CHILDHOOD AIDS NEPHROPATHY: A 10-YEAR EXPERIENCE

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The objective of this study was to define the demographic, immunologic, and clinical characteristics of children with acquired immunodeficiency syndrome (AIDS) and AIDS nephropathy, and contrast this with the existing adult data. Data from 62 pediatric patients with AIDS who were treated at SUNY Health Science Center, Brooklyn, New York, between 1983 and 1993 were analyzed. Human immunodeficiency virus (HIV) infection was acquired during the neonatal period by vertical transmission (n=60) or blood transfusion (n=2). All children with AIDS who exhibited clinical nephropathy died (n=16), with mean survival of 55.3 months. In contrast, 32 of 56 AIDS patients (70%) who did not manifest nephropathy were alive at the end of the study period. Patients with nephropathy were noted to have significantly lower CD4+ lymphocyte counts than those without nephropathy.

These observations suggest that the predominant renal lesion in pediatric patients who acquired HIV infection during the perinatal period is focal segmental glomerulosclerosis, although a variety of other histological lesions were present. As in adults, the survival in children is dismal following the onset of clinical renal disease. In contrast to the adult population in whom multiple risk factors can potentially contribute to AIDS-associated nephropathy, occurrence of nephropathy in children with vertical HIV transmission provides convincing evidence for the pathogenetic role of HIV infection. (*J Natl Med Assoc.* 1996;88:493-498.)

Key words • nephropathy • children • acquired immunodeficiency syndrome (AIDS)

Recent reports indicate a high incidence of various renal disorders in adults with acquired immunodeficiency syndrome (AIDS).[1-3] However, the available data on AIDS nephropathy in the pediatric population are limited. Reported renal abnormalities in adults include hematuria, leukocyturia, electrolyte derangements, decreased renal excretory function, and frank acute renal failure.[4] The most significant renal disorder in AIDS is AIDS nephropathy, which in adults is most frequently due to focal segmental glomerulosclerosis and characterized by heavy proteinuria (>3.5 g/day) and rapid deterioration in renal function. The reported incidence of nephropathy in adult AIDS patients ranges from 2% to 10%.[5] Despite numerous published studies, the pathogenesis of this disease remains obscure. Due to the high prevalence of intercurrent conditions capable of causing glomerular disease in adults with AIDS (eg, intravenous drug abuse, hepatitis B infection, etc), it has been difficult to discern the direct role of HIV infection in the pathogenesis of AIDS nephropathy. This study was undertaken to define the demographic, immunologic, and clinical characteristics of children with AIDS and AIDS nephropathy, and contrast this with the existing adult data

MATERIALS AND METHODS

Patients

The patient population was comprised of 72 consecutive children with AIDS who were treated at the SUNY Health Science Center, Brooklyn, New York between 1983 and 1993. Ten patients were lost to fol-

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low-up and were excluded from the study. The remaining 62 patients were comprised of 35 males and 27 females. Data from patients exhibiting AIDS without clinical evidence of nephropathy (group 1) were compared with those exhibiting nephropathy (group 2).

The diagnosis of AIDS was based on the criteria established by the Centers for Disease Control (CDC).[6,7] In all cases, antibodies to human immunodeficiency virus (HIV) were present by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot analysis. Urinalysis, hemogram, serum electrolytes, complement levels, antinuclear antibodies, anti-DNA antibody determination, and immunoglobulin levels were measured in all patients using standard laboratory techniques. T-cell subset studies were performed periodically in all patients using fluorescein-conjugated monoclonal antibodies in a fluorescence-activated cell sorter. Patients with an abnormal urinalysis, or elevated serum urea nitrogen or creatinine concentrations and patients with acid-base or other electrolyte disturbances were considered to have AIDs nephropathy and were referred to the pediatric nephrology service for further evaluation.

Presence of renal disease was investigated by microscopic examination of urinary sediment and 24-hour urine collection to measure protein excretion and creatinine clearance. Nephrosis was defined as persistent proteinuria >40 mg/m^2/hour, hypoalbuminemia (serum albumin concentration <2.5 g/dL), and presence of clinical edema. Renal failure was defined as a creatinine clearance <10 mL/minute/m^2. Serum urea nitrogen, creatinine, total protein, and albumin concentrations were measured using standard laboratory techniques.

In 11 patients, renal tissue was obtained by percutaneous renal biopsy under sonographic localization. Specimens were obtained at autopsy in two patients. The patient's poor clinical condition or parent's refusal to give informed consent precluded biopsy in the remaining patients. The renal tissue samples were fixed, cut, and stained using standard laboratory techniques and examined by light, immunofluorescent, and electron microscopy.

Nephrosis was treated according to the protocol set forth by the International Society of Kidney Diseases in Children.[8] Accordingly, patients received prednisone 60 mg/m^2 (maximum: 80 mg) daily for 4 weeks, followed by 40 mg/m^2 every other day. Remission was defined as the absence of proteinuria by dipstick on 3 consecutive days. Partial remission was defined as proteinuria between 4 and 40 mg/m^2/hour, and absence of edema. In addition to oral steroid therapy, three patients with focal segmental glomerulosclerosis were treated with cyclosporine.[9] Two patients received zidovudine in an attempt to decrease morbidity. Patients who developed end-stage renal disease were treated with peritoneal dialysis.

Data Analysis

Data were evaluated using life table analysis and two-tailed Students' *t*-test, as appropriate, and presented as mean±standard error of the mean (SEM). *P* values <.05 were considered significant.

RESULTS

Demographic and Survival Data

Group 1. This group consisted of 46 patients without clinical AIDS nephropathy. All patients in this group had vertical transmission of HIV. There were 27 males (58%) and 19 females (42%). Twenty-three were black (50%), 13 Haitian (29%), and 10 Hispanic (21%). Twenty-six mothers admitted to intravenous drug use; in the remaining cases, HIV infection was assumed to have been contracted sexually. Thirty-two patients (70%) were alive at the end of the study period. The mean survival of the 14 children who died in this group was 76±6.5 months. Causes of death in these patients included bacterial sepsis, pneumonia, and severe failure to thrive. Opportunistic infections with cytomegalovirus were noted in 4 chidren and oral thrush in 10 children. Three patients were HBsAg positive.

Group 2. This group consisted of 16 patients with clinical AIDS nephropathy. All children were infected transplacentally except for two who contracted HIV infection via blood transfusion during the neonatal period. The group consisted of eight males (50%) and eight females (50%). Six patients were black (37%), eight Haitian (50%), and two Hispanic (13%). Ten of the 14 infected mothers admitted intravenous drug use, and the remainder were considered to have contracted the infection through sexual transmission. The age of patients at the time of diagnosis of AIDS-associated nephropathy was 45±2 months. Mean survival in this group was 55±7.6 months, which was significantly less than that in group 1 ($P<.0002$) (Figure).

Immunological Data

Mean absolute CD4+ lymphocyte counts were 1142±138 in group 1 and 338±37 in group 2 ($P<.05$). Notably, 11 patients in group 1 exhibited a marked decline in absolute CD4+ helper T-lymphocyte counts from 854±48 prior to the onset of nephropathy to 173±35 cells/mm^3 ($P<.003$) after the onset of

nephropathy. Differences in CD8+ lymphocyte counts and serum immunoglobulin levels (IgA, IgM, and IgG) between the two groups were not significant. Serum complement concentrations (C3, C4, and CH50), and ANA and anti-double-stranded DNA titers were within normal limits in all cases (both groups), and differences between the groups were not statistically significant.

Clinical Features of Nephropathy

Fifteen patients presented with nephrotic-range proteinuria, one had mild proteinuria, one had renal tubular acidosis, and two exhibited hematuria along with proteinuria. Thirteen patients treated with prednisone failed to demonstrate improvement in proteinuria or creatinine clearance. Three patients with focal segmental glomerulosclerosis who were treated with cyclosporine for 12 weeks exhibited a partial remission and disappearance of clinical edema but relapsed and developed nephrotic syndrome following withdrawal of treatment. The mean survival after the diagnosis of renal disease was 9.5 months.

In the four patients who progressed to end-stage renal disease, the time from onset of nephrotic syndrome to end-stage renal disease was 6 months (range: 4 to 8 months). Three of these patients received intermittent peritoneal dialysis for a mean of 3.7 months (range: 2 to 6 months).

Opportunistic infections in this group included cytomegalovirus in six, tuberculosis in one, *Pneumocystis carinii* in two, herpes simplex in two, and recurrent oral thrush in nine. Six children had extreme malnutrition and failure to thrive secondary to intractable diarrhea. Causes of death in this group included encephalopathy in 6 cases, and pneumonia, bacterial sepsis, and extreme malnutrition in 10.

Histology

Renal biopsy specimens were available in 13 patients. Renal histology revealed focal segmental glomerulosclerosis in six cases, mesangial hypercellularity in five, tubular dysplasia in one, and minimal change glomerulopathy in one case. Tubulointerstitial lesions consisted of dilation, atrophy, fibrosis, and inflammation in six specimens.

Immunofluorescence revealed glomerular deposits of IgM in 10, IgG in 7, IgE in 5, and IgA in 3 specimens. Electron microscopy performed on nine specimens revealed subendothelial, subepithelial, or intramembranous electrodense deposits in seven of nine specimens and tubuloreticular inclusions in nine specimens examined (Table).

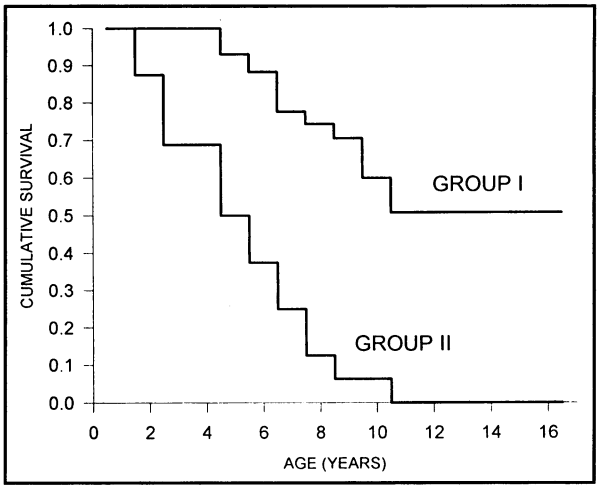

Figure. Kaplan-Meier life table analysis of survival for AIDS patients with (group 2) and without (group 1) clinical AIDS nephropathy.

DISCUSSION

Acquired immunodeficiency syndrome nephropathy is a well-known complication of AIDS in adults. However, data on AIDS nephropathy in the pediatric population are limited. The reported incidence of nephropathy in adults with AIDS ranges from 2% to 10%[5] depending on the geographic location of the reporting center and demographic characteristics of the study population, particularly the proportion of white versus black patients, intravenous drug users versus homosexuals, etc.[5,10-12]

We found a significant incidence of nephropathy in our group of children with AIDS. Based on our observations, the incidence of AIDS nephropathy in the pediatric population appears to approximate that of the adult population. Furthermore, in contrast to the adult population in which AIDS nephropathy is predominantly seen in men, in children, both sexes were affected equally.

The mean survival in AIDS patients with nephropathy was significantly lower than that seen in children without AIDS nephropathy. It is noteworthy that 100% of children with AIDS nephropathy but only 30% of those without AIDS nephropathy died during the study period. Interestingly, the incidence of end-stage renal disease in our pediatric population with AIDS nephropathy was lower than that reported in the adult population. Only 22% of our patients with AIDS nephropathy developed end-stage renal disease prior to demise compared with the reported incidence of 80% in adults with AIDS nephropathy.[13] Twelve remaining patients died secondary to infection with normal renal function, as previously indicated.

TABLE. DATA DEPICTING RISK FACTORS, HISTOLOGY, AND OUTCOME OF PEDIATRIC PATIENTS WITH AIDS NEPHROPATHY

Patient No.	Mother IVDA	Transmission	Nephrotic Syndrome	Histology	ESRD at Death
1	+	Vertical	+	No biopsy	–
2	–	Vertical	+	FSGS	+
3	+	Vertical	+	FSGS	+
4	–	Vertical	+	Mes hyperplasia	–
5	–	Transfusion	+	FSGS	+
6	+	Vertical	+	Mes hyperplasia	+
7	–	Transfusion	+	Mes hypeplasia	–
8	+	Vertical	+	Tubular dysplasia	–
9	+	Vertical	+	No biopsy	–
10	+	Vertical	+	FSGS	–
11	+	Vertical	+	FSGS	–
12	+	Vertical	+	Minimal change	–
13	+	Vertical	+	Mes hyperplasia	–
14	+	Vertical	+	FSGS	–
15	+	Vertical	Mild proteinuria	No biopsy	–
16	–	Vertical	+	Mes hyperplasia	–

Abbreviations: AIDS=acquired immunodeficiency syndrome, IVDA=intravenous drug abuser, ESRD=end-stage renal disease, FSGS=focal segmental glomerulosclerosis, and Mes=mesangial hyperplasia.

The mean survival times after the onset of renal disease and following onset of end-stage renal disease in this series were 9 and 6 months, respectively, consistent with the reported experience with adult AIDS nephropathy. Thus, as in adults, the onset of nephropathy in children with AIDS denotes a particularly poor prognosis.[14,15]

In this series, all children with AIDS exhibited nonspecific hypergammaglobulinemia (IgA, IgM, and IgE) irrespective of the presence of AIDS nephropathy. Similar observations have been noted in the adult population.[16] The role, if any, of hypergammaglobulinemia in the genesis of nephropathy remains obscure. All children in both groups had normal complement concentrations, and ANA and anti-double-stranded DNA titers.

As expected, all of our patients exhibited reversal of the normal T4:T8 lymphocyte ratio, with a decrease in the absolute levels of circulating CD4+ lymphocytes. Interestingly, the absolute CD4+ cell count showed a more precipitous decline in the AIDS nephropathy group. The reason for the accelerated decline in the CD4+ cell count with AIDS nephropathy is not clear and may be related to the effects of the associated biochemical abnormalities and greater incidence of morbid complications. The association of the precipitous decline in CD4+ lymphocytes and the shortened survival in AIDS nephropathy group is of interest and may be causally related.

As in adults, focal segmental glomerulosclerosis was by far the most common histologic lesion present on renal biopsy. Our study population consisted of 90% American and Haitian blacks. It is of interest that the incidence of idiopathic focal segmental glomerulosclerosis is higher among the black population, due presumably to a genetic predisposition to this lesion.[17,18] Other findings in our study group included mesangial hyperplasia, minimal change glomerulopathy, and tubular and interstitial abnormalities, which were consistent with previously published reports in children as well as adults. Similarly, several reports have described other types of immune complex renal diseases in adult patients with AIDS.[19,20]

It is noteworthy that three of the four children with end-stage renal disease had focal segmental glomerulosclerosis. A previous large study in AIDS children also reported a similar outcome in their population with focal segmental glomerulosclerosis.[20] The progressive nature of this lesion in children with AIDS is consistent with previous observations reported in the adult population, although the rate of progression in children appears to be slower than that in adults. A progressive form of focal segmental glomerulosclerosis has been shown to occur among intravenous drug abusers.[21,22] For this reason, intravenous drug use has been implicated in the pathogenesis of AIDS nephropathy. Although a substantial number of the mothers of the children included in our study admitted to intravenous drug abuse, the renal lesions observed in the children are unlikely to be due to intravenous drugs used by their mothers. This is because no instances of

glomerulopathy have been reported in the children of substance-abusing mothers. Second, the glomerulopathy seen in intravenous drug users without HIV infection progresses more slowly and usually is associated with hypertension, while AIDS nephropathy is characterized by rapid deterioration in renal function without significant hypertension. Moreover, similar lesions were found in children of mothers with HIV infection and no evidence of intravenous drug abuse. Therefore, the demonstrated occurrence of focal segmental glomerulosclerosis in children with AIDS supports the role of HIV infection in the pathogenesis of this renal lesion.

The mechanism by which HIV infection may cause glomerular injury is speculative. However, it may be due to the effect of HIV on tubular and glomerular cells, leading to abnormalities in cell growth and matrix protein turnover. Alternatively, HIV infection may contribute to glomerular injury by promoting the formation and deposition of immune complexes at the local and systemic levels. Finally, HIV infection somehow may help to unleash an otherwise subdued genetic predisposition for such glomerular lesions as indicated by the predominance of AIDS nephropathy in blacks.[23] With regard to the former possibilities, HIV has been demonstrated in glomerular epithelial and mesangial cells.[24,25] Thus, HIV potentially can alter glomerular function and structure by direct invasion or through remote effects.

When compared with the recent experience of Smith et al[26] in adult patients, 13 children in our series treated with steroids did not respond with reduction in proteinuria. Four patients who progressed to end-stage renal disease also were treated with prednisone without success, consistent with previous experience.[20,27] Early use of zidovudine has been reported to delay development of end-stage renal disease and reduce proteinuria.[28] Only two patients with end-stage renal disease in our series received zidovudine. The limited nature of the experience and lack of proper control in this case preclude a meaningful conclusion.

Three patients in our series with focal segmental glomerulosclerosis were treated with cyclosporine A, which led to a partial remission. Treatment in these three cases was discontinued after 3, 6, and 12 months to avoid compounding the underlying immunodeficiency. Discontinuation of cyclosporine A therapy was associated with complete relapse of nephrotic syndrome and progression to renal failure. The possible usefulness of cyclosporine in this condition merits future controlled studies.

SUMMARY

This study highlights the various demographic, histologic, and immunologic characteristics of children with AIDS and a subset of this population who develop AIDS nephropathy. Notably, vertical transmission of HIV infection and the absence of other multiple risk factors in children points to a direct role of this virus in the genesis of renal disease. However, the mechanism by which the virus induces nephropathy remains unclear. As for treatment, pediatric AIDS nephropathy seems to be resistant to conventional therapies. Further controlled studies on the prompt use of zidovudine and cyclosporine A therapy are needed.

Literature Cited

1. Rao TK, Filippone EJ, Nicastri AD, Landesman SH, Frank E, Chen CK, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med.* 1984;310:669-673.

2. Gardenswartz MH, Lerner CW, Seligson GR, Zabetakis PM, Rotterdam H, Tapper ML, et al. Renal disease in patients with AIDS: a clinicopathologic study. *Clin Nephrol.* 1984;21:197-204.

3. Pardo V, Aldana M, Colton RM, Fischl MA, Jaffe D, Moskowitz L, et al. Glomerular lesions in the acquired immunodeficiency syndrome. *Ann Intern Med.* 1984;101:429-434.

4. Vaziri N, Barbari A, Licorish K, Cesario T, Gupta S. Spectrum of renal abnormalities in acquired immune-deficiency syndrome. *J Natl Med Assoc.* 1985;77:369-375.

5. Mazbar SA, Schoenfeld PY, Humphreys MH. Renal involvement in patients infected with HIV: experience at San Francisco General Hospital. *Kidney Int.* 1990;37:1325-1332.

6. Centers for Disease Control. Acquired immunodeficiency syndrome—United States. *MMWR.* 1984;32:688-691.

7. Centers for Disease Control. Classification system of human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR.* 1987;36:225-230.

8. International Study of Kidney Disease in Children. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. A report of the International Study of Kidney Disease in Children. *J Pediatr.* 1982;101:514-518.

9. Tejani A, Butt K, Trachtman H, Suthanthiram M, Rosenthal C, Khawar M. Cyclosporine A induced remission of childhood nephrotic syndrome. *Kidney Int.* 1988;33:729-734.

10. Seney FJ, Burns DK, Silva FG. Acquired immunodeficiency syndrome and the kidney. *Am J Kidney Dis.* 1990;16:1-13.

11. Glassock RJ, Cohen AH, Danovitch G, Parsa KP. Human immunodeficiency virus (HIV) infection and the kidney. *Ann Intern Med.* 1990;112:35-49.

12. Humphreys MH, Schoenfeld PY. Renal complications in patients with the acquired immune deficiency syndrome (AIDS). *Am J Nephrol.* 1987;7:1-7.

13. Rao TK, Friedman EA, Nicastri AD. The types of renal disease in the acquired immunodeficiency syndrome. *N Engl J Med.* 1987;316:1062-1068.

14. Rao TK, Manis T, Friedman EA. Dismal prognosis despite maintenance hemodialysis in AIDS nephropathy and chronic uremia. *Trans Am Soc Artif Intern Organs.*

1985;31:160-163.

15. Ortiz C, Meneses R, Jaffe D, Fernandez JA, Perez G, Bourgoignie JJ. Outcome of patients with human immunodeficiency virus on maintenance hemodialysis. *Kidney Int.* 1988;34:248-253.

16. Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1983,309:453-458.

17. Bakir AA, Bazilinski NG, Rhee HL, Ainis H, Dunea G. Focal segmental glomerulosclerosis. A common entity in nephrotic black adults. *Arch Intern Med.* 1989;149:1802-1804.

18. Glicklich D, Haskell L, Senitzer D, Weiss RA. Possible genetic predisposition to idiopathic focal segmental glomerulosclerosis. *Am J Kidney Dis.* 1988;12:26-30.

19. Nochy D, Glotz D, Dosquet P, Pruna A, Guettier C, Weiss L, et al. Renal disease associated with HIV infection: a multicentric study of 60 patients from Paris hospitals. *Nephrol Dial Transplant.* 1993;8:11-9.

20. Strauss J, Abitbol C, Zilleruelo G, Scott G, Paredes A, Malaga S, et al. Renal disease in children with the acquired immunodeficiency syndrome. *N Engl J Med.* 1989;321:625-630.

21. Cunningham EE, Brentjens JR, Zielezny MA, Andres GA, Venuto RC. Heroin nephropathy. A clinicopathologic and epidemiologic study. *Am J Med.* 1980;68:47-53.

22. Rao T, Nicastri A, Friedman E. Natural history of heroin-associated nephropathy. *N Engl J Med.* 1974;290:19-23.

23. Bourgoignie JJ, Ortiz IC, Green DF, Roth D. Race, a cofactor in HIV-I-associated nephropathy. *Transplant Proc.* 1989;21:3899-3901.

24. Cohen AH, Sun NC, Shapshak P, Imagawa DT. Demonstration of human immunodeficiency virus in renal epithelium in HIV-associated nephropathy. *Mod Pathol.* 1989;2:125-128.

25. Green DF, Resnick L, Bourgoignie JJ. HIV infects glomerular endothelial and mesangial but not epithelial cells in vitro. *Kidney Int.* 1992;41:956-960.

26. Smith M, Pawar R, Carey J, Graham R, Jacobs G, Menon A, et al. Effect of corticosteroid therapy on human immunodeficiency virus-associated nephropathy. *Am J Med.* 1994;97:145-151.

27. Rousseau E, Russo P, Regan S. Renal complications of acquired immunodeficiency syndrome in children. *Am J Kidney Dis.* 1988;11:48-50.

28. Michel C, Dosquet P, Ronco P, Mougenot B, Viron B, Mignon F. Nephropathy associated with infection by human immunodeficiency virus: a report on 11 cases including 6 treated with zidovudine. *Nephron.* 1992;62:434-440.