower body mass index (p=0.02), and troncular localization on pulmonary CT scan (p=0.03). Syncope was more frequent in people with HIV and Pulmonary Embolism (OR: 8.7, [95% CI: 0.7 – 104.2]). In-hospital evolution was favorable in 64 (87.7 %) patients. Complications occured in 13 (17.8 %) patients. Hemorrhages (38.7 %) and nosocomial infections (38.7 %) were the most frequent complications. **Conclusion.** In our setting, one in five patients with VTE is infected with HIV. These patients are younger, have fewer or an absence of classic risk factors of VTE, and a frequent modification of hemodynamic and anthropometric parameters. More over, proximal localizations seem more frequent in people with HIV. There is no significant difference in the clinical presentation of VTE in both groups.

INTRODUCTION

Venous Thrombo-Embolic disease (VTE) is a public health problem worldwide, affecting 78 to 137 million people yearly [1,2]. It is the third most common cardiovascular disease according to the World Health Organization [3]. Epidemiological data on VTE are heterogeneous, depending on diagnostic criteria and studied populations. The burden of VTE in low-income settings in sub-Saharan Africa (SSA) is not well known as data are scanty [4–10]. This is expected to be high due to the high burden of infection with the Human Immune Deficiency Virus (HIV), a known risk factor for VTE [11]. The prevalence of HIV was estimated at 4.3 % in 2014 in Cameroon [12]. Studies have shown an association of HIV with the occurrence of VTE. The pathogenesis involves the virus itself, the presence of opportunistic infections, and treatments used. The risk of VTE in HIV infected patient is increased by 2 to 10 times compared to HIV negative patients [13]. VTE in HIV patients is associated with some peculiarities such as younger age of onset, male predominance, and the increase risk with severe immunodepression [14]. Kingue et al. [15] reported a prevalence of 11.1% of HIV in patients with VTE in Cameroon, and Kane et al. [16] reported a prevalence of 10.3% in Senegal. Specific features of VTE in HIV infected patients is not known in our setting. This cross-sectional study aimed at characterizing the epidemiological, clinical, imaging, and outcome specificities of VTE in HIV infected and non-HIV infected patients in Yaounde.

METHODOLOGY

Study design and setting

This cross-sectional study was carried out in three teaching hospitals in Yaounde–Central Hospital, Jamot Hospital, and the University Teaching Hospital. These are tertiary hospitals in Yaounde, the capital city of Cameroon (SSA). They have a catchment population of about 2 million inhabitants.

Study population: We retrospectively recruited patients (clinical records) admitted for VTE between January 2013 and July 2017. We reviewed the clinical records of adult patients, aged ≥ 18 years, of both sex, admitted for VTE confirmed with Doppler ultrasound and/or pulmonary CT scan. Patients with incomplete files or files with missing key data were excluded.

Variables and Measurements

We collected data on socio-demography (age, sex, and profession), clinical presentation, venous Doppler/pulmonary CT scan, and outcome (survival versus death). Risk factors for VTE recorded were age ≥ 65 years, varicosity of the lower limbs, prolong rest/immobilsation (> 3 weeks), high adiposity (BMI > 25 Kg/m^2), pregnancy/early post-partum (< 6weeks), recent surgery, use of oral contraception in women, cancer, nephrotic syndrome, genetic thrombophilia, vascular trauma, anti-phospholipid syndrome, and chronic inflammatory diseases. We also recorded the associated co-morbidities: Chronic Obstructive Pulmonary Disease (COPD), Asthma, and confirmed HIV (positive Western blot). Doppler ultrasound of the lower limbs was performed in case of suspicion of Deep Vein Thrombosis (DVT). Positive echographic criteria included direct signs (direct visualization of endoluminal clot), and indirect signs (incompressibility with venous dilatation, upstream venous stasis, increased flow of collateral veins and alteration of venous flow). The localization and extension of thrombi were specified. Pulmonary CT scan was performed in case of suspected Pulmonary Embolism (PE) (clinical or echocardiographic). The diagnosis of PE included direct signs (direct visualization of endoluminal clot or defect), and indirect signs (oligemia, reduction in pulmonary arterial flow or vessel size). Intra-hospital evolution was recorded. It was of two types: favorable (improvement in clinical presentation and return at home) or unfavorable (PE occurrence in case of DVT, intensive care referral or death). Complications related to treatment and hospitalization were also recorded (bed sores, infections, bleeding).

Sample size and Statistical analysis

A consecutive sample of all eligible cases were considered for this study. Data were analyzed using the software IBM-SPSS 20. We have presented discrete variables as counts and percentages, and continuous variables as mean (standard deviation). We used Khi squared test, Student t-test, and ANOVA were appropriate. We calculated the odds for each parameter studied in those infected with HIV compared with those not infected with HIV. A p value < 0.05 was considered significant for the observed differences or associations.

Ethical consideration

This work was approved by the institutional review board of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde 1. Administrative authorization was obtained from the hospital administration. We carried out this work in accordance with the declarations of Helsinki. We report this work following the STROBE checklist.

RESULTS

Participants

A total of 73 cases of VTE were included, of which 32 (43.8%) were males, and 15 (20.5%) patients had HIV infection associated with VTE. Their mean age was 53.4 ± 17 years (HIV infected: 40 ± 8.5 years versus non-HIV infected: 56 years, p<0.001). The 40 to 59 years age group were the most frequent–33 (45.2%) patients. Ten males were infected with HIV, and had greater risk of having VTE (OR: 3.3, [95% CI: 0.9 - 10.8]).

Main data

Hypertension (30.1%) and diabetes (9.6%) were the most common comorbidities. The risk factors of VTE are presented in Table 1.

Table I: Comparison of VTE risk factors in both groups

Risks factors	Overall	HIV+,n (%)	HIV-, n (%)	OR (95% CI)	P value
Old age	21 (28.8)	0 (0)	21 (36.2)	7.4 (0.9– 60)	0.004
Immobility	34 (46.6)	5 (33.3)	29 (50)	0.5 (0.2 – 1.6)	0,24
Overweight/obesity	46 (63)	7 (46.7)	39 (67.2)	0,4 (0.1 – 1.4)	0.14
Varicose veins	2 (3.7)	0 (0)	2 (3.4)	1.3 (0.1-13)	1.0
Thrombosis past history	2 (2.7)	1 (6.7)	1 (1.7)	4.1 (0.2 – 69.2)	0.37
Puerperium	4 (5.5)	0 (0)	4 (6.9)	0.9 (0.1 – 9.3)	0.57
Surgery	4 (5.5)	0 (0)	4 (6.9)	0.9 (0.1 – 9.3)	0.57
Prior admission	16 (21.9)	1 (6.7)	15 (25.9)	0.2 (0.03 – 1.7)	0.16
Contraceptive use	3 (4.1)	1 (6.7)	2 (3.4)	2 (0.2 – 23.7)	0.5
Cancer	3 (4.1)	0 (0)	3 (5.2)	0.9 (0.1 – 9)	1.0
Long trip	15 (20.5)	5 (33.3)	10 (17.2)	2.4 (0.7 – 8.6)	0.28
Genetic thrombophilia	1 (1.4)	0 (0)	1 (1.7)	2 (0.2 – 23)	1.0
Chronic infectious and inflammatory diseases	9 (12.3)	3 (20)	6 (10.6)	2.2 (0.5 – 9.9)	0.38
No risk factor	3 (4.1)	3 (20)	0 (0)	20.7 (2.1 – 203)	0.007

Obesity/overweight (63%), immobilization (46.6%), prior admissions (21.9%), long trip (20.5%) were the most common risk factors. In those with HIV, older age was not a risk factor of VTE (p=0.004), and the absence of classic risk factor of VTE was common (p=0.007). People with HIV had a greater risk of VTE recurrence than non-HIV infected cases (OR: 4.1, [95% CI: 0.2 – 69.2]), and were more proned to have VTE during long trip (OR: 2.4: [95% CI: 0.7 – 8.6]), when having chronic infectious or inflammatory diseases (OR: 2.2, [95% CI: 0.5 –9.9]), or with oral contraceptive use (OR: 2, [95% CI: 0.2 – 23.7]). Reduced systolic blood pressure and BMI, and increase of respiratory rate were significantly higher in those with HIV (Table II).

Table II: Comparison of Mean (± SD) hemodynamic and anthropometric parameters between the two groups

Variables	Overall	HIV+	HIV-	P value
Systolic BP (Mean ± SD)	129.2 ± 23.3	118.5 ± 21.9	131.9 ± 23.01	0.04
Diastolic BP (Mean ± SD)	82.5 ± 14.3	81.8 ± 17.1	82.7 ± 13.6	0.82
Heart Rate (Mean ± SD)	97.03 ± 20.1	102.7 ± 18.3	95.6 ± 20.5	0.22
Respiratory rate (Mean ± SD)	24.2 ± 9.7	28.6 ± 8.5	23.1 ± 9.7	0.04
Temperature (Mean ± SD)	37.5 ± 9.7	37.2 ± 0.9	37.5 ± 0.8	0.17
SaO2 (Mean ± SD)	88.02 ± 9.1	87 ± 4.4	88.4 ± 10.4	0.65
BMI (Mean ± SD)	29.3 ± 5.5	26.5 ± 4.3	30.1 ± 5.6	0.02

Isolated DVT was found in 40 (54.8 %) patients, an isolated PE in 23 (31.5 %) patients, and an association DVT + PE in 10 (13.7 %) patients. Among people with HIV, 8 had isolated DVT, 4 isolated PE and 3 DVT+PE. DVT was located in the left lower limb, right lower limb and bilaterally in 24 (48 %), 23 (46 %) and 3 (6 %) patients respectively. There was no difference in the clinical presentation of DVT between people with HIV and HIV non-infected patients (Table III).

Table III: Comparison of clinical signs between both groups

Variables	Overall	HIV+,n (%)	HIV-,n (%)	OR (IC at 95%)	P value
DVT signs					
Limb pain	47 (34.4)	11 (73.3)	36 (62.1)	1.7 (0.5 – 5.9)	0.42
Calf stiffness	44 (60.3)	11 (73.3)	33 (56.9)	2.1 (0.6 – 7.3)	0.25
Limb volume > 3 cm	42 (57.5)	10 (66.7)	32 (55.2)	1.6 (0.5 – 5.4)	0.24
Homans sign	34 (46.6)	9 (60)	25 (43.1)	1.9 (0.6 – 6.3)	0.24
PE signs					
Dyspnea	34 (100)	11 (73.3)	23 (62.1)	1.7 (0.5 – 5.9)	0.42
Chest pain	23 (67.6)	5 (71.4)	18 (66.7)	1.3 (0.2 – 7.8)	0.81
Faintness	3 (8.9)	1 (14.3)	2 (7.3)	4.3 (0.2 – 79.6)	0.37
Syncope	3 (8.9)	2 (28.5)	1 (3.7)	8.7 (0.7 – 104.2)	0.1
Cough	15 (44.1)	4 (57.1)	11 (40.7)	1.9 (0.4 – 10.4)	0.67
Hemoptysis	9 (26.5)	2 (28.6)	7 (25.9)	1.1 (0.2 – 7.3)	1.0
Tachypnea	29 (85.3)	6 (85.7)	23 (85.2)	1.04 (0.09 – 11.1)	1.0
Tachycardia	23 (67.6)	4 (57.1)	19 (70.4)	0.6 (0.1 – 3.1)	0.66
Localisation					
Left Lower Limb	24 (32.9)	6 (40)	18 (31)	1.5 (0.5 – 4.8)	0.55
Right Lower Limb	23 (34.5)	6 (40)	17 (29.3)	1.6 (0.5 – 5.2)	0.54
Both lower limbs	3 (4.1)	0 (0)	3 (5.2)	0.9 (0.1 – 9.3)	1.0

Distal extension (OR: 3.8, [95% CI: 0.2 – 66.2]), and iliac localization (OR: 3.5, [95% CI: 0.9–13.9]) of clot were not significantly more frequent on Doppler ultrasound in people with HIV having a DVT (Table IV). Syncope (OR: 8.7, [95%

CI: 0.7–104.2]) was not significantly more frequent in people with HIV having PE. Troncular lesions on the chest CT scan were significantly predominant in people with HIV having PE compared to those not infected (p=0.027), and there was no statistically significant difference as regards to lobar lesions on the CT scan (OR: 3, [95% CI: 0.5 – 16.6]) (Table IV).

Table IV: Doppler Ultrasound and pulmonary CTA scan comparison between both groups

Variables	Overall	HIV+,n(%)	HIV-,n(%)	OR (95% CI)	P value
Extension Doppler US (n = 50)					
Distal	2 (4)	1 (9.1)	1 (2.6)	3.8 (0.2 – 66.2)	0.4
Proximal	30 (60)	5 (45.5)	25 (64.1)	0.5 (0.1 – 1.8)	0.31
Extensive	18 (36)	5 (45.5)	13 (33.3)	1.7 (0.4 – 6.5)	0.49
Localization (n = 50)					
Soleal	7 (14)	2 (18.2)	5 (12.8)	1.5 (0.3 – 9.1)	0.64
Tibial	16 (32)	4 (36.4)	12 (30.8)	1.3 (0.3 – 5.2)	0.73
Fibular	8 (16)	2 (18.2)	6 (15.4)	1.2 (0.2 – 7.1)	1.0
Popliteal	39 (78)	8 (72.7)	31 (79.5)	0.7 (0.1 – 3.2)	0.69
Femoral	39 (78)	8 (72.7)	31 (79.5)	0.7 (0.1 – 3.2)	0.69
Iliac	16 (32)	6 (54.5)	10 (25.6)	3.5 (0.9 – 13.9)	0.14
Inferior Vena Cava	2 (4)	0 (0)	2 (5.1)	1.3 (0.12 – 13.5)	1.0
Site on the CT scan (n=33)					
Unilateral	14 (42.4)	1 (14.3)	13 (50)	0.2 (0.02 – 1.6)	0.2
Bilateral	19 (57.6)	6 (85.7)	13 (50)		
Localisation on CT scan (n=33)					
Troncular	11 (33.3)	5 (71.4)	6 (23.1)	8.3 (1.3- 54.4)	0.03
Lobar	12 (36.4)	4 (57.1)	8 (30.8)	3 (0.5 – 16.6)	0.38
Segmental	23 (69.7)	3 (42.9)	20 (76.9)	0.2 (0.04 – 1.3)	0.16
Sub Segmental	10 (30.3)	0 (0)	10 (38.5)	0.3 (0.03 – 2.57)	0.07

Most of the patients (61.6 %) were treated with anti-vitamin K (acenocoumarol and fluindione), 34.2 % with Rivaroxaban, and 4.2 % didn't receive any anticoagulant therapy. People with HIV having VTE were more likely to be treated with Rivaroxaban (p=0.02). Two third of people with HIV were on highly active antiretroviral therapy (HAART) at the time of VTE diagnosis. Mean duration of HAART was 59 ±3.2 months. All treatments were first line regimen. Mean CD4 count was 352 ± 308 cells/mm³ (range: 17 to 989 cells/mm³.

Intra-hospital evolution was favorable in 64 (87.7 %) patients. Complications occured in 13 (17.8 %) cases. Hemorrhages (38.7 %) and nosocomial infections (38.7 %) were the most frequent complications. There was no significant difference on the evolution in both groups. However, favorable evolution was more frequent in people with HIV (OR: 2.2, [95% CI: 0.25–19.4]), and hemorrhagic complications were rarer (OR: 0.8, [95% CI: 0.05–11.3]) (Table V).

Tableau V: Comparison of disease course and complications

Variables	Overall	HIV+,n (%)	HIV-,n (%)	OR (95% CI)	P value
Complications	13 (17.8)	3 (20)	10 (17.2)	1.2 (0.3 – 5.04)	0.72
Nosocomial infections	5 (38.5)	2 (66.7)	3 (30)	4.6 (0.3 – 73.4)	0.51
Hemorraghes	5 (38.5)	1 (33.3)	4 (40)	0.8 (0.05 – 11.3)	1.0
Bed sores	3 (23.1)	0 (0)	3 (30)	0.9 (0.1 – 9)	1.0
PE	1 (7.7)	0 (0)	1 (10)	2 (0.1 – 23)	1.0
Evolution					
Unfavorable	9 (12.3)	1 (6.7)	8 (13.8)	0.4 (0.05 – 3.9)	0.68
Favorable	64 (87.7)	14 (93.3)	50 (86.2)		

DISCUSSION

VTE is still poorly known in Africa. Few studies, especially on the prevalence and risk factors have been carried out [4–7,10,16]. HIV infection associated with the occurrence of VTE has been shown for a long time [13]. However, the prevalence HIV infection in VTE is unknown in Africa, and Cameroon in particular [7,9,16–18].

This study has some limitations due to the retrospective design. Many files of patients with probable VTE were not found, and data were missing for some patients. HIV serology was not routinely proposed to all patients with VTE. Due to the small number of HIV-positive patients, some comparisons including ECG and echocardiography findings could not be performed.

HIV infection increases the risk of vascular (arterial and venous) diseases occurrence. VTE incidence is increased by 2 to 10 times during HIV infection [13]. The prevalence of HIV infection was 20.5 % in patients with VTE. This is comparable to 19% reported by Tonye et al. [7] in a semi urban area in Cameroon, but lower

than the 45% reported by Zabsonre et al. [17] in Burkina Faso, and the 51.9% reported by Awolesi et al. [18] in South Africa. This could be explained by increase HIV testing among VTE patients, and higher national HIV prevalence respectively.

Most studies of VTE in people with HIV reported an early occurrence of disease, with an age of onset around 40 years [16,19,20], similar to our findings. This could be related to premature cell ageing linked to HIV. VTE risk occurrence was more frequent in males with HIV.

We found that the absence of classic risk factors of VTE was more frequent in people with HIV having VTE, and older age was not a risk factor of VTE in this group. This was similar to that reported by Bibas et al. [13]. VTE recurrence could be more frequent in people with HIV than others. This is consistent with that reported by Sullivan et al. [21] HIV is associated with pro-thrombotic status. Prior admission was not a VTE risk factor in people with HIV contrary to that reported by Awolesi et al. [17], Sullivan et al. [21], and Ahonkai et al. [22]. This is probably due to the fact that all the people with HIV were recruited in hospital, unlike those in these studies.

Modifications of hemodynamic and anthropometric parameters were found in people with HIV. These were reduced systolic blood pressure and BMI, and increased respiratory rate (Table II). Reduced systolic blood pressure in people with HIV having VTE could be related to their young age, and the low rate of hypertension in this group. Increased respiratory rate and low BMI could be linked to chronic infections in this group (HIV and tuberculosis). Similar to that reported by Kane et al. [16], there was no significant difference in the clinical presentation of DVT and PE between people with HIV and HIV non infected patients [16]. PE and tuberculosis were more frequent in people with HIV.

The significant predominance of troncular lesions as opposed to lobar lesions of PE on pulmonary CT scan in people with HIV could be linked to the non significantly predominant iliac localization of DVT in those patients.

People with HIV were more frequently treated with Rivaroxaban than non HIV patients. A favorable course was common in this group. This course of disease could be related to the fact that people with HIV were younger, and did not have any other comorbidities than infections. Hemorrhagic complications were rare in people with HIV on anticoagulant therapy.

CONCLUSION

This study is the first of its type in Cameroon. We showed that HIV infection is frequent in patients with VTE. People with HIV were younger, had less or an absence of classic risk factors of VTE, and a frequent modification of hemodynamic and anthropometric parameters. There was no significant difference in the clinical presentation of VTE in both groups. The iliac, lobar and troncular localizations were more frequent in people with HIV. Due to the high prevalence of HIV infection among VTE patients, there is a need to conduct prospective studies to better assess biological mechanisms of HIV associated VTE.

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