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HUMAN IMMUNODEFICIENCY VIRUS ASSOCIATED NEPHROPATHY IN PERINATALLY INFECTED HIV CHILDREN IN CALABAR, NIGERIA. CLINICAL FEATURES, TREATMENT AND OUTCOME.

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ABSTRACT

BACKGROUND

Renal disease is increasing being recognized as a significant cause of morbidity and mortality in HIV positive patients. Human Immunodeficiency virus associated nephropathy (HIVAN) is the most common type of HIV related renal disease and rapidly progress to end stage renal disease(ESRD). There is paucity of report on true prevalence of HIVAN in African. This study was aimed at determining the prevalence of HIVAN, clinical features, treatment and outcome, in Calabar Nigeria.

METHODS/SUBJECTS:

This was a retrospective review of all renal patients managed by Pediatric nephrology unit of University of Calabar Teaching Hospital from January 2016 to December 2022 enrolled in the Renal register. During the period of study 215 patients had renal diseases out of which 15 had HIVAN. The following information were extracted from the HIVAN patients; Demographics and clinical data as well as mode of transmission, laboratory investigations, renal Ultrasound scan, treatment and Outcome were obtained and analyzed using SPSS version 20.

RESULTS

There were 215 cases of renal diseases seen during the study period of which 15 had HIVAN giving a prevalence of 6.9% There were 5 males and 10 females giving a ratio of 1:2, age range 69-192months. with a mean age of 127±43.7months All received HAART and had acquired HIV infection through vertical transmission.

8 (53%) of patient were asymptomatic with 6 (40%) presenting with both legs and facial swelling. Nephrotic range proteinuria was a common presentation seen in 40% of the patients and 5(33.3%) had hypertension. Only 4 (33%) had eGFR<60 ml/min/1.73m2 and 2(16%) had ESRD. Two were lost to follow-up and 4 (26%) died with two requiring dialysis.

CONCLUSION:

HIVAN is common in patients with renal diseases and there is need to monitor patient at initiation of HAART and at risk patients with low CD4+ count and exposure to nephrotoxic HAART.

KEY WORDS

HIVAN, Children, HAART

INTRODUCTION

Renal disease associated with Human Immuno deficiency virus (HIV)HIV may be acute or chronic, with a wide spectrum of diseases. HIVAN is the most common form of HIV – related renal disease. It is a clinicopathological entity that include proteinuria, azotemia, focal segmental glomerulosclerosis or mesangial hyperplasia and tubulointerstitial disease1. disease.[1] There is a wide geographical variation in the

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prevalence of HIVAN as it ranges from 4.7% to 38%. Studies 2/3 in USA estimate the prevalence to be between 3.5-12%, with a predilection for Black. It is more common in male than female4 and occur in age of 2 to 3 years. Strauss et al5 and Chaparro et al6 reported a prevalence of 15% and 34.3% respectively. Studies[7'8'9] in Nigeria show a varying prevalence of 12 – 31%. Risk factors for development of HIVAN include CD4+ cell count less than 200 cells/ ml, high viral load, male gender and long use of HAART combination[10].

Children with HIVAN typically present with proteinuria frequently in the nephrotic range but no haematuria on urinalysis, They also have rapidly progressive renal insufficiency, almost invariable detectable viral load, and large or normal echogenic kidney. Children with HIVAN have relatively normal blood pressure.

Steel Duncan et al [11] reported that children with HIVAN had advanced HIV disease and nephrotic syndrome with a few patients having chronic kidney disease, while Anochie et al [12] in her analysis of ten children, reported generalized edema 60%, hypertension 50%. nephrotic range proteinuria 40% and 90% had renal failure with elevated creatinine and urea.

The disease is caused by direct infection of renal epithelial by HIV in genetic susceptible host [2'17]. Podocyte and tubular dysfunction result from expression of viral genes in particular nef and vpr and subsequent deregulation of numerous host factors including critical signal pathway, inflammatory mediators and others [14] Childrenchildren more frequently show mesangial hyperplasia in combination with microcytic tubular lesions.

Anti retroviral therapy is the mainstay of treatment as it causes supression of viral load with significant slow viral replication[15] ACEIs has the beneficial effect of improved renal dynamic, reduced hemodynamic, reduced proteinuria or cytokine modulation. Kimmel et al[16] reported enhanced renal survival in the captopril treated compared to controls.

HIVAN remain a leading cause of end stage renal disease and there is paucity of data regarding the prevalence of HIVAN in this locality thus study aimed at determine the prevalence of HIVAN in Calabar, Nigeria.

METHODOLOGY

This was a retrospective review of all cases of HIV associated nephropathy seen in the Paediatric nephrology clinic of University of Calabar Teaching hospital from January 2016 to December 2022. which was retrieved from the renal register. During the period of study, they were 215 cases of renal diseases enrolled in the register. HIV nephropathy was defined as persistent proteinuria >+1 on dipstick, estimated GFR < 60 ml / min/ 1.73m ^{2} and positive finding on renal USS of normal or enlarged kidney with increased cortical echogenicity. The University of Calabar Teaching Hospital situated in Calabar municipality. Calabar is the capital city of Cross Rivers State in the Niger Delta Region of Nigeria. It serves the whole of Cross Rivers State and the neigbouring State of Akwa-Ibom, Abia, Ebonyi, Benue and Cameroon. Ethical approval was obtained from Ethical Committee of the University of Calabar Teaching Hospital.

The following data were extracted from renal register; Demographic and Clinical data (age, sex, mode of transmission, type of HAART/ duration, (HAART was categorized to nephrotoxic, HAART, non-nephrotoxic HAART and non ARV nephrotoxic drugs,) clinical stage and immunological stage using CD4+ count by revised WHO paediatric clinical stage and WHO paediatric immunological staging respectively [17'18] others are the laboratory tests, serum creatinine for eGFR using schwartz formulae, CD4+ count and persistent proteinuria by dipstick. Obtained data were entered and analysed using SPSS version 20 mean, standard deviation, percentages and frequencies were calculated.

RESULTS

PREVALENCE OF HIVAN/ CHARACTERISTICS OF HIV ASSOCIATED NEPHROPATHY (HIVAN) SUBJECTS AT DIAGNOSIS.

During the period of study, 215 subjects had renal diseases, out of which 15 had HIVAN given a prevalence of 6.9%.

HIVAN was defined as persistent proteinuria>+1, eGFR<60ml/min/1.73m^2 and positive renal ultrasound finding of normal or enlarged kidney with increased cortical echogenicity.

There were 5 males and females giving a ratio of 1:2. The age range was 69 – 192 months with a mean age of 127.1 mth + 43.7mths.[1]

All subjects received highly active anti-retroviral therapy (HAART). 13(86.7%) received non-nephrotoxic HAART with 2(13.3) receiving nephrotoxic HAART and all had HIV Infection through vertical transmission. The duration of HAART Therapy was 3 years to 12 years with mean duration of 5 years.

8(53%) of the subjects were in clinical stage 3 and 4, while 3(13.3%) and 4(20%) were in stage 1 and stage II respectively. 10 (60%) of the subjects had mild and severe level of immunosuppression, while 1(6.6%) had advanced immunosupression with CD4+>200cell\ul (Table I)

CLINICAL FEATURE OF SUBJECTS WITH HIVAN AT DIAGNOSIS TABLE 2

8 (53%) of the subject with HIVAN were asymptomatic with 6(40%) having leg swelling and facial swelling. others had symptoms like weight loss and abdominal pain (13%)
Persistent proteinuria in the nephrotic range was seen in 6(40%) of subjects while non nephrotic range was seen in 40% of the subjects.

Blood Pressure: Systolic blood pressure range from 85 – 160mmhg with a mean of 109+23.12mmhg. 9(60%) of subjects had normal systolic Blood pressure with 5(33%) having hypertension. Diastole Blood Pressure range from 40-120mmhg with mean of 70.9 +21.7mmhg with 8(53%) having normal diastolic pressure and 5(33%) having diastolic hypertension.

Estimated GFR ranging from 9.6 – 140.2 ml/min/1.73m2. 8(66.0%) had eGFR> 60ml/min/1.73m2 while 4(33%) had < 60ml/min/1.73m2 with two subjects having eGFR<15min/1.73m2.

TREATMENT AND OUTCOME

All subjects received HAART with the combination of NVR.-AZT – LAM being the most common combination therapy with adjunct therapy of ACELs.
Two of the subjects were lost to follow up, and four (40%) died during the period of study, while two were referred for dialysis.

DISCUSSION:
Human immunodeficiency virus associated nephropathy (HIVAN) is a major cause of morbidity and mortality in HIV infected patients. It usually occur in advanced disease and often lead to End stage renal disease

TABLE I: CLINICAL CHARACTERISTIC OF HIVAN SUBJECTS AT DIAGNOSIS

VARIABLE	FREQUENCY	PERCENTAGE
Demographic Characteristic		
Sex: Male	5	33.3%
Female	10	66.6%
TOTAL	**15**	**100%**
Age 0 – 60 months	2	12.3
60 – 120 months	4	26.7
120 months	9	60.0
TOTAL	**15**	**100**
Mode of HIV Transmission		
MTCT Confirmed	15	
MTCT Suspected	0	100
Blood Transfusion	0	
Others	0	
TOTAL	**15**	**100**
RECEIVING ART		
YES	15	100
NO	-	
Duration of Therapy Mean 5.2years		
<3	4	26.7
4 – 6	8	53.3
7 – 9	2	13.3
10 – 12	1	6.7
TOTAL	**15**	**100%**

TYES OF HAART	FREQUENCY	PERCENTAGE
Nephrotoxic	2	13.3
Non-Nephrotoxic	13	86.7
TOTAL	15	100%
Non-Nephrotoxic HAART		69.2%
NVP AZT – 3TC		
ABC-NVP – 3TC	13	23.07
OTHER	1	7.69
TOTAL	**13**	
CLINICAL Stage		
1	3	13.3%
2	4	26.7%
3	2	13.3%
4	6	40.0%
TOTAL	15	100%

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Two of the subjects were lost to follow up, and four (40%) died during the period of study, while two were referred for dialysis.

DISCUSSION
Human immunodeficiency virus associated nephropathy (HIVAN) is a major cause of morbidity and mortality in HIV infected patients. It usually occur in advanced disease and often lead to End stage renal disease (ESRD)[20]

In this study, the prevalence of HIVAN WAS 6.8% using the following defining eritena; persistent proteinuria>+1, eGFR<60ml/min/1.73m2 and positive finding on renal ultrasound of normal or enlarged kidney with increased cortical echogenicity. This was similar to study by Udenwa et al 21 who reported a prevalence of 8.9% in Port Harcourt Nigeria. Others authors 6,22,23 had higher prevalence. While lower rate of 3.1% was reported in Uyo, Nigeria8. The difference in prevalence may be explained by difference in defining criteria, (in above study 3 criteria were used, while some authors only screened for proteinuria) methodology, simple size and duration of studies. Most studies with high prevalence had only one point measurement of proteinuria with dipstick.

Severe renal impairment, estimated GFR<60ml/min/1.73m2 was seen in 4 subjects (33.1%) similar to study in Kwa-zula mata South Africa24. Lower rate of 5% and 13.3% was reported by Ezeonwu, et al25 and Esezobor et al26 in Nigeria, respectively. Severe renal impairment of eGFR<60ml/min/1.73m2 is found in association with low CD4+<350 cell/ml, past exposure to Tenofovir (TDF), female gender, long period of HAART,27,28. The five subjects with eGFR>60ml/min/1.73 had severe immunosuppression with clinical stage 4 disease and two had exposure to nephrotoxic HAART; Tenofovir (TDF) and Dolutegravir. This underscores the need of monitoring the renal function at initiation of HAART and for at risk patient with exposure to tenofovir and other nephrotoxic HAART.

Sonography evaluation of renal echogenicity or morphology can reliably predict HIVAN diagnosis as documented by various authors29, 30. Increased echogenicity correlates with CD4+ and GFR. Increased echogenicity may be connected with wide spread tubular generative changes such as tubular epithelial edema and hypertrophy, enlarged hyperchromatic nuclei, prominent nuclei mitotic figure as well as focal apoptosis31. In this study, positive renal USS finding was seen in (53%) of patients, similar to study by Eze et al 29 and was more in subjects with severe immunosupression. Lower rate of 8.4% (cortical echogenicity with normal size kidney) was reported by Obajimal et al 32 with no correlation between echogenicity and CD4+ level.

Nephrotic range proteinuria (40%) was a common presentation among subjects with HIVAN, consistent with other studies 33,34.

While most subject (63%) had normal blood pressure with 33% having hypertension. Children with HIVAN have relatively normal blood pressure. Hypertension occurred in 50% subjects in Nigerian Study12. Most of the subjects with hypertension had severe renal impairment with deterioration or decline in GFR, there is reduced nephron; increase sodium retention and extra cellular volume expansion with activation of sympathetic nervous systems and hormonal system which ultimately leads to hypertension. Also hypertension may warrant a search for other form HIV related renal disease other than HIVAN. Thus a renal biopsy is required to make a definitive diagnosis of HIVAN.

HAART is the mainstay of treatment in HIV associated nephropathy. All subject received HAART with a mean duration of 5 years and angiotensin Converting Enzymes Inhibitors (ACEIs). However corticosteriods was not used in these subjects as its use in children is controversial though evidence of beneficial effect has been documented in Adults35. Two of the subjects were lost to follow up and four died (40%) during the period of study, consistent with studies in Nigeria21,33 though as high as 70% mortality rate was reported in a series of s HIVAN in Nigerian children. Two required dialysis and could not access renal replacement in this centre and were referred to a facility in a neighbouring state.. The prognosis for renal survival is worst in patient with AIDS especially those with CD4+ less than 50cell\ul Most who died had CD4+>50 cell/ul.

In conclusion. The prevalence of HIVAN is high especially in those with low CD4+ count and on nephrotoxic ARV and there is a need for periodic screening to prevent progression to endstage renal disease.

LIMITATION OF STUDY

This study is limited by lack of renal biopsy to confirm the definitive diagnosis of HIV associated nephropathy due to cost and lack of facilities for histopathological study in this centre.

CONFLICT OF INTEREST

None

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