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THE TELL-TALE PROPINQUITY OF RENAL ULTRASONOGRAPHY, SERUM CREATININE, CD4 COUNTS IN HIV PATIENTS AND IT'S RECIPROCITY WITH ANTI-RETROVIRAL THERAPY: A 2 YEARS STUDY FROM NORTH EAST INDIA

Radiology

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ABSTRACT

INTRODUCTION: There is no derivable data in literature regarding the ultrasonographic findings in HIV assoiated renal damage and its correlation with serum creatinine level and CD4 counts in North East Indian population. The impact of antiretroviral therapy (ART) on the progression of renal disease is not substantiated. This necessitated the conduct of this study.

AIMS AND OBJECTIVE: To establish a consociation between renal ultrasound findings and serum creatinine levels, CD4 cell counts in adult patients with HIV associated renal damage; and to study the effects of anti-retroviral therapy on these findings.

MATERIALS AND METHODS: A total of 102 serologically proven HIV positive patients with increased serum creatinine were subjected to renal ultrasonography. Two study groups were formed including n1= 50 HIV positive on anti-retroviral therapy (HOART) and n2= 52 HIV not on ART (HNOART). This data was correlated with the serum creatinine and CD 4 counts.

STATISTICAL ANALYSIS: The data obtained were recorded on Data sheet and analyzed using SPSS for windows version 16. RESULTS: The patients aged between 20 and 52 years. Of the 102 cases studied (i.e. 204 kidneys), ultrasound showed abnormal echogenicity in 200 kidneys (98%). Renal dysfunction was found to be commoner in patients not on antiretroviral medication (37.8%) than patients on antiretroviral medications (27.3%). Majority of patients on ART had lower grades of renal echotexture. The lower the CD4 count, the higher the degree of the renal echogenicity. Although, the higher the serum creatinine levels, the higher the degree of the renal echogenicity.

CONCLUSION: The degree of the renal echogenicity was found to be inversely proportional to the CD4 cell counts, but showed positive linear correlation with increasing serum creatinine level. Prognosis worsens with higher serum creatinine and lower CD4 cell counts. The anti-retroviral medications help retard the progression of renal damage.

KEYWORDS

HIV, Kidney, Ultrasonography, Serum creatinine, CD4, Anti-retroviral therapy.

INTRODUCTION

HIV infection has changed its impact in the form that the disease which once amounted to a death sentence is now commonly treated as a chronic infection. There is a growing cohort of geriatric HIV infected patients world-over. According to the UNAIDS estimates published in June 2016, 36.7 million people globally were living with HIV by the end 2015. A major contributor to the changing HIV epidemiology has been the effective usage of highly active anti retroviral therapy (HAART). Globally, 18.2 million people were accessing antiretroviral therapy by June 2016. In 2015, 1.1 million people died from AIDS-related causes worldwide, compared to 2 million in 2005 (1).

The HIV virus has multi-system involvement of the human body, and imaging shows these processes which result from HIV infection. Neurologic, respiratory, and gastrointestinal complications have all been extensively described in the medical literature; however, renal manifestations and, in particular, their imaging characteristics, are less well deliberated upon.

Renal manifestations occur at all stages of the infection. Renal manifestations in HIV infection can be classified according to their underlying etiology as follows (2):

1. Direct infection of the kidneys with HIV virus, known as HIV-associated nephropathy.
2. Renal disease related to infection, especially opportunistic infections affecting the kidney (eg, fungal infections, tuberculosis).
3. Drug-related renal diseases—in particular, those resulting from the use of highly active antiretroviral therapy (HAART) (eg, indinavir induced calculi) and other potentially nephrotoxic drugs that are used in HIV-infected patients to treat opportunistic infections, such as amphotericin and cotrimoxazole.
4. Neoplasia causing renal disease, including Kaposi sarcoma and lymphoma.
5. Vascular causes of renal disease, including renal artery stenosis related to HAART-induced hyperlipidemia or HIV-related dyslipidemia, hemolytic uremic syndrome, renal infarction, and Thrombotic microangiopathies [HIV-associated thrombotic thrombocytopenic purpura (TTP) / haemolytic uremic syndrome (HUS)]
6. HIV immune complex diseases.
   HIV-related renal impairment can present as an acute or chronic renal disease (3). The commonest cause of renal failure in HIV patients is the syndrome of HIV-associated nephropathy (HIVAN), and therefore, warrants increased surveillance and adaptation of dosages of HIV drugs. More recently, HIV-associated nephropathy was identified as the third leading cause of end-stage renal disease in African-Americans between the ages of 20 and 64 years (4).

The striking feature of HIVAN is its predominance in black patients. Most patients with HIVAN are of African origin, (5, 6) presenting late in the course of their HIV-1 infection. It has also been described in female patients and in patients of other ethnicities and greater age (4). Once diagnosed, rapid progression to renal failure and end-stage renal disease (ESRD) necessitating dialysis, was the norm in the pre-antiretroviral therapy era. Death is usually due to other HIV-related problems. Because HIVAN typically occurs late in the course of HIV-1 infection, risk factors for its development include a low CD4 cell count (<200 cells/cmm) and a high viral burden (7). The biochemical feature of HIVAN is rising serum creatinine and/ proteinuria (>3 g/24 h) (8, 9). Prognosis worsens with higher serum creatinine and lower CD4 cell counts (8).

Imaging findings may suggest the diagnosis of HIV-associated nephropathy, but it should be stressed that the diagnosis remains histologic. The imaging modality most commonly used in the assessment of renal dysfunction is US, followed by CT. Magnetic resonance (MR) imaging is used if US and CT findings are inconclusive or in patients with allergies to iodine-based contrast material. Renal ultrasound is affordable, noninvasive, and readily available and does not involve the use of ionizing radiation.

Imaging findings that are suggestive of HIV associated nephropathy and have been reported in the literature include normal-sized or enlarged kidneys, globular shape of kidneys, increased cortical echogenicity, heterogeneity of the renal parenchyma, renal pelvi-caliceal thickening, and loss of the renal sinus fat.

There is lack of data from North East India regarding renal involvement in HIV disease. Hence this study was undertaken to find the spectrum and impact of treatment on renal diseases in North Eastern Indian HIV/AIDS patients as visualized on ultrasonography.

AIM OF THE STUDY

The aim of this study was to establish a relationship between renal echogenicity and serum creatinine levels / CD4 cell counts in adult patients with HIV associated renal disease in North East India and to study the impact of ART on progression of renal disease..

SETTINGS & STUDY DESIGN

This cross sectional study was conducted in a secondary care hospital in North-Eastern India. The hospital is a nodal agency for the HIV positive population of the region.

ETHICAL CONSIDERATION

Approval to carry out the study was obtained from the ethical and research committee of the hospital. The data collected from the participants were kept with utmost confidentiality and patients had a choice to deny consent or opt out of the study at any stage.

MATERIALS AND METHODS

Total number of serologically confirmed HIV positive indoor as well as outdoor patients visiting hospital from Oct 15 to Sep 17=382 (N)

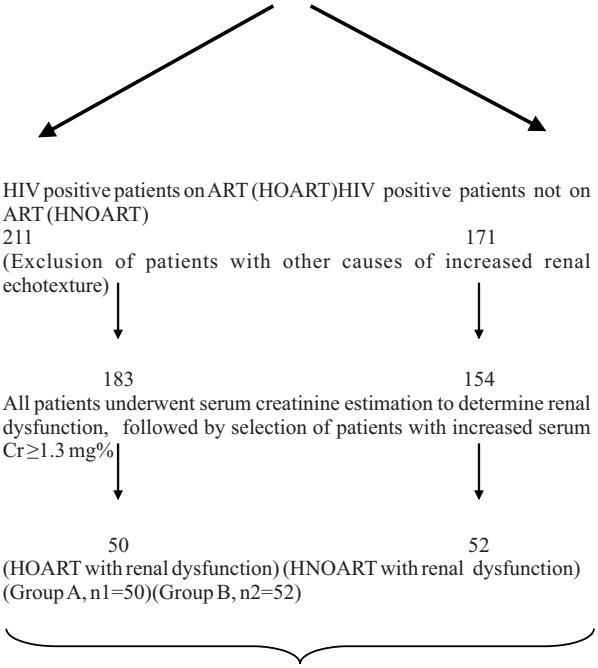

Fig 1: Cross sectional study design

DATA SELECTION

Inclusion criteria

Adult patients with serologically confirmed HIV infection who may have presence of constitutional symptoms such as fatigue, malaise, anorexia and pruritus ; and raised serum creatinine level.

Exclusion criteria

Patients who refused to consent, patients on immunosuppressive drug therapy, patients with hypertension, diabetes mellitus, nephrotic syndrome, collagen vascular diseases.

DATA COLLECTION

On the enrolment into the study after satisfying the inclusion criteria, a questionnaire was administered to each patient and details regarding demographic data (age, sex, and marital status), CD4 cell counts, serum creatinine level and grade of the renal echogenicity were documented. Blood specimen for CD4 cell counts and serum creatinine level was collected and sent to the chemical pathology laboratory of the hospital for all the patients in the study.

Renal ultrasound was carried out on all the patients who satisfied the inclusion criteria using Wipro GE Logiq 3 Pro US scanner machine with a phased array transducer (3.5–15 MHz).

OUTCOME MEASURES

Renal Size: Kidneys were considered large when length exceeded 13cm, normal when length was 9-13 cm, and small if length was less than 9 cm.

Grading of the renal echogenicity:

- Grade 0: Normal; when the renal cortex is less echogenic than the liver or spleen.
- Grade I: When the renal cortex is of the same echogenicity with the liver or spleen.
- Grade II: When the renal cortex is mildly to moderately more echogenic than the liver or spleen,
- with some loss of corticomedullary distinction.
- Grade III: When the renal cortex is severely echogenic obliterating the highly echogenic renal sinus.

Kidneys were subjectively judged as to whether they have a globular appearance. Cortico-rnedullary definition and renal sinus visibility were assessed. Evidence of parenchymal heterogeneity with or without echogenic striations was checked for bilaterally.

Serum creatinine was assessed using semi-automated analyser and CD4 cell counts were assessed using flow cytometer.

STATISTICAL ANALYSIS

The data obtained were analyzed using SPSS for windows version 16.

RESULTS

One hundred two HIV-infected patients with clinical and laboratory features of HIV-nephropathy were enrolled into cross-sectional study. There were 89 (87%) males and 13 (13 %) females. Their ages ranged between 20 and 52 years (Mean = 34 ± 9.8). Table 1 shows the frequency of HIVAN in the different age groups.

Age Group	Number	%
20-29	11	10.8
30-39	73	71.6
40-49	17	16.7
>50	1	0.9

Table1: Age groups of the study patients

The most prone age groups occurred between 30 and 39 years. Married men were the majority in the study representing 80%.

Ninety three of the patients had one or more of the risk factors for HIV infection: 85 were men or women who were heterosexual, 7 were drug users, one received multiple blood transfusions, and nine had no known risk factors.

Renal dysfunction, as determined by raised serum creatinine was found to be commoner in patients not on antiretroviral medication (37.8%), compared with patients on antiretroviral medications (27.3%). (p=0.04)

	With renal dysfunction	Without renal dysfunction
HOART	50 (27.3 %)	133
HNOART	52 (37.8%)	102

Table 2 : Distribution of renal dysfunction in two study groups

Figure 2 shows the distribution of the renal echogenicity. It reveals normal echogenicity in 2 (2 %) patients, grade I echogenicity in 38 patients (37%), grade II echogenicity in 36 patients (35%) and grade III echogenicity in 26 patients (~26%). The renal echogenicity varied differently between HNOART and HOART groups. In the HOART group, majority of patients had grade 1 renal echotexture (62%), whereas in the HNOART group, majority of the patients had grade 3 renal cortical echotexture (42.3%). Homogenous echogenic parenchymal pattern (diffuse) was seen in 92% of patients while 8% had heterogeneous echogenic renal parenchymal (patchy) patterns.

The loss of cortico-medullary definition (CMD) was observed in 40 patients (38%) while it was preserved in 62 patients (60%). Among the 40 patients with loss of CMD, 28 (70%) had decreased conspicuity of the renal pyramids while the pyramids were invisible in 12 (30%).

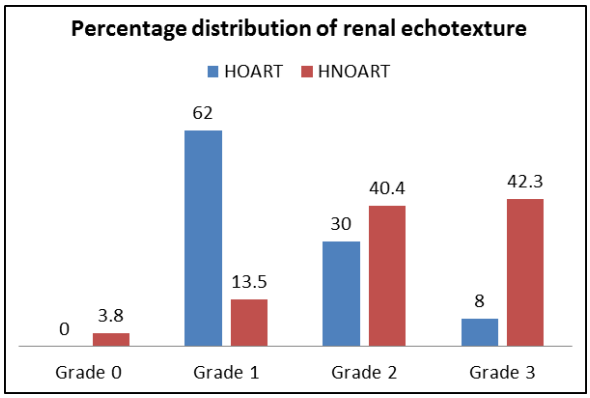

Fig 2: Percentage distribution of the renal echotexture in two study groups

Table 3 shows the serum creatinine level of the patients studied. In the HOART group, majority (64%) patients had serum creatinine values from 1.9 to 2.3 mg%, whereas in the HNOART group, the majority (55.7%) of patients had serum creatinine values ≥ 2.4 mg%.

Serum Cr	HOART	HNOART
1.3-1.8	8	9
1.9-2.3	32	14
≥2.4	10	29

Table 3 : Distribution of serum creatinine in two study groups

Table 4 is the summary of the CD4 counts of the patients studied. Most of the patients (61.8%) had a CD4 count of less than 200 while only 38.2% patients had a CD4 of >200. The range of CD4 counts was between 42 and 651.

Cd4 count	Freq	Percentage
0-100	28	27.5
101-200	35	34.3
201-300	25	24.5
301-400	14	13.7

Table 4 : Distribution of CD4 counts among the study patients

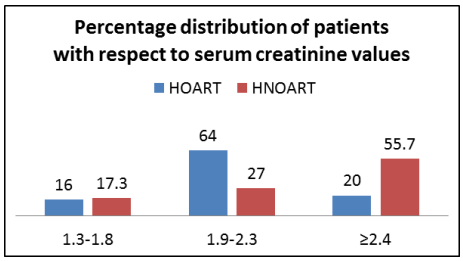

Fig 3: Percentage distribution of the serum creatinine level in two study groups

Table 5 shows the relationship between renal cortical echogenicity and serum creatinine level. There was a statistical significant correlation between the serum creatinine and the degree of the renal echogenicity (r = 0.9). Patients with grade III renal cortical echogenicity (26%) had much higher values of raised creatinine levels (≥ 2.4 mg/dl) as compared to the lower value of raised creatinine (1.9-2.3 mg%) in those patients with grade I renal cortical echogenicity (37%). The higher the raised serum creatinine level, the greater the degree of the renal echogenicity.

	Renal echogenicity			
Serum Creatinine	**0**	**I**	**II**	**III**
1.3-1.8	2	8	3	4
1.9-2.3	0	26	11	9
≥ 2.4	0	4	22	13

Table 5 : Distribution of CD4 counts among the study patients

Table 6 shows the relationship between renal cortical echogenicity and CD4 counts. There was significant negative correlation between the degree of renal echogenicity and CD4 count (r = -0.9). Those patients with CD4 count above 200 (61.5%) showed lower grade (grade 0 or grade I) of renal cortical echogenicity while most of the patients with CD4 count below 200 (77.8%) had grade II or III renal cortical echogenicity. The lower the CD4 count, the higher the degree of the renal echogenicity.

Figures 4 shows various ultrasonographic findings in the study patients.

	Renal echogenicity			
CD 4 count	0	I	II	III
0-100	0	4	5	19
101-200	0	10	21	4
201-300	1	16	6	2
301-400	1	8	4	1

Table 6 : Distribution of CD4 counts among the study patients

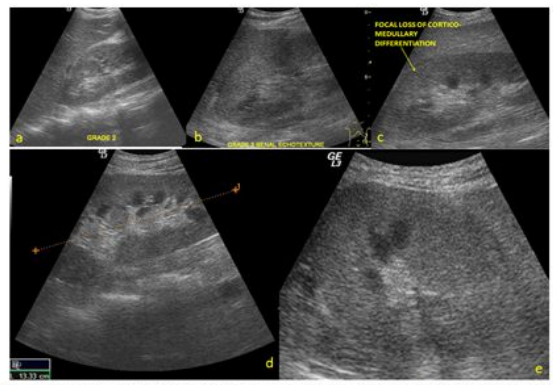

Fig 4: Ulatrasonographic images displaying increased renal cortical echogenicity grade 2 in fig (a), grade 3 in fig (b); focal loss of cortico-medullary differentiation in fig (c); renomegaly in fig (d); and loss of renal sinus fat in axial image (e) at the level of renal sinus.

DISCUSSION

The age distribution of the study patients is 20-52 yrs which is similar (5, 10) to the age range in this study.

Preliminary studies showed that collapsing FSGS was not rare in Indian HIV positive population, but classical HIV associated nephropathy was not seen. The serum creatinine can rise because of multiple reasons in HIV infected patients. Although classical features of HIVAN have been described in African patients indicating a genetic predisposition, renal damage has been lately reported in Indian population as well. Gupta et al described that renal involvement was seen to be common in Indian patients with HIV. Renal biopsy is considered beneficial in seropositive patients with proteinuria especially with low CD4 count for early diagnosis and treatment of renal lesion (3).

Males (87%) outnumbered females (13%) in the study. This is in accordance with the previous studies on Indian population by Vali et al (11).

Schaffer et al mentioned that HIV associated renal damage causes increased renal echogenicity and they recommended that serial sonograms may be useful in monitoring progressive renal involvement (12). Atta et al provided evidence that, among patients with human immunodeficiency virus and kidney disease, the highest and lowest levels of sonographic echogenicity have diagnostic value in respectively establishing or excluding human immunodeficiency virus-associated nephropathy(13).

We adopted the scheme of grading the renal echotexture used by Hricak et al (14). The degree of increasing echogenicity was found to be directly proportional to the severity of the disease, and this is in agreement with our study. The main pathologic explanation for this ultrasonographic appearance is the increased tubular abnormalities observed in these patients.

At US, HIV-associated nephropathy may manifest as normal-sized or enlarged kidneys or increased parenchymal echogenicity. The majority of patients with HIV-associated nephropathy have normal-sized kidneys. The initial enlargement of the kidney is in an axial dimension, with the kidney losing its reniform shape and becoming more bulbous. Nephromegaly has been described in up to 20% of patients with HIV-associated nephropathy but is not thought to be specific for any parenchymal disease (9, 15).

Increased parenchymal echogenicity at US is the most characteristic feature of HIV-associated nephropathy and is broadly defined as cortical echogenicity greater than that of the liver and equal to or approaching that of the renal sinus. It may manifest as patches of increased echogenicity and has been reported to occur in up to 89% of patients with HIV-associated nephropathy (9).Our study had this figure of 98% primarily because our study involved HIV positive patients with raised serum creatinine.

Our study found a statistically significant correlation between the degree of increased renal echogenicity and the raised serum creatinine level (direct exponential relationship). A series of studies even though did not directly correlate serum creatinine levels to the renal echogenicity, but many of them showed that there is a rapid rise in creatinine levels among patients with HIV associated renal damage (8, 9, 16), resulting in renal failure.

A series of studies (8, 9, 17) found that the degree of the renal echogenicity varies with the degree of immunosuppression (using CD4 T-lymphocyte count of <200 cells/cmm as a marker of significant immunosuppression). This implies that the degree of renal cortical echogenicity is inversely proportional to the CD4 count. Patients with CD4 lymphocyte count above 200 cells/cmm commonly have a lesser degree of the renal echogenicity. This study also found a statistically significant negative correlation between CD4 count and the renal echogenicity ($r = -0.9$).

A low occurrence of renal involvement found in patients already on ART suggests some renoprotective effect of ART. Antiretroviral therapy (ART) preserves kidney function in patients with human immunodeficiency virus (HIV)-associated nephropathy (HIVAN). Emerging data also document substantial renal benefits of ART in the general HIV-infected population, which is associated in part with suppression of HIV-1 viral replication.(3, 18)

CONCLUSION

The degree of the renal echogenicity was found to be inversely proportional to the CD4 cell counts, but showed positive linear correlation with increasing serum creatinine level. Prognosis worsens with higher serum creatinine and lower CD4 cell counts.

RECOMMENDATION

Renal ultrasonography should be used to prognosticate the progression to advanced renal disease in HIV positive patients with clinical/ laboratory evidence of renal damage. Anti–retroviral therapy has renoprotective effects.

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