Original article

Renal manifestations of HIV infected highly active antiretroviral therapy naive children in India

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Background: **There are several studies on renal manifestations in human immunodeficiency virus (HIV) infected children from American and African regions, but similar studies from India are lacking. A cross-sectional study was carried out in 28 HIV infected antiretroviral therapy (ART) naïve children coming to the pediatric HIV clinic.**

Methods: **Demographic data of the children, clinical presentations including blood pressure, detailed laboratory investigations (serum creatinine, glomerular filtration rate), urine analysis (urine morphology, urine albumin, pus cells, and red blood cells), and CD4 counts were collected.**

Results: **Of the 28 children, 15 (53.6%) had renal manifestations with a male to female ratio of 1:1.5. The most common renal manifestation in our study was abnormal glomerular filtration rate (GFR) in 11 (44.0%) of 25 children. This was followed by pus cells in urine in 6 (21.4%) of the 28 children while 3 (10.7%) of them had proteinuria. The mean age of children with renal manifestations was 5.04±2.75 years as compared to those without renal manifestations who had a mean age of 7.38±2.95 years (*P*=0.0390). CDC class and sex were not associated with renal manifestations.**

Conclusions: **Our study suggests that reduced GFR is the common renal manifestation, particularly in younger children. Other renal manifestations are related to proteinuria. The lack of correlation of CDC classification with renal manifestations mandates screening of children with HIV for renal disease. A more detailed study of renal manifestations in HIV-infected children is needed.**

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Key words: **children; human immunodeficiency virus; renal manifestations**

Introduction

Human immunodeficiency virus (HIV) infection is a multisystemic illness, which leads to acquired immunodeficiency syndrome (AIDS) if left untreated. A variety of renal abnormalities among HIV-infected patients have been described. These abnormalities include HIV associated nephropathy (HIVAN), HIV-related immune complex disease, nephropathy secondary to antiretroviral therapy (ART) or antibiotics, thrombotic microangiopathy, and diseases related to common comorbidities such as opportunistic infections.[1] The broad spectrum of clinical presentations includes acute renal failure (ARF), nephrotic syndrome, progressive chronic renal dysfunction, proteinuria, tubular dysfunction and electrolyte disturbances.[2] There are several studies regarding renal manifestations in children from American and African regions[2-7] with HIVAN reported more in the black race and less commonly reported among other races including Asians. Thus, there may be difference in renal manifestations in HIV infected children in different races. Renal manifestations in HIV infected highly active antiretroviral therapy naïve children from India have rarely been reported. So this preliminary study was conducted to contribute to the information on the magnitude of renal involvement in HIV infected children.

Methods

A cross-sectional study of 28 HIV infected ART naïve children who came to the Pediatric HIV Clinic at our hospital in 2007 was conducted for a month. Their demographic data (age, gender, height, and weight), clinical examination and detailed history were collected. The patients were classified into class N, A, B and C according to clinical stages of HIV disease defined by

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the CDC classification.[8]

Renal screening was done in form of blood pressure recording (on 3 visits: once at the time of initial examination, second when the patient came for investigations and third when the patient arrived with reports at the clinic), urine examination for proteinuria and hematuria as well as infection, urine albumin/creatinine ratio and serum creatinine. Hypertension was diagnosed if systolic or diastolic blood pressure was more than 95th centile for age, height and gender on all 3 occasions.[9] Serum creatinine of more than 0.8 mg/dL was considered high. Glomerular filtration rate (GFR) was estimated with the Schwartz formula.[10] Age specific cut off limits were used to define abnormal GFR values. Proteinuria was considered if urine albumin was more than 1+ in absence of fever or urine albumin/creatinine ratio was more than 0.2 mg/mmol in children aged more than 2 years and 0.5 mg/mmol in children aged less than 2 years.[11] Hematuria was diagnosed if urine showed more than 10 red blood cells/high power field.[12] CD4 counts were reviewed in those patients who could afford the test. Investigations for opportunistic infections were done when required. Degree of immune suppression was determined on the basis of age specific CD4 counts and percentage of total lymphocytes as described in the WHO guidelines.[13] Malnutrition was defined as both weight and height below 3rd percentile as compared to age and sex matched children using modified Agrawal's growth charts.[14,15] The presence of more than 10 white cells/high power field along with a positive urine culture was considered as urine tract infection. The prevalence of renal dysfunctions in these children was calculated and types of renal dysfunctions in form of hematuria, proteinuria or abnormal GFR were noted. Patients with acute febrile illness were excluded from the study.

Statistical analysis of the data was made using SPSS version 13.0 and OpenEpi software. The Chi-square test and Fischer's exact test were used for analysis of proportions. *P* values less than 0.05 were considered statistically significant.

Results

The age of the 28 patients at presentation ranged from 1 year to 13 years (mean: 6.13±3.03 years). There were 11 boys and 17 girls, with a male to female ratio of 1:1.5. The patients were divided into 3 age groups. Eleven (39.3%) patients were below 5 years, 14 (50.0%) were at age of 5-10 years and 3 (10.7%) were above 10 years. Four (14.3%) patients belonged to CDC class A, 22 (78.6%) to CDC class B, and 2 (7.1%) to CDC class C. CD4 counts were determined in 26 patients. Among them, four (15.4%) patients had no mild immunosuppression, 17 (65.4%) had moderate immunosuppression and 5 (19.2%) had severe immunosuppression. Co-infections included tuberculosis in 18 (64.3%) patients, Klebsiella urinary tract infection in 1, herpes zoster in 1, pneumocystis carinii pneumonia in 1, and bacterial pneumonia in 1.

Of the 28 patients, 15 (53.6%) had renal manifestations. The mean age of the 15 patients was 5.04±2.75 years and that of 13 patients without renal manifestations was 7.38±2.95 years (*P*=0.0390). Eleven (44.0%) of 25 tested patients had abnormal GFR value as the commonest manifestation. In the 11 children, 7 (63.6%) females and 4 (36.4%) males, 8 (72.7%) children were below 5 years and 3 (27.3%) between 5-10 years (*P*=0.3297 and *P*=0.1185, respectively). Other manifestations included presence of pus cells in 6 (21.4%) children and proteinuria in 3 (10.7%). Two (7.1%) children had abnormal serum creatinine levels and only one (3.6%) had hypertension with a blood pressure of 160/100. The patient was treated with nifedipine. None of the 3 patients had red blood cells in urine. Malnutrition was seen in 15 (53.6%) of the 28 children. The mean level of urine albumin was 26.4±33.3 mg/dL with a range of 4.0 mg/dL to 145.0 mg/dL. The mean level of serum creatinine was 0.6±0.2 mg/dL with a range of 0.4 mg/dL to 0.8 mg/dL. GRF

Table. Association of clinical and investigational features with age, sex and CDC classification

Clinical features and investigation	Age group				Gender			CDC classification			
	<5 y (*n*=11)	5-10 y (*n*=14)	>10 y (*n*=3)	*P* value	Male (*n*=11)	Female (*n*=17)	*P* value	A (*n*=4)	B (*n*=22)	C (*n*=2)	*P* value
Abnormal GFR (*n*=25)	8	3	0	0.1583	4	7	0.7422	1	9	1	0.9158
Urine albumin positive	1	2	0	0.7021	1	2	0.8232	1	2	0	0.7937
Abnormal creatinine (*n*=25)	2	0	0	0.7700	1	1	0.7634	0	2	0	0.8433
Hypertension	1	0	0	0.8929	1	0	0.3929	0	1	0	0.9286
Pus cell in urine	2	1	1	0.3184	0	4	0.0822	1	3	0	0.7302
Malnutrition	7	6	2	0.5218	4	11	0.1420	2	11	2	0.2778

GFR: glomerular filtration rate.

values were calculated only for 25 children. The mean GFR value was 90.6±22.1 mL/min with a range of 52.9 mL/min to 156.2 mL/min. Renal manifestations related to age, gender and CDC class are depicted in the Table.

Discussion

Renal disease may occur in children with asymptomatic and symptomatic HIV infection. Its manifestations include proteinuria, nephrotic syndrome and renal failure. Glomerulopathy takes place in up to 15% of children with HIV infection but the occurrence of tubular dysfunction is less understood.[16]

In the present study, we determined renal dysfunction in HIV infected children. Despite the small sample size of this study, we found that over 50% of the children had renal abnormalities. Because we did not check HIV negative children for renal disease, the findings could not be ascribed to HIV infection itself. We found a low GFR when estimated by the Schwartz formula in 44% of the patients. However, this may not be highly accurate in view of stunting or other co-infections such as tuberculosis that may occur with HIV disease. It is difficult to confirm that the estimated low GFR was due to HIV-related renal involvement. Yet it is still a good non-invasive and economical marker for close monitoring of renal functions in the patients. Although low GFR is seen commonly in females and in children less than 5 years old, it is not statistically significant. Since similar studies on GFR values are lacking, a large population based study would be necessary to confirm our findings.

A Nigerian study[17] found a prevalence rate of 12% for proteinuria in HIV infected children. The prevalence in our study was 10.7%, which is similar to the Nigerian study. Chaparro et al[7] also found that 33% of HIV infected children had proteinuria. Proteinuria is believed to be the earliest and most consistent clinical finding for the diagnosis of HIV-associated nephropathy. Control of viral load by ART is associated with the improvement of proteinuria and a decrease in mortality rate in HIV infected children. HAART appears to have a significant positive impact on averting or modifying the development and progression of nephropathy in children.[7] Thus, HIV infected children should be regularly screened for the presence of proteins in urine, and if it is found, proteinuria should be quantitated and the children should be screened for renal disease by imaging and renal function tests.

Six children in our study showed pus cells in urine; however, only one child grew Klebsiella in the culture, suggesting that though pus cells are common in HIV infected children, a diagnosis of urinary tract infection (UTI) should be dependent on urine culture. Asharam et al[18] also reported that there is no significant effect of HIV/AIDS on UTI in children.

Burns and colleagues[19] reported that HIV associated nephropathy may be an early manifestation of renal disease. In our study renal manifestations were not significantly related to age, gender or CDC class, indicating that the manifestations are not always associated with the clinical severity of HIV.

Although this study was carried out in pre-ART era in India, we believe that the findings are relevant to the present day and it undelines the need for regular screening of these children for renal involvement. Following HAART, Ahuja et al[20] reported a reduced prevalence of renal manifestations to 3.5% among African Americans. Since our study was done on ART naïve patients, the effect of ART on these renal manifestations should be assessed.

In conclusion, our study suggests that reduced GFR is the common renal manifestation, particularly in younger children. Other renal manifestations are related to proteinuria. The lack of correlation with CDC classification of renal manifestations mandates screening all children with HIV for renal disease. Since this is a preliminary study, a more detailed study of renal manifestations in HIV infected children is needed. Urine examination on regular intervals would be necessary to screen for the presence of protein in urine, and if it is present, further quantification of proteinuria and screening for renal dysfunction are required. Early intervention by ART may be needed in these patients to prevent progression of the disease.

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References

1 HIV InSite, 2008. http://hivinsite.ucsf.edu/InSite?page=kb-04-01-10 (accessed December 17, 2008).
2 Anochie IC, Eke FU, Okpere AN. Human immunodeficiency virus associated nephropathy (HIVAN) in Nigerian children. Pediatr Nephrol 2008;23:117-122.
3 Strauss J, Abitbol C, Zilleruelo G, Scott G, Paredes A, Malaga S, et al. Renal disease in children with acquired immunodeficiency syndrome. N Engl J Med 1989;321:625-630.
4 Ray PE, Rakusan T, Loechelt BJ, Selby DM, Liu XH, Chandra RS. Human immunodeficiency virus-associated nephropathy in children from the Washington D.C. area: 12 years' experience.

Semin Nephrol 1998;18:396-405.
5 Abbott KC, Hypolite I, Welch PG, Agodoa LY. Human immunodeficiency virus/acquired immunodeficiency syndrome-associated nephropathy at end-stage renal disease in the United States: patient characteristics and survival in the pre highly active antiretroviral therapy era. J Nephrol 2001;14:377-383.
6 Esezobor CI, Iroha E, Onifade E, Akinsulie AO, Temiye EO, Ezeaka C. Prevalence of proteinuria among HIV-infected children attending a tertiary hospital in Lagos, Nigeria. J Trop Pediatr 2010;56:187-190.
7 Chaparro AI, Mitchell CD, Abitbol CL, Wilkinson JD, Baldarrago G, Lopez E, et al. Proteinuria in children infected with the human immunodeficiency virus. J Pediatr 2008;152:844-849.
8 Centers for Disease Control and Prevention, 1994. http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm (accessed June 30, 2011).
9 Luma GB, Spiotta RT, Hypertension in children and adolescents. Am Fam Physician 2006;73:1558-1568.
10 Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259-263.
11 Davies AG, Postlethwaite RJ, Price DA, Burn JL, Houlton CA, Fielding BA. Urinary albumin excretion in school children. Arch Dis Child 1984;59:625-630.
12 Strasinger SK. Urinalysis and body fluids, 3rd ed. Philadelphia: F.A. Davis Company, 1994.
13 Steel-Duncan J, Miller M, Pierre RB, Dunkley-Thompson J, Palmer P, Evans-Gilbert T, et al. Renal manifestations in HIV-infected Jamaican children. West Indian Med J 2008;57:246-252.
14 Agarwal DK, Agarwal KN, Upadhyay SK, Mittal R, Prakash R, Rai S. Physical and sexual growth pattern of affluent Indian children from 6-18 years of age. Indian Pediatr 1992;29:1203-1282.
15 Agarwal DK, Agarwal KN. Physical growth in Indian affluent children (Birth - 6 years). Indian Pediatr 1994:31:377-413.
16 Ray PE. Taking a hard look at the pathogenesis of childhood HIV-associated nephropathy. Pediatr Nephrol 2009;24:2109-2119.
17 Eke FU, Anochie IC, Okpere AN, Eneh AU, Ugwu RN, Ejilemele AA, et al. Microalbuminuria in children with human immunodeficiency virus (HIV) infection in Port Harcourt, Nigeria. Niger J Med 2010;19:298-301.
18 Asharam K, Bhimma R, Adhikari M. Human immunodeficiency virus and urinary tract infections in children. Ann Trop Paediatr 2003;23:273-277.
19 Burns GC, Paul SK, Toth IR, Sivak SL. Effect of angiotensin-converting enzyme inhibition in HIV-associated nephropathy. J Am Soc Nephrol 1997;8:1140-1146.
20 Ahuja TS, Borucki M, Funtanilla M, Shahinian V, Hollander M, Rajaraman S. Is the prevalence of HIV associated nephropathy decreasing? Am J Nephrol 1999;19:655-659.

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