Evaluation of renal profile in asymptomatic HIV patients with special reference to proteinuria

Ocena profilu nerkowego u pacjentów z bezobjawowym zakażeniem wirusem HIV, ze szczególnym uwzględnieniem białkomoczu

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Key words: human immunodeficiency virus (HIV), HIV-associated nephropathy, proteinuria, risk factors, prevalence.

Słowa kluczowe: HIV, HIVAN, białkomocz, czynniki ryzyka, częstość występowania.

Abstract

Introduction: Renal disease has now become a well-recognised complication of HIV infection. If not recognized early it frequently progresses to end stage renal disease, thus becoming a major cause of morbidity and mortality.
Aim of the research: The purpose of this study was to know the prevalence of renal dysfunction in asymptomatic HIV patients in terms of proteinuria and various risk factors associated with it and to study the histopathological lesions associated in patients with nephrotic range proteinuria.
Material and methods: We conducted a cross-sectional, single-centre study on 100 asymptomatic HIV patients aged between 18 and 50 years. Baseline investigations including kidney function tests and CD4 count were done on in all patients. Proteinuria was defined as 1+ on urine dipstick in spot urine sample. Urine microalbumin was measured by immunoturbidimetry or nephelometry. 2-D ultrasonography was done to determine kidney size and echogenicity. Renal biopsy was done in patients with nephrotic range proteinuria.
Results: The total prevalence of proteinuria among the study subjects was 21%. It was significantly associated with older age, lower CD4 counts, higher serum creatinine, and lower haemoglobin levels. There were no significant differences between patients with and without proteinuria with regard to sex and concurrent antiretroviral therapy. Proteinuria was also associated with increased kidney size and echogenicity. In the patients with nephrotic syndrome focal segmental glomerulosclerosis was the most common histological pattern. A progressive decline in glomerular filtration rate was observed as the disease progressed in terms of duration of disease and decrease in CD4 count.
Conclusions: Renal dysfunction in HIV is dependent on a variety of host and immunological factors. Careful screening can help identify the subjects who are at higher risk. Various simple investigations such as 2D ultrasonography and urine dipsticks can serve as an effective screening tool.

Streszczenie

Wprowadzenie: Choroba nerek jest powszechnie uznawanym powikłaniem zakażenia wirusem HIV. Jeżeli schorzenie nie jest odpowiednio wcześnie rozpoznane, często prowadzi do schyłkowej niewydolności nerek, która jest jedną z głównych przyczyn chorobowości i śmiertelności.
Cel pracy: Ustalenie częstości występowania zaburzeń czynności nerek u pacjentów z bezobjawowym zakażeniem wirusem HIV, ze szczególnym uwzględnieniem białkomoczu oraz związanych z nim czynników ryzyka, a także analiza zmian histopatologicznych występujących u pacjentów z białkomoczem w przedziale wartości nerczycowych.
Materiał i metody: W przekrojowym badaniu jednoośrodkowym uczestniczyło 100 pacjentów z bezobjawowym zakażeniem wirusem HIV w wieku 18–50 lat. U wszystkich tych osób przeprowadzono badania dotyczące czynności nerek oraz liczby komórek CD4. Białkomocz określono jako dodatni (1+) wynik testu paskowego próbki moczu. Stężenie mikroalbuminy w moczu oznaczano metodą immunoturbidymetrii lub nefelometrii. Wielkość i echogeniczność nerek badano za pomocą ultrasonografii 2D. U pacjentów z białkomoczem w przedziale wartości nerczycowych przeprowadzono biopsję nerek.
Wyniki: Całkowita częstość występowania białkomoczu wśród uczestników badania wyniosła 21%. Odnotowano istotny związek białkomoczu ze starszym wiekiem, mniejszą liczbą komórek CD4, większym stężeniem kreatyniny w surowicy oraz niższym poziomem hemoglobiny. Nie stwierdzono istotnych różnic między pacjentami z białkomoczem i bez białkomoczu w zależności od płci i jednocześnie prowadzonego leczenia przeciwwirusowego. Białkomocz wiązał się również z powiększeniem nerek i wzrostem ich echogeniczności. U pacjentów z zespołem nerczycowym najczęściej stwierdzano obraz histologiczny typu FSGS. Odnotowano postępujące zmniejszenie współczynnika przesączania kłębuszkowego w miarę progresji choroby – dotyczyło to czasu jego trwania i liczby komórek CD4.
Wnioski: Zaburzenia czynności nerek w przebiegu zakażenia wirusem HIV są uwarunkowane wieloma czynnikami immunologicznymi oraz zależnymi od pacjenta. Przy identyfikacji pacjentów z grupy zwiększonego ryzyka mogą być pomocne dokładne badania przesiewowe. Skutecznymi narzędziami przesiewowymi okazują się proste badania, np. ultrasonografia 2D oraz test paskowy moczu.

Introduction

Human immunodeficiency virus (HIV), the virus that causes AIDS "acquired immunodeficiency syndrome" has become the world's most serious health and developmental challenge in our era. With the use of highly active antiretroviral therapy (HAART) survival among persons with HIV infection has improved significantly over the last decade. As patients with HIV disease live longer with anti-retroviral therapy, patients are experiencing the complex, interacting effects of HIV infection itself, ART, and the worldwide diseases of development, including atherosclerosis, metabolic syndrome, type 2 diabetes, and end stage renal disease (ESRD).

Soon after the discovery of HIV reports of renal failure were published which attributed this complication to the effects of virus replication inside the kidney [1]. With the growing knowledge about the disease and better screening tools, renal disorders are now encountered at all stages of HIV infection ranging from the fluid and electrolyte imbalances commonly seen in hospitalised patients to ESRD. Various risk factors which predispose patients of HIV to increased susceptibility of renal damage include co-infection with hepatitis B and C, cigarette smoking, and injection drug use. Use of some antiretrovirals and other medications further increase the risk due to their nephrotoxicity. Renal involvement in HIV is also dependent on variety of host factors such as female sex, black race, level of HIV viral load, low CD4 count, and other comorbid conditions.

Clinically renal involvement may manifest as acute kidney injury, HIV-associated nephropathy (HIVAN), HIV-related immune complex disease, nephropathy secondary to ART, thrombotic microangiopathy, and diseases related to common comorbidities such as amyloidosis from heroin skin popping or HCV-related membranoproliferative glomerulonephritis [2]. Out of all presentations the most dramatic is HIVAN, formerly known as AIDS-associated nephropathy and is usually associated with higher viral RNA levels and lower CD4 counts. Depending on the immunological status, the patient may present as asymptomatic proteinurea as well as with end stage renal disease.

The other most distinctive feature of HIVAN is the malignant nature of the syndrome and the rapidity with which renal function deterioration occurs even in the absence of additional renal injury. The development of ESRD in HIVAN also marks the beginning of a progressive clinical deterioration, ending in death in most patients in less than a year despite maintenance dialysis [3]. Epidemiologic data suggest that effective control of viral replication with ART can prevent the appearance of HIV-associated nephropathy whereas the institution of ART after the diagnosis of HIVAN may prolong renal survival.

Aim of the research

Therefore, considering the nature of disease, it becomes essential to screen all HIV infected patients for kidney disease since institution of effective therapy at right time can effectively modulate the course of the disease. So this study was planned to assess the prevalence of renal dysfunction in asymptomatic HIV patients. The primary aim of the study was to know the prevalence of renal dysfunction in terms of proteinuria and various risk factors associated with it and to study the histopathological lesions associated in patients with nephrotic range proteinuria.

Material and methods

The present study was conducted on one hundred adult HIV positive patients of age between 18 and 50 years, registered in the ART Centre of our institute, and who were asymptomatic at the time of enrolment in the study. The study was approved by the PG board of studies of the institute and the Ethical Committee of the University. A pre-informed written consent for enrolment in the study was obtained. Patients who were co-infected with hepatitis B or C were excluded from the study. Other patients who were excluded were those with diabetes, hypertension, any other cause of chronic kidney disease such as chronic pyelonephritis, autosomal dominant polycystic kidney disease, lupus nephritis, serum creatinine > 1.5 mg%, taking nephrotoxic drugs including tenofovir, and those having confounding factors for microalbuminuria such as fever, heavy exercise, cardiac failure, hyperglycaemia, acute illness, urinary tract infection, and prostatic disease.

This study included both treatment naïve patients and patients who were already started on antiretroviral therapy of fixed combination of zidovudine, lamivudine and nevirapine. However all patients who were exposed to any other antiretroviral drug were excluded to avoid any discrepancy caused by effect of drug on kidney directly.

Each patient was subjected to detailed history and general physical examination. Baseline investigations done in each patient included complete haemogram, kidney function tests, blood sugar, and serum albumin. Glomerular filtration rate was calculated for each patient using the Cockroft-Gault formula [4].

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight in kg} \times (0.85 \text{ for females})}{\text{Serum creatinine}} \times \frac{1}{72}.$$

CD4 cell count in patients was determined at a fixed time of day (8:00 a.m.) using a specific monoclonal antibody and fluorescence-activated cell-sorter analysis (BD FACS count™ system and reagent-BD Biosciences). Urine examination was done by dipstick method. Urine microscopic examination was also done to rule out confounding factors, such as urinary tract infection indicated by presence of pus cells. Pro-

teinuria was defined as 1+ on urine dipstick examination. Microalbuminuria was defined as urinary albumin 30–300 mg/day or spot urine albumin/creatinine ratio > 3.5 mg/mmol for females and > 2.5 mg/mmol for males. Urine microalbumin was measured by immunoturbidimetry or nephelometry. Those patients with a positive test for proteinuria were proceeded for 24-hour urine collection to quantify the amount of protein in the urine (by Biuret method). For study purposes these patients were divided into categories according to the amount of total protein excreted per 24 h: microalbuminuria (30–300 mg), microalbuminuria (> 300 mg) and nephrotic range proteinuria (> 3.5 gm).

2-D ultrasonography was done on all patients enrolled in the study. Parameters studied were bilateral kidney size and echogenicity. Kidney size was considered normal in the range of 9–12 cm. Less than 9 cm was considered shrunken and more than 12 cm was considered as enlarged kidney size. Patients with nephrotic range proteinuria underwent an ultrasound guided renal biopsy to establish a histopathological diagnosis, after explaining all risks and benefits involved and after taking an informed consent.

Statistical analysis

The data collected during the study was analysed using SPSS.20.0 version. To examine differences between categorical variables the χ^2 test was used. Independent sample *t*-test was used to compare the means of two separate sets of independent samples. To predict the relationship between a categorical dependent variable and an independent variable, logistic regression was used. For comparison of means of more than two samples the analysis of variance (ANOVA) test was used and *p*-values obtained to determine the statistical significance. Pearson correlation coefficient was calculated to assess the correlation between two variables. The *p* values were two tailed and probability level of significant difference was set at < 0.05.

Results

Among the hundred patients included in the study 66 were males and 34 females. All of the patients were in the age group 18–50 years. For study purpose they were divided into three subgroups i.e. 18–24 years, 25–34 years, and 35–50 years. The younger age group had 16 patients and the remaining two age groups had 42 patients each. Fifty-six study subjects were already taking anti-retroviral therapy at the time of enrolment; none of them included any nephrotoxic drug. According to glomerular filtration rate (GFR), patients were categorised into five stages of chronic kidney disease (CKD). Out of 100, 44 patients had normal renal functions with GFR > 90 ml/min/1.73 m^2 with no structural abnormality. 25 patients were in stage 1, 21 patients were in stage 2, 9 patients were in stage 3, and one patient in stage 4. The total prevalence of proteinuria among the study subjects was 21%. Out of these, 5 patients (24%) had microalbuminuria and rest 16 had macroalbuminuria (76%).

Renal biopsy was performed in 5 patients. The most common pattern on histopathology was focal segmental glomerulosclerosis present in 3 patients, and in the remaining 2 patients one had mesangioproliferative glomerulonephritis and the other had non-specific chronic tubulointerstitial changes. Only 1 patient had findings of classical HIVAN i.e. collapsing form of focal segmental glomerulosclerosis.

The mean age of patients with proteinuria was 39.04 ±6.21 years. The presence of proteinuria was significantly higher ($p = 0.006$, $OR = 4.55$) in patients of age group 35–50 years as compared to patients of age 25–34 years (Table 1). As evident from Table 2, patients having proteinuria had lower mean CD4 count ($p < 0.001$) (Figure 1), longer duration of disease ($p < 0.001$), lower haemoglobin levels ($p < 0.05$), and higher serum creatinine ($p < 0.001$). There was no statistically significant association of proteinuria with gender ($p = 0.104$) and ART intake ($p = 0.54$).

On ultrasonographic examination, increased kidney size ($p < 0.001$, $OR = 34.07$) and grade II–III increased echogenicity ($p < 0.001$, $OR = 80$) was found to be significantly associated with the presence of proteinuria.

Table 1. Prevalence of proteinuria in different age groups

Age group [years]	Patients having proteinuria (*n* = 21)	Patients without proteinuria (*n* = 79)
18–24	0	16
25–34	5	37
35–50	16	26

Table 2. Different variables compared in patients with and without proteinuria

Parameter	Patients having proteinuria	Patients without proteinuria
CD4 count [cells/µl]	214 ±141.64	437 ±125.45
Duration of disease [months]	36 ±15.68	17 ±12.98
Haemoglobin [mg/dl]	10.2 ±1.26	11.2 ±1.77
Serum creatinine [mg%]	1.2 ±0.28	0.8 ±0.12

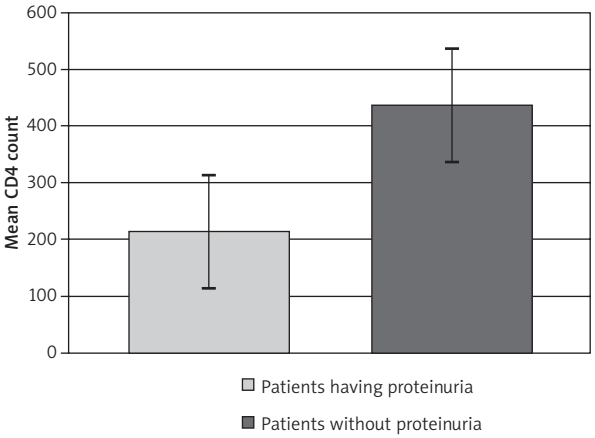

Figure 1. Relation of proteinuria with CD4 count

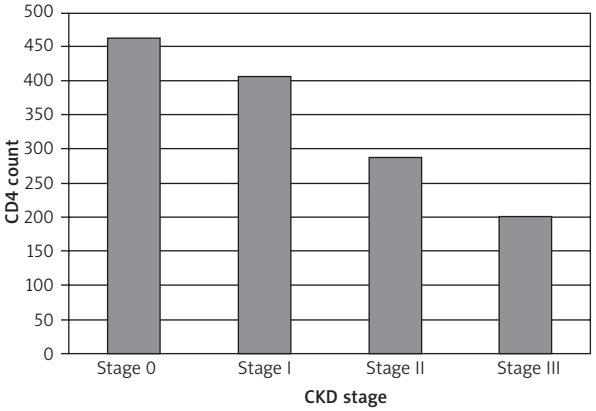

Figure 2. Relation of CD4 count with stage of CKD

Table 3. Relation of CD4 count with CKD stage

Stage	Mean CD4 count [cells/µl]	Value of *p*
0	464.91 ±89.39	< 0.001
I	408.96 ±154.88	
II	289.57 ±169.17	
III	203.78 ±147.75	

In the study group mean CD4 count was higher in non-CKD patients (464.91 ±89.39 cells/µl) as compared to CKD patients. As depicted in Table 3, a decrease in CD4 count was associated with progression of stage of CKD ($p < 0.001$) (Figure 2). Further GFR and duration of disease were found to have an inverse relation ($R = -0.58$, $p < 0.001$) and the increasing duration of disease was contributing 34% to progressive fall in GFR (Figure 3).

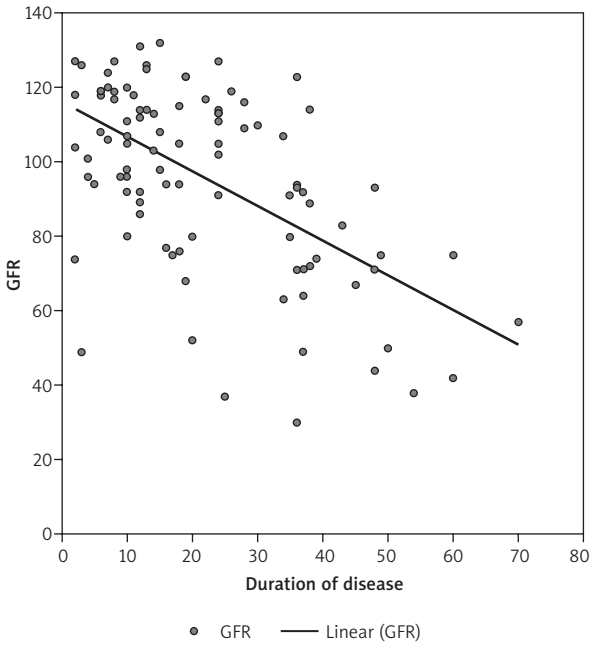

Figure 3. Relation of duration of disease with GFR

Discussion

Since its discovery in the early 1980s, HIV/AIDS has been a major burden on global health and economy. It has been a major cause of morbidity and mortality, affecting almost every organ system and causing opportunistic infections and malignancies due to a persistent immunocompromised state. Currently, there are approximately 35 million people living with HIV all around the world [5]. The prevalence of HIV patients in south and southeast Asia was estimated to be around 3.9 million in the year 2012 [6]. In India the first AIDS case was detected in 1986 and since then HIV infection has been reported in all states and union territories. India has now the third largest number of people living with HIV/AIDS. As per the annual report of 2012–2013, there are an estimated 2.9 million people currently living with HIV/AIDS in India with an adult prevalence of 0.27% in 2011 [7].

With the advent of early diagnostic tests and low threshold of suspicion, patients are diagnosed early in the course of disease and thus the presentation of classical AIDS complex is decreasing and patients are frequently reporting with morbidity related to increased survival with depressed immunity and its effects on major organ systems. Renal dysfunction in HIV was first reported in the mid-1980s by Rao *et al.*, characterised by nephrotic syndrome and azotaemia marked by rapid progression to severe uremia [1]. With time, renal disease has now become a well- recognised complication of HIV infection. In a study, overall relative risk of renal disease was found to be increased by 3.87 among HIV-infected people compared to HIV-uninfected people [8]. With rampant HIV infection in developing countries, HIV-associated renal disease can be expected to add a significant health and economic burden to these regions.

In our study the prevalence of proteinuria was found to be 21%. This was comparable to results of a study done by Longo *et al.*, which found the prevalence of proteinuria to be 20.5% among patients of HIV [9]. Hailemariam *et al.* reported proteinuria in 18% of the HIV affected Caucasian population and Janakiraman reported a prevalence of 27% in South India [10, 11]. However, Various studies done in African countries have reported a prevalence of 5–45% [12, 13]. In our study the prevalence was lower than that of African countries because the black population is known to be at higher risk for nephropathy due to variation in chromosome 22 containing MYH9 and ApoL1 genes [14].

Out of the 21 patients, 5 patients had microalbuminuria and 16 patients had macroalbuminuria, out of which 5 patients had nephrotic range proteinuria. The reason for the lower number of patients diagnosed with nephrotic syndrome can be understood by the fact that renal dysfunction in HIV has a very rapidly progressive course. Because of absence of oedema, many patients are not aware of their condition and thus do not seek medical attention even while they are having massive proteinuria. Thus in the absence of ART these patients have a very small window period during which they progress from stage of nephrotic syndrome to complete renal failure requiring dialysis.

On histopathological examination of renal biopsy specimens of 5 patients with nephrotic range proteinuria, 3 patients had findings suggestive of focal segmental glomerulosclerosis with only 1 patient having collapsing subtype; the remaining 2 patients had tip lesions. One patient had diagnosis of membranoproliferative glomerulonephritis and the remaining one patient showed chronic non-specific tubulointerstitial nephritis. In the study by Janakiraman *et al.* HIVAN was present in 70% of patients, the remaining diagnoses were of chronic tubulointerstitial nephritis, membranous glomerulopathy and diffuse proliferative glomerulonephritis [11]. However, in a study by Gupta *et al.* the most common lesion on renal biopsy was mesangioproliferative glomerulonephritis [15]. Studies from Europe have found a low incidence of HIVAN in Caucasian and Asian patients as compared to blacks [16, 17]. The exact cause of this discrepancy is not entirely clear, although racial predisposition, viral genotype, and other immunomodulatory host susceptibility factors may play a role [11].

Patients of older age group were found to have 4.55 times higher risk of renal involvement with HIV as compared to younger patients. Similar results were found in the meta-analysis done by Islam *et al.*, who determined that the relative risk of renal disease in HIV patients by 10-year increment in age was 1.54 [8]. This could be explained due to the combined effects of age-related decline in GFR, microvascular effects of atherosclerosis superimposed on renal damage caused by HIV itself.

No gender difference was found, and males and females were found to have equal risk of renal dysfunction. However, this finding may be confounded by the fact that the proportion of males in our study was higher than that of females.

Among the immunological factors proteinuria was found to be inversely associated with CD4 count, which is considered to be an indirect measure of HIV viral load. Since kidney dysfunction occurs due to direct invasion of HIV and its replication inside kidney, more kidney damage is expected when there is a higher systemic viral load.

Duration of disease was directly related to risk of having renal dysfunction. Patients who were having disease for more than 2.5 years had higher prevalence of proteinuria than those who were comparatively newly diagnosed. Findings of this study were in contrast to observations of Varma *et al.*, who did not find any correlation between duration of disease and proteinuria [18]. With the longer duration of disease, patients have experienced more episodes of acute kidney injury (AKI) due to various causes such as dehydration due to diarrhoea, nausea/vomiting, or due to nephrotoxicity of drugs of ART, thus the residual insult of these episodes of AKI might add to renal damage caused by HIV. This could possibly explain our finding of association of renal injury with duration of disease.

Patients with proteinuria were found to have lower level of haemoglobin as compared to those without proteinuria. Similarly, in Nigeria patients with proteinuria had lower mean packed cell volume (PCV) as compared to those who had normal renal profile [19]. This association was explained in the study by Janakiraman *et al.*, who said that the possible mechanisms could be haemodynamic alterations, lymphokine induction, or direct viral invasion of renal tissue in patients with HIVAN [11]. Furthermore, renal hyperfiltration may result in increased urinary loss of erythropoietin along with protein and decreased production/degradation ratio of erythropoietin [20].

The presence of proteinuria was also associated with higher serum creatinine. In general, serum creatinine and urinary protein excretion both serve as good markers of renal dysfunction. Thus a rise in serum creatinine also serves as a poor prognostic marker for future renal failure.

Kidney size and echotexture as evaluated by 2-D ultrasonography were found to be major determinants of risk of renal dysfunction. Patients with increased kidney size had 34-times higher risk of renal dysfunction, whereas grade II–III increased echogenicity was associated with 80-times higher risk. The increase in kidney size and echotexture is due to the hyperplasia and hypertrophy of visceral epithelial cells along with mesangial hyperplasia and cellular infiltrates caused due to direct HIV infection.

In this study, CD4 count was considered as a measure of immune status, and GFR was used to grade the level of kidney dysfunction. After evaluating the profile of all study subjects it was concluded that lower levels of CD4 count were associated with advanced stages of CKD. This can be explained by the fact that immunodeficiency serves as one of the strongest predictors of progression of renal dysfunction. Islam Fakhrul *et al*. estimated the pooled relative risk of CKD among people with late-stage HIV infection to be 3.32, as compared to other people living with HIV [8].

Furthermore, an inverse relationship was found between duration of disease and GFR. Among all other factors, duration of disease was found to contribute 34% to the decline of GFR.

Conclusions

Therefore, in this study it was observed that the prevalence of proteinuria in asymptomatic HIV patients in this region was 21%. It was significantly associated with older age, lower CD4 counts, higher serum creatinine, and lower haemoglobin levels. There were no significant differences between patients with and without proteinuria with regard to sex and concurrent antiretroviral therapy. Proteinuria was also associated with increased kidney size and echogenicity. In the patients with nephrotic syndrome focal segmental glomerulosclerosis was the most common histological pattern. A progressive decline in GFR was observed as the disease progressed in terms of duration of disease and decrease in CD4 count.

A major limitation of the study was the small sample size of 100 subjects. Due to the cross-sectional nature of the study, we could not evaluate various factors associated with progression of renal disease and impact of ART on course and outcome of renal dysfunction.

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