Research in Health Science
ISSN 2470-6205 (Print) ISSN 2470-6213 (Online)
Vol. 4, No. 1, 2019
www.scholink.org/ojs/index.php/rhs

Original Paper

Human Immunodeficiency Virus Nephropathy in Central Africa: The Value of Renal Ultrasound

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Received: February 8, 2019 Accepted: February 19, 2019 Online Published: February 27, 2019

doi:10.22158/rhs.v4n1p54 URL: http://dx.doi.org/10.22158/rhs.v4n1p54

Abstract

Introduction: *HIV-Associated Nephropathy may shorten the life expectancy of affected patients. Its early detection is beneficial for the indication of treatment and hence prevention of progression to the end-stage of renal failure. The final diagnosis requires renal biopsy which may be difficult in some African area; clinical and ultrasound criteria may be helpful. The aim of this study was twofold: to characterize renal sonographic changes in HIV-positive patients with HIV associated Nephropathy and to investigate the correlation between renal sonographic changes and histological lesions in central Africa.*

Methods: *A prospective and multi-center study conducted from January 2013 to July 2015 included, for renal ultrasound evaluation of the length, thickness and echogenicity, forty two of the 334 biologically confirmed HIV-positive patients who presented with significant proteinuria suggestive of HIV associated Nephropathy. And transcutaneous renal biopsy with histopathology has been performed in 16 patients of them. Statistical analyzes were used.*

Results: *There were 100 men and 234 women; proteinuria was positive in 42 patients, (12.6%). The average length of the kidneys was 111 ±8 mm (normal), with 10% of patients with pathological values (5% with kidneys of reduced size and 5%, increased size). The kidneys had an average thickness of 44 ±5 mm (normal), with 21% of patients presenting an increase in renal thickness. Quantitative echogenicity was calculated at 1.492 ±0.793 (normal), with 79% of patients with increased quantitative echogenicity. Of the 16 patients biopsied, all had tubulo-interstitial lesions, and 75% of them associated with glomerular lesions. In simple correlation analysis, tubular dilatation was positively and significantly related to quantitative echogenicity (r = 0.67, p < 0.01) and to renal parenchyma thickness (r = 0.67; 0.85, p ≤ 0.05). The relationship between the other parameters studied did not reach statistical significance. In multiple linear regression, glomerular hyalinosis, glomerular proliferation, tubular dilatation, tubular atrophy, interstitial fibrosis, and interstitial inflammation emerged as the main determinants of quantitative echogenicity; however, the relationship was statistically significant only for tubular dilatation (β = 0.305, p = 0.034).*

Conclusion: *The present study showed the characteristic of renal change and the relation with histology found in central Africans patients.*

Keywords

HIVAN, ultrasound, histopathology, correlation

1. Introduction

Human Immunodeficiency Virus associated Nephropathy (HIVAN), resulting from direct infection of kidney cells, is the clinical form of chronic kidney disease most encountered in HIV Infection/AIDS (Sumaili et al., 2009; Longo et al., 2012; Ikpeme, Ekrikpo, Akpan, & Ekaidem, 2012). It was first described in the HIV epidemic in U.S. urban centers serving large numbers of HIV-positive persons of African descent (Rednor & Ross, 2018). Kidney disease, which is a common complication of HIV infection and its treatment (Ross, 2014), may shorten the lifespan of affected patients. Its early detection may be beneficial for the indication of treatment and hence prevention of progression to the end-stage renal failure requiring dialyze (Ikpeme, Ekrikpo, Akpan, & Ekaidem, 2012; Husain et al., 2018). Although the kidney biopsy remains the gold standard to make the definitive diagnosis (Waheed & Atta, 2014), it is often not performed in many regions of sub-Saharan Africa (Wearne & Okpechi, 2016). And clinical criteria such as proteinuria, laboratory characteristics such as Apolipoproetin-1 genetic polymorphism and sonographic changes are the predictors of the disease (Ikpeme, Ekrikpo, Akpan, & Ekaidem, 2012; Wearne & Okpechi, 2016).

Ultrasonographically, HIVAN is known as an increased echogenicity of normal or enlarged kidney size (N'Gbesso, Vakou, & Keita, 1998; Wyatt, 2008). Studies concerning central African's patients are lacking. Thus, the aim of this study was twofold: to characterize renal sonographic changes in HIV-positive patients with HIVAN and to investigate the correlation between renal sonographic changes and histological lesions in this part of Africa.

2. Patients and Methods

This is a prospective and multi-centric study conducted in Kinshasa, central Africa, from January 2013 to July 2015 which included, for renal ultrasound evaluation, forty two of the 334 biologically confirmed HIV-positive patients who presented with significant proteinuria suggestive of HIVAN. The latter was histopathologically confirmed in only 16 patients who underwent transcutaneous conclusive renal biopsy. HIV/AIDS infection has been classified with reference to the clinical stages of the World Health Organization (WHO). Patients with clinical, biological and/or ultrasonographic manifestations of conditions causing renal damage (primary glomerulopathy, sickle cell disease, liver disease, urological pathology) or risk factors for chronic renal disease (hypertension, diabetes, chronic use of nephrotoxic drugs secure or not) were not included in the study.

The proteinuria of the 24 hours was determined according to the method of Esbach (Oian & Stokkle, 1981). Ultrasonographic examination of the kidneys was performed by two experimented sonologists to access renal length between 85 and 120mm, thickness of 30 and 45mm (Figure 1) (Agboton, Yepke, Vigan, Gandji, Kloussa, Aguemon, ... Boco, 2014; Moghazi, Jones, Schroepple, Kraisith, Mc Clellan, Hennigar, & O'Neill, 2005) and echogenicity by densitometric method (Manley & O'Neill, 2001). One ultrasound machine (Siemens Sonoline Antares, Mountain View, CA, USA, 2004) equipped with a 3.5 MHz curved probe was used. A consensus was used to solve disagreements. The study was approved by the ethics committee of our hospital.

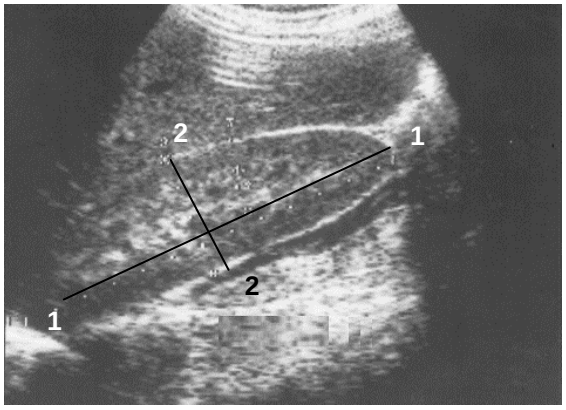

Figure 1. The Length or Bipolar Axis is the Maximum Longitudinal Dimension (1); the Thickness is the Greatest Distance Taken on an Axis Perpendicular to the Middle of the Bipolar Diameter (2)

The images previously printed on thermal paper and scanned were each converted into a digital file with a capacity of 8 bits, the size of 300 pixels and stored on the format tag in the software Photoshop CS2 version 9.0. The computerized processing of each image used Scion Corporation's Scion image software. For each image (Figure 2), a first surface was delineated in the renal cortex between two medullar pyramids and less than 7 mm from the renal capsule; this allowed the measurement of the average cortex pixel density (DPM cortex). A second surface, delimited at the level of the liver at the same distance from

the probe as the third without the interposition of costal acoustic shadows, portal vessels and bile ducts, had made it possible to measure the average pixel density of the liver (DMP liver). A small area in the black region was located outside the acoustic field of the image; this one allowed to determine the maximum density of pixel (DPMax). Finally, a small area was delimited in the white margin of the image surrounding the print; it allowed to determine the minimum pixel density (DPMin).The difference between DPMax and DPMin was the range of available densities (GDD) for each image. At the two DMPs (liver and cortex) of each image, the DPMin was subtracted to have the net pixel density (DNP) which was then divided by the GDD to obtain the partial pixel density of the renal cortex (DPP cortex) and the liver (DPP liver). The ratio between DPP renal cortex and DPP of the liver gave an arithmetic value, the reverse of which represented the value of the echogenicity of the renal cortex. Values between 0.810 and 0.987 were considered normal values; therefore, values above the maximum values were considered increased (Manley & O'Neill, 2001).

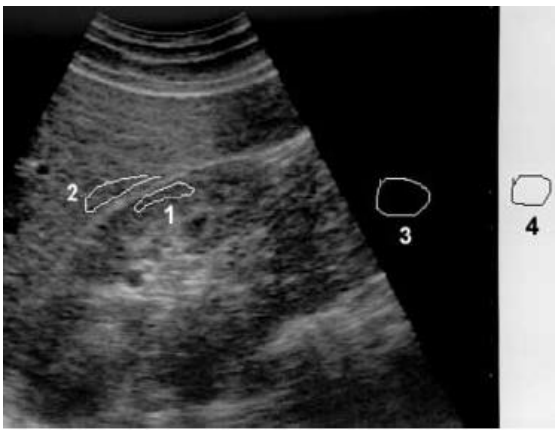

Figure 2. Measurement of the Different Optical Densities of the Pixels; the Areas of Interest of the Renal Cortex (1), the Adjacent Liver (2), the Black Band Outside the Acoustic Field (3) and the White Band Surrounding the Print (4) were Respectively Delimited: According to John A. Manley & W. Charles O'Neill

A second method based essentially on the expertise of the human eye described by Hricak et al. (1982) compares the echogenicity of the renal cortex with that of the liver or spleen and proposes a stratified classification of 0 to 3 (Figure 3), depending on whether the echogenicity of the renal cortex is lower (stage 0), equal (stage 1), higher with preservation of corticomedullary differentiation (stage 2) than that of liver and spleen and finally equal to the renal sinus with loss of corticomedullary differentiation (stage 3). This classification, according to the authors can allow the appreciation of the degree of the renal insufficiency from the echographic point of view.

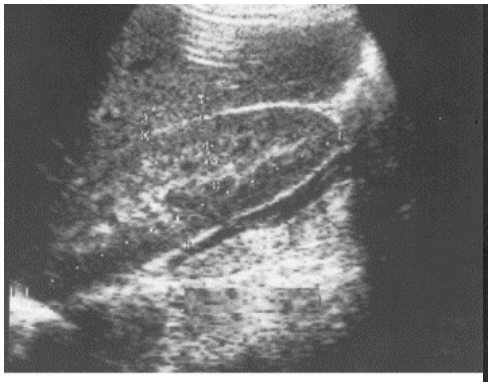

Figure 3a. Corresponding to Stade 0

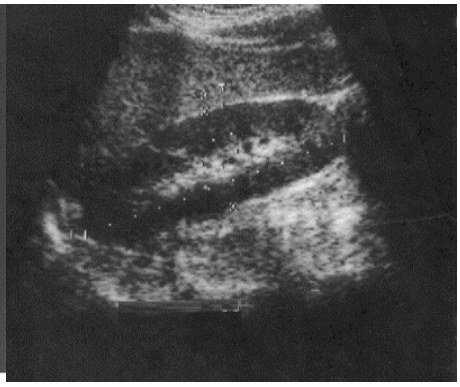

Figure 3b. Corresponding to Stade 1

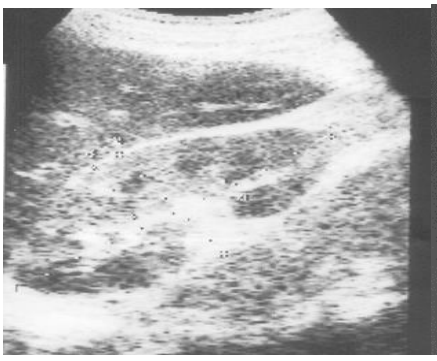

Figure 3c. Corresponding to Stade 2

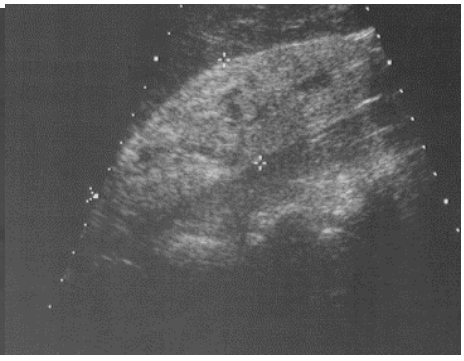

Figure 3d. Corresponding to Stade 3

Biopsy punctures of the right kidney were made after completion of the pre-biopsy stitches, the appropriate material being lacking.

For the histopathological examination of renal biopsy specimens, the reading was based on the search for 6 histological lesions: Glomerular lesion (glomerular hyalinosis, glomerular cell proliferation,) and tubule-ntertitiel leion (cystic dilation of the tubes, tubular atrophy, interstitial inflammation and interstitial fibrosis). Each histological lesion was evaluated according to a severity score ranging from 0 to 2 for respectively endocapillary proliferation and hyalinosis and from 0 to 3 for the rest of histological lesions. The severity scores of the different lesions were classified as follows : glomerular cell proliferation (score 0: absent, score 1: mesangial or endocapillary, score 2: mesangial and endocapillary), glomerular hyalinosis (score 0: absent, score 1: segmental and focal, score 2: segmental and diffuse), inflammation and interstitial fibrosis, tubular atrophy (score 0: absent, score 1: slight, ie less than 30% of the renal parenchyma, score 2: moderate 30-60% of renal parenchyma, score 3: severe 70% to 100% renal parenchyma). At the end, the following gradation of lesions based on the severity of the different histological lesions was established on a scale of 1 to 3: grade 1 or mild lesions (score 3, 4 and 5), grade 2 or moderate lesions (score 6 and 7) and grade 3 or severe lesions (score> 7) (Moghazi, Jones, Schroepple, Kraisith, Mc Clellan, Hennigar, & O'Neill, 2005).

To access the objectives of the study, statistical analyzes were performed using Statistical Package for Social Sciences software, version 21.0. The comparison of the proportions was made using the Chi

square test or Fischer exact as the case may be. The relationship between renal echogenicity and histopathological parameters was investigated using Spearman's simple correlation and multiple linear regressions. p <0.05 defined the level of statistical significance.

3. Results

During a period of 7 months, proteinuria was sought in 334 HIV positive patients including 100 men and 234 women; it was positive in 42 patients, a frequency of 12.6%. The demographic, clinical and laboratory characteristics of the study population are summarized in Figure 4 and Table 1.

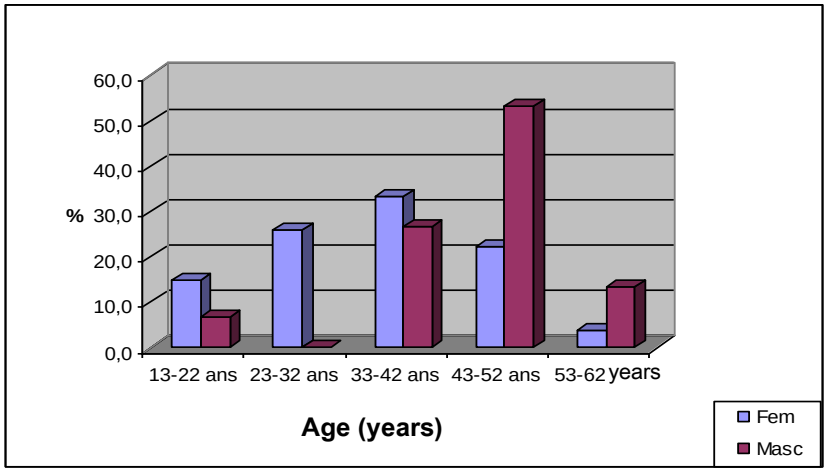

Figure 4. Distribution of Patients by Age and Gender

Table 1. Clinico-biological Characteristics of Patients in the Study

Variables	Total	M	F
N	42	15	27
Age (years)	39 ±13	45 ±12	35 ±12*
Stages HIV infection (WHO)			
Stage 1 (%)	*16*	*2*	*14*
Stage 2 (%)	*36*	*12*	*24*
Stage 3 (%)	*41*	*17*	*24*
Stage 4 (%)	*7*	*5*	*2*
Protéinuria (g/24h) †	0,5(0,3-3)	0,8(0,3-4)	0,5(0,3-3)
- *Moderate* (%)	*76*	*26*	*50*
- *Massive* (%)	*24*	*10*	*14*

Data expressed as mean ± standard deviation or relative frequency.

† Data expressed as median (interquartile space).

*****p≤0,05; ******p≤0,01; *******p≤0,001.

With reference to the classification of the World Health Organization (WHO), patients were distributed in all stages of HIV infection with the majority in stage 3.

Table 2 presents the renal ultrasound parameters of the patients.

Table 2. Ultrasound Characteristics of Patients in the Study

Variables	All	M	F
N	42	15	27
Biométry			
Lenght (mm)	106 ±11	106 ±10	106 ±11
-Normal	90	28	62
- Decreased (%)	*5*	*2*	*3*
- Increased (%)	*5*	*5*	*0*
Thichness (mm)	42 ±5	41 ±4	43 ±5
-Normal	71	24	47
- Decreased %)	*8*	*6*	*2*
- Increased (%)	*21*	*14*	*7*
Quantitative echogenicity	1,790 ±0,490	1,689 ±1,108	1,382 ±0,543
Normal	21	09	12
Increased (%)	*79*	*26*	*53*

Data expressed as mean ± standard deviation or relative frequency.

*****p≤0,05; ******p≤0,01; *******p≤0,001.

The average length of the kidneys was measured at 111 ± 8 mm with 10% of patients with pathological values (5% with kidneys of reduced size and 5%, increased size).

The kidneys had an average thickness of 44 ± 5 mm with 21% of patients presenting an increase in renal thickness.

Quantitative echogenicity was calculated at 1.492 ± 0.793 with 79% of patients with increased quantitative echogenicity.

Of the 42 programmed renal biopsies, only 24 have been performed, including 8 inconclusive biopsies.

The histopathological lesions and their degree of severity in the subgroup of patients who underwent transcutaneous renal biopsy are summarized in Table 3. Of the 16 patients biopsied, all have tubulo-interstitial lesions, and 75% of them had also with glomerular lesions.

Table 3. Histopathological Data of Patients with HIVAN (N = 16)

	Hyalinosis	Prolif ération	Dilation	Atrophy	Fibrosis	Inflammation
Median	0,50	0	2	2	1	2
IQS	0-1,75	0-1	0,25-3	0-2	0-2	2-3
Average	0,75	0,38	1,69	1,25	1,06	2,31
Score 0(%)	50	56	25	31	31	0
Score 1(%)	25	25	13	13	38	12
Score 2(%)	25	19	31	56	25	44
Score 3(%)	--	--	31	0	6	44

Data expressed as median scores and interquartile space or relative frequencies.

The lesions were moderate to severe for interstitial inflammation (88%), cystic dilatation of the tubes (62%) and tubular atrophy (56%) whereas they were minor for hyalinosis (25%), proliferation cellular (25%) and interstitial fibrosis (38%); all lesions were grade 2 and 3 (88%)

Table 4 presents the simple correlation coefficients between medians of histological lesion scores and renal ultrasound parameters in the subgroup of patients who underwent transcutaneous renal biopsy. In simple correlation analysis, tubular dilatation was positively and significantly related to quantitative echogenicity ($r = 0.67$, $p < 0.01$) (Figure 2) and renal parenchyma thickness ($r = 0.67$; 0.85, $p \leq 0.05$). The relationship between the other parameters studied did not reach statistical significance.

Table 4. Spearman (r) Correlation Coefficients for the Relationship between Medians of Histological Data Scores and Ultrasound Data of HIVAN-infected Patients (N = 16)

Parameters	Length Kidneys	Thickness kidney	Quantitative echogenicity
Hyalinosis	0,096	-0,153	-0,358
Prolif ération	0,084	0,056	0,084
Dilation	0,057	0,176	0,674**
Atrophy	0,150	-0,104	0,101
Fibrosis	0,133	-0,167	0,113
Inflammation	-0,225	-0,103	0,042

*****p≤0,05; ******p≤0,01; *******p≤0,001.

In multiple linear regression (Table 5 and Figure 5), glomerular hyalinosis, glomerular proliferation, tubular dilatation, tubular atrophy, interstitial fibrosis, and interstitial inflammation emerged as the main determinants of quantitative echogenicity; however, the relationship was statistically significant only for tubular dilatation ($\beta = 0.305$, $p = 0.034$).

Table 5. Histological Determinants of Quantitative Echogenicity in Multiple Linear Regression Analysis for Patients with HIVAN (N = 16)

	Bêta	Standard Error	P value
Constant	*1,147*	*0,455*	*0,033*
Hyalinosis	*-0,236*	*0,216*	*0,303*
Prolifération	*0,135*	*0,219*	*0,553*
Dilation	*0,305*	*0,122*	*0,034*
Atrophy	*0,169*	*0,127*	*0,216*
Fibrosis	*0,188*	*0,191*	*0,352*
Inflammation	*-0,185*	*0,167*	*0,295*

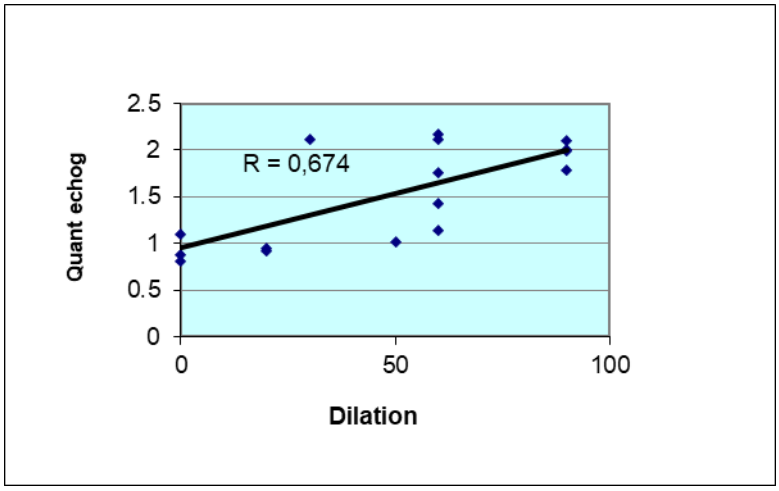

Figure 5. Relationship between Quantitative Echogenicity and Tube Dilation of HIVAN Patients

Therefore, all increase of one unity for cystic dilatation of the tubes increase the quantitative echogenicity of the renal cortex by 0.305.

Table 6 shows histological lesions between kidneys with normal echogenicity and those with increased echogenicity for patients with HIVAN. When comparing the two subgroups of patients, tubular dilatation emerges as the only discriminating factor with a predominance of this lesion in patients in whom cortical echogenicity is increased ($p \leq 0.01$).

Table 6. Median Histology Scores Compared between Kidneys with Normal Echogenicity and Those with Increased Echogenicity for Patients with HIVAN

Histological lesion	Both groups	Normal echogenicity	Increased echogenicity
N	16	4	12
Hyalinosis	0,5 (0-1,75)	2 (0,5-2)	0 (0-1)
Prolif ération	0 (0-1)	0,5 (0-1)	0 (0-1)
Dilation	2 (0,25-3)	0 (0-0,75)	2 (2-3) **
Atrophy	2 (0-2)	1,5 (0,25-2)	2 (0-2)
Fibrosis	1 (0-2)	1(0,25-1)	1 (0-2)
Inflammation	2 (2-3)	2 (1,25-2,75)	2,5 (2-3)
Extended	0-100		

4. Discussion

In this study conducted in central Africa, the prevalence of HIVAN was 12.6%. Fifteen patients were male (36%) and 27 female (64%). The average age was 39years old, with extremes ranging from 13 to 62 years and with reference to the classification of the WHO, patients were distributed in all stages of HIV infection with the majority in stage 3. This observation is consistent with the data from the literature that report late detection of HIV infection in sub-Saharan Africa with or without renal impairment (Valeriane Leroy, 2004). It is also known that the majority of AIDS cases in Africa are in the age range between 20 and 49 years old with a female predominance (Valeriane Leroy, 2004). The predominance of women may be explained by women's greater vulnerability to HIV, and this vulnerability is due to biological, socio-cultural a socio-economic determinants.

The present study found that the majority of patients with HIVAN (90%) had normal size kidneys. The size of the kidneys in HIVAN remains controversial. The observation of a high frequency of normal sized kidneys in the present study is at odds with that made in 2012 by Ulu et al. in Nigeria (Ulu, Agbaji, & Agwu, 2012) who reported a significant negative correlation between kidney size and degree of immunodepression ($p < 0.01$) as well as age ($p < 0.01$) in 302 patients. These authors concluded that the size of the kidneys in HIVAN increased with the decrease of the CD4 level; the CD4 count was not taken into account in our study.

Our observation corroborates that of Adeyekun et al. (2011) in Nigeria. They founded in 2011 in 120 patients, despite high immunodepression (63.8% of patients with a CD4 + count <200 cells / mm3), a normal size kidney with a frequency of 85%; kidneys of small size and increased size were observed, respectively, in 7% and 8% of patients. They concluded that kidney size, taken alone, was not a useful predictor of renal involvement in HIV/AIDS infection. A high incidence of normal size kidneys (74.38%) has also been reported by Agoda-Koussema et al. (2011) in Togo in 281 patients. The disparity observed in kidney size between studies can be explained by differences in the selection of

patients (patient age, degree of immunodepression, proteinuria, comorbidities and treatments received). In our series, the selection was done consecutively with regard to clinical of renal impairement.

Twenty percent of patients had increased renal thickness; this result is in agreement with American observations realized in 1999 (Di Fiori, Rodrigue, Kaptein, & Ralls, 1998) and Ivorian in 1998 (N'Gbesso, Vakou, & Keita, 1998). In the Ivorian study, 71% of patients had kidneys with increased thickness; these authors thought that this morphological alteration would be very suggestive of HIVAN. In the US study, 7 HIV-positive patients were followed longitudinally and, in the long term, 3 patients had enlarged kidneys that the authors described as "globular kidneys". This morphological alteration could be related to the aforementioned factors related to renal length.

In contrast to kidney size, the majority of patients (79%) with HIVAN in our series had increased quantitative echogenicity. Our observation is in agreement with that made by Ulu et al. and by Agoda-Koussema et al. which reported an increased frequency of echogenicity, respectively, of 77.7% and 88.19%.

In a study conducted by Hamper on 36 patients, 77% of patients had echogenicity of the renal cortex less than or equal to that of the liver and spleen, while 23% had superior echogenicity classified as grade 2 and 3 according to Hricack. According to this author, the interstitial tubulo compartment occupies the majority of the renal volume; the glomerulus occupies only 8.6 ± 1.5% of this volume. As a result, interstitial tubulo lesions contribute more to the hyper echogenicity of the renal cortex and the role of glomerulosclerosis implicated by most authors is only secondary.

On the other hand, it disagrees with Adeyekun et al. who found an increased frequency of echogenicity, respectively, of 41.7% and 6.7%. The latter authors concluded that increased echogenicity was not frequently observed in HIVAN even in subject with a CD4 + count <200 mm3 / ml.

Twenty one percent of patients had kidneys with normal echogenicity while they had glomerular lesions on histopathological examination. This observation is due to the fact that the interstitial tubulo compartment is 5 times larger than the glomerular compartment and as a result, interstitial tubulo lesions have more ultrasound translation compared to glomerular lesions (Hamper, Goldblum, Hutching, Sheth, Dahnert, Bartlett, & Sanders, 1988).

The predominance of tubulo interstitial lesions may therefore justify the high number of hyperechoic kidneys.

Of the 24 kidney biopsies performed, 8 were inconclusive due to a lack of adequate biopsy puncture equipment. Various other reasons have either contraindicated the biopsy or made it impossible, because of atrophic kidneys, denial biopsy by fear or for cultural reasons, patients missing and died during the period the study. All these reasons show the relevance of the feasibility of kidney biopsies in our environments.

Inflammation and interstitial fibrosis, cystic dilatation and tubular atrophy were the histological lesions with the highest severity score. Tubulo-interstitial lesions are an invariable component of HIVAN and appear in a greater proportion compared to glomerular lesions (Wyatt, 2008). The same observations

were made in our study. The predominance of severe tubule-interstitial lesions in the present study have a prognostic value because these different histological lesions are well-established factors of progression from renal damage to end-stage renal failure and death in the absence of the dialysis (Weiner, Goodman, & Kimmei, 2003). This observation also emphasizes the need for prevention and screening for kidney damage in the early stages of the disease to slow progress towards advanced stages (Weiner, Goodman, & Kimmei, 2003).

Cystic dilatation of the tubules had emerged as the only independent determinant significantly associated with increased quantitative echogenicity. The relationship between quantitative echogenicity and cystic dilation of the tubules has already been reported by Hamper et al. (1988). This relationship could be explained in agreement with Hamper (1988) and Moghazi (2005), by innumerable interfaces produced by the ectasising dilation of the renal tubes. To this end, Manley and O'Neill (Manley & O'Neill, 2001) had previously reported that increased diuresis and subsequent dilation of the renal tubules were the basis for the increased echogenicity of the renal cortex.

Regarding the diagnostic value of changes in renal echogenicity, Atta et al. (2003), in a study realized in 2004 in Baltimore (USA) on the correlation between sonographic and histological parameters, had already shown that the sensitivity and specificity of the highest echogenicity score for the diagnosis of HIVAN was 40% and 95%, respectively. The probability of HIVAN diagnosis based on the highest echogenicity score was 7.4% (95% CI 1.3-73.0, P = 0.006). This probability for the two lowest echogenicity scores was 0.08. These authors concluded that in patients with HIVAN, the highest and lowest levels of echogenicity confer diagnostic value, respectively, in establishing and excluding HIVAN.

5. Limitations of the Study and Future Research Directions

The interpretation of the results of this study must take into account certain limitations. First, the cross-cutting nature of this study precludes any possibility of establishing a causal relationship between the different variables of interest. Second, the small sample size does not give enough power to statistical tests to identify potential associations between variables of interest. Third, the hospital character of the study does not generalize the results obtained to all HIV positive patients with HIVAN.

Future research will focus on each of these biases to allow an estimate of the significance and robustness of the findings under low resource regions.

This study carried out locally in Central Africa, despite these limitations, seems to be the first one as far as we are aware. It provides valuable information on the ultrasound characteristic of renal sonographic changes of HIVAN and the correlation between renal sonographic changes and histological lesions.

6. Conclusion

The normal sized and hyperechoic kidneys were found in the majority of patients with significant proteinuria suggestive of HIVAN.

But kidneys of normal size and echogenicity can carry glomerular lesions without interstitial tubulo involvement, hence the interest of systematic control of proteinuria in health facilities that care for HIV-positive patients.

Tubulo-interstitial lesions with cystic dilation of the tubes were the only independent determinant significantly associated with increased echogenicity.

Thus renal ultrasound may therefore, in the region where biopsy is not possible, guide the diagnosis of HIVAN. However, given the limitations of this study, a study with a large sample of patients with HIVAN would validate or not the findings of this study.

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