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Glomerulonephritis in HIV/AIDS: Current Trend and New Insights

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ABSTRACT

The rampage of the Human Immunodeficiency Virus (HIV) infection and Acquired Immune Deficiency Syndrome (AIDS) is growing phenomenally. Though, several countries are reporting success in reducing HIV infection rates, the rate of new infections are still growing and the number of people living with HIV has continued to rise. The epidemic remains centred in sub-saharan Africa; with only about 10% of the world population, the sub-continent is home to over two-third of the global HIV population. As the sub-saharan Africa bears a disproportionate burden of HIV/AIDS, and with the improvement in recent years in the management of HIV/AIDS by more access to antiretroviral drugs; long term complications of HIV/AIDS including renal involvement will be expected to increase and contribute significantly to burden of chronic kidney disease (CKD) in the sub-region. This review discusses glomerular diseases associated with HIV/AIDS, with emphasis on the better described HIV-associated Nephropathy (HIVAN). HIV-associated Nephropathy is a leading cause of Endstage Renal Disease (ESRD) worldwide, and most particularly among the black population. Over the years there has been greater understanding of the pathogenesis of its pathogenesis, pathologic features, clinical presentation and treatment. New trends and developments in pathogenesis, presentation and management of this disorder are discussed.

Keywords: *Glomerulonephritis, HIV/AIDS, Sub-Saharan Africa, Management, Prevention*

INTRODUCTION

The term 'glomerulonephritis' (GN) covers broadly a spectrum of disorders associated with glomerular inflammation. Glomerulonephritis are leading causes of Chronic Kidney Disease (CKD) in the tropical World [1, 3] and may occur as a primary renal disorder, limited to the kidney or as a secondary manifestation of a systemic disorder [2]. The distribution and pattern of GN differ considerably in different parts of the globe due to differences in environmental, nutritional and socio-economic factors [1, 2]. Infections and infestations are leading causes of GNs in the tropical region [1, 3]. Human Immunodifficiency virus (HIV) and malaria are particularly relevant in the tropics [3, 4]. HIV infection is a major global public health problem, particularly in sub-saharan Africa [5]. Over 38 million people are believed to be living with HIV/AIDS worldwide, with the majority in Sub-saharan Africa, in a disproportionate pattern as only 10% of the world population lives in the sub-continent [5]. As the sub-saharan Africa bears a disproportionate burden of HIV/AIDS and coupled with the improvement in recent years in the management of HIV/AIDS by better access to and increased efficacy of antiretroviral medications; long term complications of HIV/AIDS including renal involvement may increase and contribute significantly to burden of CKD in the sub-region.

Limited data is available on renal involvement in HIV/AIDS in the sub-saharan Africa [4]. The overwhelming literature on the topic results from studies in North America and Western Europe [2, 4]. A few cross-sectional reports and case series available point to a high burden of HIV related renal diseases in Sub-saharan Africa [6, 8]. HIV-associated nephropathy is now the third leading cause of end-stage renal disease (ESRD) in African Americans between the ages of 20 and 64 years in USA [9]. Statistics in the USA estimate the incidence of HIVAN to be between 3.5% and 12% [10, 11]. The implication of this is that, of the estimated number of those living with HIV worldwide, 26 million are in Africa [5]. If the US data for HIVAN are then extrapolated to

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Africa, between 0.9 and 3.1 million people can be predicted to have HIVAN. These figures predict a high burden of CKD to tackle with in the coming decades. This potentially large number of patients poses daunting challenges for physicians and nephrologists practicing in the Sub-Saharan Africa.

Renal involvement is a common manifestation of HIV infection and presents with several pathologic entities. A collapsing form of focal segmental glomerulosclerosis (FSGS) labelled as HIVAN is known to be the predominant form of the various renal manifestations [4, 9]. HIV infection is also linked with other types of renal involvement, manifesting with different pathologic entities and/or manifestations. Of note, irrespective of the specific histopathological lesion or aetiology of renal involvement, the presence of markers of CKD such as albuminuria/proteinuria and/or decreased renal function is associated with increased mortality and worse prognosis in HIV/AIDS [4, 9]. This review discusses the various glomerular lesions associated with HIV/AIDS, with focus on the most commonly encountered and described lesion of HIV-associated Nephropathy.

1. 'Traditional' Glomerulonephritides and HIV/AIDS

Several types of glomerular lesions apart from the classical lesions associated with HIVAN are linked to HIV/AIDS [4, 9]. Postinfectious glomerulonephritis may be more common in HIV/AIDS than in the general population, because of varied acute and chronic infections as a result of profound immunosuppression. Membranous nephropathy has been described particularly in association with concurrent hepatitis B & C virus infections. Membranoproliferative glomerulonephritis associated with concurrent hepatitis C infection or mixed cryoglobulinaemia has also been reported [4]. Another commonly reported glomerular lesion is an immune complex glomerulonephritis with IgA deposits in which the IgA is directed against HIV antigens [4, 9]. Rarely, a pattern of IgA nephropathy, mediated by idiotypic IgA antibodies reactive with IgG or IgM antibodies directed against HIV antigens may be encountered. These lesions result from HIV antigen-specific immune complexes that are derived from the circulation and from in situ complex formation [12]. Lupus-like glomerular lesions have also been reported [13], with characteristic 'full-house' appearance on renal biopsy staining for IgG, IgA, IgM, C3, and C1q. Thrombotic thrombocytopenic purpura (TTP) and Haemolytic Uraemic Syndrome (HUS) have been reported in patients with HIV infection; the mechanism by which this occurs is not understood, but directendothelial injury may be involved [14]. The glomerulonephritides may have varied clinical features at presentation ranging from isolated proteinuria, nephrotic syndrome, microscopic hematuria and/or renal impairment. There is the risk of progression to ESRD. The management of these several lesions is as in non-HIV infected patients [4].

2. HIV-Associated Nephropathy

This is the best described and probably the commonest renal manifestation encountered in HIV/AIDS [4, 9]. There is no evidence in the literature to suggest a definitive way other than renal biopsy to distinguish patients with HIVAN from patients with other glomerular diseases than HIVAN. However, patients with glomerular diseases other than HIVAN are less likely to be black, more likely to have hepatitis B virus infection, and generally have a greater mean $CD4^+$ lymphocyte count [9, 14].

The manifestations stem from asymptomatic renal biopsy changes with a collapsing focal glomerulosclerosis (FSGS) and often severe tubulointerstitial injury, to clinical manifestation with isolated proteinuria and in some cases full blown nephrotic syndrome [15, 16]. The characteristic HIVAN lesions can be seen in patients with asymptomatic or primary HIV infection, but most commonly associated with advanced HIV infection and marked immunodepression [16].

Epidemiology

Epidemiological studies have pointed out to an increased risk of HIVAN among blacks. HIVAN had a stronger association with black race than with any other cause of CKD except sickle cell anaemia [14, 15]. The reason for the increasing predilection among blacks is not yet clear. It occurs in 2 to 10 percent of HIV-infected patients, usually associated with a high viral load [17, 18]. But the incidence has declined dramatically with effective HIV therapy, from 26 to 7 per 1000 patient years at risk, particularly if initiated before the development of AIDS [4, 9]. In addition to black race, low $CD4^-$ count and family history of CKD are associated with development of HIVAN. Many of the reported data were obtained prior to the use of combined highly active antiretroviral therapy (HAART). The effect of this regimen on the devel-

opment of HIV nephropathy is still unknown.

Pathogenesis

The mechanism of HIVAN is still not well understood and remains a matter of controversies [19]. Experimental studies suggest the role of HIV infection of glomerular endothelial and mesangial cells [20]. Initially, glomerular epithelial cells were thought to be immune to infection. But with improved technology of polymerase chain reaction (PCR) and hybridization, glomerular cells were reported to harbour viable HIV [21]. HIV can also infect tubular cells, and can persist as a reservoir of viable and replicating infectious agents in these cells. The mechanism of cellular entry is still unclear since the HIV co-receptors; CCR5 and CXCR4 required for infection do not appear to be expressed in intrinsic kidney cells, with or without ongoing inflammatory processes [22]. Human Immunodeficiency virus may induce FSGS by stimulating the release of cytokines that are responsible for or contribute to the glomerular and tubular injury. Studies in the transgenic mice suggest that fibroblast growth factor and transforming growth factor-beta (TGF-â) may play a role in the matrix accumulation, fibrosis, and tubular injury associated with HIVAN [23]. The viral gene products may also directly induce cell-cycle progression, resulting in epithelial cell de-differentiation and collapse. The pathogenic importance of this feature was provided by the observation in transgenic mice that the administration of a cyclin-dependent kinase inhibitor lessened or even reversed renal disease [24].

Pathology

HIV-associated nephropathy is characterized by a constellation of pathologic findings involving glomerular, tubular, and interstitial tissues. Glomerular lesions include focal segmental glomerulosclerosis (FSGS), with prominent collapse of the glomerular capillary tuft. This is associated with tubular dilatation and atrophy, and flattening of tubular epithelial cells and lymphocytic interstitial infiltrates. HIV-associated FSGS may be distinguished histologically from idiopathic FSGS and other secondary FSGS with some characteristics findings. There is predominance of collapse and sclerosis of the entire glomerular tuft, rather than segmental injury as in the primary FSGS [25]. Moreover, in HIV-associated FSGS, there is a proliferative microcyst formation, and presence of dense tubuloreticular structures in the glomerular endothelial cells on electron microscopy. The only other disorder in which these structures are seen is lupus nephritis. However, lupus is associated with characteristic clinical and serologic abnormalities and with marked immune complex deposition in the glomeruli, findings that are not typically seen with HIV-induced FSGS [25].

Clinical features and diagnosis

The Patients with HIVAN usually presents with severe proteinuria and sometimes even in the nephrotic range (> 3 g/24h). However, despite the presence of proteinuria often in the nephrotic range, most patients with HIVAN do not have significant peripheral oedema. Patients with HIVAN are usually not hypertensive, a remarkable finding considering that more than 90% of black patients with CKD from other causes exhibit hypertension [9, 15, 26]. The clinical presentation of HIVAN differs from those seen with other glomerular disorders such as postinfectious glomerulonephritis and IgA nepropathy. Active urinary sediment, mild proteinuria and hamaturia are predominant in the postinfectious glomerulonephritis and IgA nepropathy. Patients with HIV-related FSGS may follow a progressive course in which ESRD frequently develops within couple of months [26]. Severe glomerular injury and marked damage to the tubular cells are linked to the rapid rate of progression to ESRD, which is rare in other forms of FSGS. Diagnosis and treatment of HIVAN at an early stage may prevent further disease progression. Microalbuminuria is reported as an early marker of HIVAN, and screening for its presence may be beneficial as demonstrated in a study in South Africa [6].

Laboratory studies are non-specific in HIVAN. Urinalysis is commonly unremarkable with the exception of proteinuria. In most chronic kidney diseases, the kidneys become progressively smaller with time. In HIVAN, however, renal ultrasound commonly reveals bilateral echogenic kidneys that are often enlarged. The predictive value of renal ultrasound to rule in or exclude the diagnosis of HIVAN has not been studied prospectively as yet [15, 16]. The only reliable way to confirm a diagnosis of HIVAN is by renal biopsy. Since firmly establishing the diagnosis of HIVAN versus a different kidney disease is important to guide treatment and provides prognostic information, clinicians should have a low threshold for obtaining renal biopsies in HIV-1-se-

ropositive patients with significant proteinuria and/or renal impairment.

Renal biopsy may be considered in seropositive patients who present with persistent microalbuminuria, especially with low CD4 counts irrespective of renal function [9, 15]. But many nephrologists do not performed a renal biopsy in patients with presumed HIV-related FSGS. It has been reported that many of such patients may have different renal lesions when biopsied [15]. But this is more particular in white patients who are at much lower risk for HIV-related FSGS than blacks. Confirming the presence of FSGS is utmost importance as potential therapies for this disorder become available.

Management

Prevention

Human Immunodeficiency virus infection appears to be a risk factor for developing CKD. Although no studies have examined the utility of systematic screening for early kidney disease in preventing progression of renal dysfunction in HIV-infected patients, there is evidence that early treatment of CKD is beneficial [11, 16]. Prevention of CKD due to HIV in Africa should become a major priority. This would enable early detection and treatment of HIVAN and other related diseases in order to prevent or delay progression to ESRD. As HIV infection is a risk factor for the development of CKD, the HIV Medicine Association of the Infectious Diseases Society of America recommends screening for CKD in HIV-infected patients; screening tests should be similar to those for patients with diabetes mellitus to detect early renal involvement [16]. Assessment for existing kidney disease is recommended at the time of HIV diagnosis, with regular follow up and monitoring. Extensive evaluations (including quantification of proteinuria, renal ultrasound, and renal biopsy) and referral to a nephrologist are recommended for patients with proteinuria of grade by dipstick analysis or GFR <60 mL/min per 1.73 m^2

Treatment

Conservative

There is no evidence-based effective treatment for HIVAN, due to lack of randomised, controlled trials evaluating the beneficial impact of any form of therapy. Highly active antiretroviral therapy (HAART), angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, *Corticosteroids, cyclosporine* and other immunosuppressants have been tried severally. Initial data of treatment with *zidovudine (*AZT) were conflicting. It was noted that FSGS developed in many patients being treated with AZT [16]. Some other studies showed beneficial effects with AZT in retarding the progression of HIVAN, particularly with smaller degrees of proteinuria, and mild renal dysfunction [27], and most particularly if used in conjunction with angiotensin converting enzyme inhibitor (ACEI) [28]. But these observations with monotherapy are no longer applicable since HAART is part of standard care in virtually all HIV-infected patients. Limited evidence suggests that such combination therapy containing protease inhibitors and ACEI may be beneficial in HIVAN [28, 29]. In a small retrospective cohort study of 19 patients with HIVAN, the use of protease inhibitors as part of a HAART regimen significantly slowed the rate of progression of renal dysfunction [29]. There are some data to suggest that HAART may also prevent the development of HIVAN [30]. In a retrospective study of patients with HIV infection followed up for HIVAN, the risk of nephropathy was 60 percent lower among patients treated with HAART, and no cases were reported among patients who began HAART therapy prior to overt AIDS [30]. However, longer follow-up is required to determine whether HAART is truly protective. Moreover, the ACE inhibitors and/or angiotensin II receptor blockers (ARBs) may even be of some long-term benefit as demonstrated in diabetic nephropathy and other forms of CKD [31, 32]. There are conflicting reports with the use of steroids in the management of HIVAN. Initial reports suggested a lack of steroid response in children treated for HIVAN [33]. However, later studies have found that some patients do respond appropriately [34, 35]. *Cyclosporine* may also be of benefit in some patients. In one study of HIV-induced FSGS in children, remission of proteinuria and improved renal function was demonstrated with cyclosporine [33]. International Guidelines have already recommended treatment with HAART to retard progression of HIVAN [36]. With their established renoprotective effects, ACE inhibitors and/or ARBs are beneficial in the absence of profound renal impairment. However, care is needed in their prescription as HIVAN is usually diagnosed late in the course of HIV infection and most have advanced CKD at the time of diagnosis. In the absence of effective treatment with

antiretroviral drugs, ACE-inhibitors, or prednisone, most patients with HIVAN progress to ESRD within 1-4 months of the diagnosis being established.

Renal Replacement Therapy in Patients with HIVAN

1. *Dialysis*

The optimal mode of dialysis therapy in HIV-infected ESRD patients is not clearly defined. There is no evidence to support one modality over the other; and both haemodialysis and peritoneal dialysis can be considered as appropriate [37]. The viability of haemodialysis treatment in this group of patients has been shown among Nigerians [38]. Haemodialysis and peritoneal dialysis appear to be equally effective. Of note, patients infected with HIV may require dialysis due to disorders unrelated to the viral infection such as diabetic and hypertensive CKD, but the commonest encountered disorder is HIVAN. Using data available from the United States Renal Data System (USRDS) relating to patients treated between 1995 and 2000, HIVAN accounted for approximately 1 percent of all prevalent ESRD patients in US [39]. Mortality among HIV-infected dialysis patients most closely correlates with the course of infection rather than the presence of ESRD [40]. Overall, improved survival is associated with an earlier stage of HIV infection at the initiation of renal replacement therapy (RRT), younger age, higher CD4 counts, and availability of HAART [41].

The main specific issues relating to the provision of dialysis among this category of the ESRD population include whether there is a need for isolation and the use of effective cross-infection management. There has been no recommendation for routine isolation and/or the use of dedicated machines for HIV-infected patients undergoing dialysis, because of the low likelihood of cross-transmission of the HIV [42]. Traditional Infection control measures prevent HIV transmission and several Nephrologists are of the opinion that if health care workers on dialysis units make routine use of these measures, no special isolation of HIV-positive dialysis patients is necessary [42].

The other issue relates to dialysis access infections and complications rate in these patients as compared with the ESRD population without HIV/AIDS. Limited data from case series have indicated a significant increase in access infections and thrombosis rates in HIV/AIDS patients [43]. However, it is to be noted that most of the studies of haemodialysis access in this setting included a majority of injection drug users (IDU). Complication rates are higher in IDU as a result of sclerosis of upper extremity veins and active drug abuse [44]. It is therefore difficult to distinguish effects of HIV infection independent from those of IDU.

In Sub-saharan Africa, where reuse of dialysers is a common practice, it might prove a dilemma in the treatment of patients of HIVAN. The CDC recommendation for the care of HIV-infected haemodialysis patients is routine dialysis unit precautions and optional reuse of the dialyser by the same patient if necessary [42]. But if sterilization procedures are inadequate, it is better not to use reprocessed dialysers. On the other hand, peritoneal dialysis complications may be higher. A higher incidence of peritonitis was reported in HIV-infected ESRD individuals than in ESRD patients without HIV infection [45]. Other studies have reported peritonitis rates comparable to that of the general ESRD population without HIV infection [46]. The differences in the reported rates of peritonitis may be related to disparities in the risk factors for HIV infection encountered in different centres [46].

Renal Transplantation

Human immunodeficiency virus infection was traditionally considered an absolute contraindication for transplantation [47]. With the advent of HAART, HIV infection is no longer an absolute contraindication for transplantation. The main issue in considering this option is the risk associated with further immunosuppression resulting in increased morbidity and mortality. Since the availability of HAART, the prognosis of HIV infection has dramatically improved. There have been significant decreases in morbidity and mortality, and for many individuals with well-controlled viral replication, HIV/AIDS is now a chronic manageable disease [48]. But the decision to transplant a specific patient should be individualized until the results of ongoing prospective studies in this subject become available [36]. Patients can be considered for a transplant with well-controlled disease. A number of studies have demonstrated excellent outcomes in HIV-infected patients who undergo renal transplantation [49]. Patient survival was superior to that observed with HIV infected dialysis patients, while allograft survival is similar to that observed with non-HIV pa-

tients [49]. Drug level monitoring is extremely important to minimise interactions between anti-rejection and antiretroviral medications.

CONCLUSION

With the growing rate of HIV/AIDS and relatively better survival than it was in the previous decades, HIVAN and other HIV-related renal diseases may pose greater challenges in future, particularly in the Sub-Saharan Africa. Early detection and treatment of HIVAN is paramount in HIV-positive individuals. HIVAN is the most common cause of CKD in HIV-1 seropositive patients and disproportionately affects patients of African descent. Patients with HIVAN are usually diagnosed late in the course of the HIV illness, when they present with evidence of renal insufficiency and proteinuria. The availability of HARRT and the conventional renoprotection measures such as the use of ACE inhibitors and/or ARBs may prevent progression to ESRD. Appropriate renal replacement therapy may be considered for those who reached the ESRD. There is a dire need for well-designed, prospective studies evaluating the natural history of kidney diseases in HIV-infected patients in Africa to match those currently going on in the North America and several parts of Europe. Prospective, randomized controlled trials for the treatment of HIVAN and other HIV-related proteinuric renal disease are also needed.

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