# Human Immunodeficiency Virus-Associated Nephropathy (HIVAN) in Indian Children

Prabha Senguttuvan*, S. Gowtham and P. Soundararajan

*Department of Nephrology, Sri Ramachandra Medical University, Chennai, India*

**Abstract:** Human immunodeficiency virus-associated nephropathy (HIVAN) in children has not been reported in India. In a single centre study, we analyzed 8 children diagnosed with HIVAN from 2007 to 2010. There were 6 boys and 2 girls with a male to female ratio of 3:1. Their ages ranged between 5 yrs to 11 yrs with a peak age of 8 years. The routes of HIV transmission were vertical in 5, blood transfusion in 2 and unknown in one. The presentation included generalized edema 100%, hypertension 2/8 (25%) and macroscopic hematuria 1/8 (12.5%). On evaluation by urine dipstick, all children had proteinuria and urine PCR showed nephrotic proteinuria (>3). 5/8 (62.5%) had extra renal involvement: 2 children had hepatosplenomegaly and 3/8 (37.5%) children had pulmonary tuberculosis and were on highly active antiretroviral therapy (HAART) and antituberculous treatment (ATT). Renal disease was the presenting problem in 4/8 (50%) and the remaining 4 (50%) were referred from the HIV clinic. The duration of HIV infection to the development of HIVAN was unknown in 4/8 (50%) nephrotic patients but in those referred from HIV clinic, it ranged between 5 months to 2 yrs. CD4 count ranged from 700 to 2465/mm$^3$. All the children had enlarged kidneys bilaterally, except for one child who had normal sized kidneys with increased echogenicity and loss of corticomedullary distinction. He was not biopsied and he progressed to renal failure. Renal biopsy in other 7 children showed FSGS in 4 (57%) and collapsing FSGS in 2 (28.5%), and early segmental sclerosis with IgA deposits in one child (14.2%). 7/8 who had nephrotic proteinuria were initiated on steroids.

**Keywords:** Collapsing glomerulopathy, human immunodeficiency virus-associated nephropathy, Indian children, nephrotic syndrome.

## INTRODUCTION

Renal disease in HIV infection in children is an increasing problem. The renal involvement of HIV includes acute renal failure, progressive chronic renal dysfunction, HIV–associated nephropathy (HIVAN), proteinuria, nephrotic syndrome, tubular functional abnormalities and electrolyte disorders. HIVAN is a unique entity developing as a result of HIV gene expression in renal tissues [1]. Strauss *et al.* reported a prevalence of childhood HIVAN of 10-15% in HIV- infected African American children [1]. Proteinuria is the first sign of HIVAN [2].

## PATIENTS AND METHODS

The study was conducted from 2007 to 2010 at the Institute of Child Health and Hospital for Children, Chennai. The child's age, clinical presentation and blood pressure were recorded. Hypertension was defined as blood pressure >95$^{th}$ percentile for age and gender. The routes of infection, investigations like blood urea, serum creatinine, serum albumin, serum cholesterol, HIV, Hepatitis B and C screening, CD+4 cell count, urinalysis, random protein creatinine ratio (PCR), histological pattern, treatment and outcomes were reviewed. Outcome was measured in terms of mortality and loss to follow up.

The diagnosis of HIVAN was made by presence of persistent proteinura of >1+ by urine dipstick with one or more of the following:

1. Abnormal urinary sediment
2. Presence of enlarged echogenic kidneys by renal ultrasound
3. Histological finding of focal segmental glomerulo-sclerosis (FSGS)
4. Microcystic tubular dilatation, a childhood variant of HIVAN in absence of significant podocyte lesion

If nephrotic proteinuria was present (urine PCR>3), oral prednisolone at a dose of 2 mg/kg daily was started. If no remission is seen as indicated by disappearance of proteinuria by 4 weeks, they were termed as steroid-resistant and renal biopsy was done.

## RESULTS

During the 2 year period, 160 children tested HIV positive and 8 (5%) patients with overt HIVAN were identified. Age range was between 5 to 11 years (mean 8 years) comprising of 6 boys and 2 girls. There were 4 (50%) children each in the age distribution of 5-8 years and 9-11 years. Renal disease was the presenting symptom in 4/8

*Address correspondence to this author at the Department of Nephrology, Sri Ramachandra Medical University, Chennai, India;
E-mail: prabha_sen@hotmail.com

1874-303X/14 

**Table 1. Clinical data of patients at diagnosis of human immunodeficiency virus – associated nephropathy (HIVAN).**

| Patient Number | Age (Yrs) | Sex | Transmission Route | Clinical Presentation | Lab Data | | CD4 (Cells/mm$^3$) | Urinalysis | Renal Biopsy | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | s.alb (g/dl) | s.cr (mg/dl) | | | | |
| 1. | 10 | M | Vertical | Edema Pulmonary TB | 2.0 | 0.8 | 700 | P+++ | Collapsing FSGS | Died |
| 2. | 5 | M | Transfusion | Edema Pulmonary TB | 1.4 | 0.4 | 1000 | P+++ | FSGS | Died |
| 3. | 7 | F | Vertical | Edema Pulmonary TB | 2.0 | 0.9 | 1500 | P+++ | FSGS | Died |
| 4. | 7 | M | vertical | Edema Hypertension | 2.3 | 1.0 | 900 | P+++ | Not done | Died |
| 5. | 6 | F | Transfusion | Edema Hepato-splenomegaly | 2.2 | 1.0 | 1200 | P+++ | FSGS | Alive |
| 6. | 10 | M | vertical | Edema Hypertension Hepato-splenomegaly | 1.8 | 0.8 | 1800 | P+++ | Collapsing FSGS | Died |
| 7. | 8 | M | unknown | Edema | 2.1 | 0.7 | 1600 | P+++ RBC +++ | early segmental sclerosis with IgA | Alive |
| 8. | 11 | M | vertical | Edema Hepatosplenomegaly | 2.0 | 0.6 | 2465 | P+++ | FSGS | Alive |

(50%) and the remaining 4 (50%) were referred from the HIV clinic. Routes of HIV transmission was vertical in 5 (62.5%), through blood transfusion in 2 (25%) and both the donors were their respective fathers, and the source was unknown in one child. Their clinical presentation included generalized edema 100%, hypertension 2/8 (25%), and macroscopic hematuria 1/8 (12.5%). 5/8 (62.5%) had extra renal involvement; 2 had hepatosplenomegaly and 3 children with pulmonary tuberculosis were on HAART and antituberculous treatment. Duration of HIV to the development of nephrotic syndrome was not known as they came first to the renal OPD, but in those referred cases from HIV unit, it ranged between 5 months to 2 yrs. All children had ephrotic proteinuria. 7/8 had serum albumin <2.0 gms/dl. The serum creatinine levels were normal at presentation in all the children. Ultrasound showed grossly enlarged kidneys in all the children except one child who had normal sized, hyperechogenic kidneys with loss of corticomedullary differentiation and he was not biopsied. CD4 count ranged from 700 to 2465/mm$^3$ (mean 1270 cells/mm$^3$). Hepatitis B and C were negative in all the children. 7 children underwent renal biopsy which showed collapsing FSGS in 2 (28.5%), FSGS in 4 (57%) and early segmental sclerosis with IgA deposits indicating IgA nephropathy in one child (14.2%). As the CD4 cell count was >500 cells/mm$^3$, 5/8 of the children were not on HAART. 3 children with pulmonary tuberculosis were treated with HAART. Of the 7 children who were treated with oral prednisolone, 6 were steroid resistant and one child was a frequent relapser (biopsy-early segmental sclerosis with IgA deposits) requiring low dose steroids to keep him in remission. The boy whose ultrasound showed loss of corticomedullary differentiation and was not biopsied progressed to ESRD over a period of 12 months. He was initiated on CAPD and died 6 months later. 4/8 (50%) progressed to CKD; 3/8 over a 3 year period and 1/8 entered CKD by 2 years and all 4 children eventually died. All of the remaining 3 (37.5%) living children, one recruited in 2008 (transfusion induced) and 2 in 2009, were on follow up at the time of study with stable renal function (Table **1**).

## DISCUSSION

There are very few reports about HIV-associated nephropathy in children [4]. This is the first report from India.

In children, renal involvement is early [5] and inevitable. The short duration of symptoms may indicate that HIVAN could be an early presentation of HIV infection [6]. Several mechanisms for pathogenesis have been implicated. HIV-1 virus may directly affect the growth and differentiation of glomerular and tubular epithelial cells, increase recruitment of infiltrating mononuclear cells and cytokines, and up-regulate renal heparin sulphate proteoglycans [1, 4]. Other agents that can lead to associated renal disease are opportunistic infections, nephrotoxic agents and immunological abnormalities [5]. Hypertension may be seen in patients with long-standing nephropathy [12]. A study from Washington found that early stages of HIV-associated nephropathy (HIVAN) in children were associated with

enlarged echogenic kidneys, proteinuria and urine microcysts. The progression to end stage renal disease is slow in children [3, 5]. Strauss *et al.* reported a less fulminant course in children compared to adults [2]. But some studies also show that HIVAN can progress to ESRD at a very rapid rate, varying from weeks to months.

Treatment guidelines for managing HIVAN are few [7, 8]. According to the Cochrane review [14] beneficial drugs include antiretrovirals, steroids, angiotensin-converting enzyme inhibitors (ACEI) and cyclosporine. Steroids and ACEI appeared to improve the kidney function of patients in the observational studies [10]. There are no randomized trials to prove its role in the optimal management of HIVAN. But 6/8 children in our study were steroid resistant and there are reports about its limited benefit in children with HIVAN [9, 11]. KDIGO guidelines recommend that antiretroviral therapy should be initiated in all patients with biopsy-proven HIV-associated nephropathy, regardless of CD4 count. But there is no RCT that evaluates the value of HAART therapy in patients with HIVAN. Our HIV specialists who decide on the antiretroviral therapy mainly go by the CD4 counts and hence we could not initiate HAART in our patients.

A small number of children with HIVAN and ESRD have received dialysis and the prognosis for children with HIVAN is better than that of adults [13]. Renal transplantation may be a viable treatment option for patients with ESRD and should be performed at centers with adequate experience in this area.

All children at the time of HIV diagnosis should be assessed for co-existing renal involvement with blood pressure monitoring, urine analysis for proteinuria and GFR estimation.

## CONCLUSION

HIVAN occurs in HIV-infected children. Mortality remains high from renal failure due to lack of HD facilities for HIV patients and high cost of PD. Early screening and treatment with antiviral therapy may improve outcome. As chronic kidney disease associated with perinatal HIV infection has been reported [16, 17], prevention of childhood HIV infection by perinatal and blood transmission remains the ultimate goal. Screening for HIV is mandatory for all nephrotic children. CKD in these children is inevitable but the progression of the disease is slow. Treatment remains a challenge. Eggers and Kimmel estimated that patients with HIV still have a 10-fold greater risk of developing ESRD compared with the general population [15].

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

[1] Strauss J, Abitbol C, Zilleruelo G, *et al.* Renal disease in children with acquired immunodeficiency syndrome. New Engl J Med 1989; 321: 625-30.

[2] Abitbol CL, Strauss J, Zilleruelo G, Montané B, Rodriguez E. Validity of random urine to quantitative proteinuria in children with human immunodeficiency virus nephropathy. Pediatr Nephrol 1996; 10: 598-601.

[3] Ray PE, RakusanT, Loechelt BJ, Selby DM, LiuXH, Chandra S. Human immunodeficiency virus associated nephropathy in children from the Washington DC area: 12 years experience. Semin Nephrology 1998; 18: 396-405.

[4] Ray PE, Xu L, Rakusan T, Liu XH. A 20 years history of childhood HIV-associated nephropathy. Pediatr Nephrol 2004; 19: 1075-92.

[5] Burns GC, Paul SK, Toth IR, Sivak SL. Effect of angiotensin-converting enzyme inhibition in HIV- associated nephropathy. J Am Soc Nephrol 1997; 8: 1140-6.

[6] Ifeoma C, Anochie FU, Eke A, Okpere N. HIVAN in Nigerian children. Pediatr 2008; 23: 117-22.

[7] Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV medicine association of the infectious diseases society of America, Clin Infect Dis 2005; 40: 1559-85.

[8] No authors listed. HIV-related nephropathy in children: The situation in Spain. An Esp Pediatr 1993; 39: 489-92.

[9] Rao TKS, Friedman EA, Nicastri AD. The types of renal disease in the acquired immunodeficiency syndrome. N Engl J Med 1987; 316: 1062-8.

[10] Ross MJ, Klotman PE, Winston JA. HIV associated nephropathy; case study and review of literature. AIDS patient care STDS 2000; 14: 637-45.

[11] Strauss J, Zilleruelo G, A bitbol C, Montane B, Pardo V. Human Immune deficiency virus nephropathy. Pediatric Nephrol 1992; 7: 220-5.

[12] Ahuja TS, Abbott KC, Pack L, Kuo YF. HIV-associated nephropathy and end-stage renal disease in children in the United States. Pediatr Nephrol 2004; 19: 808-11.

[13] Yahaya I, Utham OA, Utham MMB. Interventions for HIV associated nephropathy. The Cochrane Database of Systematic Reviews 2011.

[14] Eggers PW, Kimmel PL. Is there an epidemic of HIV infection in the US ESRD program? J Am Soc Nephrol 2004; 15(9): 2477-85.

[15] Bhimma R, Purswani MU, Kala U. Kidney disease in children and adolescents with perinatal HIV-1 infection. J Int AIDS Soc 2013; 16: 18596.

[16] Purswani MU, Chernoff MC, Mitchell CD, *et al*. Chronic kidney disease associated with perinatal HIV infection in children and adolescents. Pediatr Nephrol 2012; 27(6): 981-9.

[17] KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int supplement 2012; 2 (2): 243-51.

Received: January 26, 2014 Revised: May 22, 2014 Accepted: June 15, 2014