HIV-RELATED RENAL DISEASE — A CLINICAL AND PRACTICAL APPROACH IN THE SOUTH AFRICAN CONTEXT

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Human immunodeficiency virus-related renal diseases occur in up to 10% of patients infected with HIV. The majority of such patients are black and the commonest pathology seen is HIV-associated nephropathy (HIVAN). This is a clinicopathological entity characterised by proteinuria and rapidly developing renal failure and histologically by a collapsing variant of focal and segmental glomerulosclerosis with acute tubular necrosis and mild interstitial inflammation. It may progress rapidly to end-stage renal disease (within 6 months). HIVAN appears to be the commonest cause of renal disease in HIV-infected patients in South Africa, although the exact prevalence is unknown. The disease affects predominantly black males, although it has been described in patients of mixed race. Current thoughts with regard to pathogenesis revolve around the role of HIV in the renal epithelium and the effects of cytokines, including transforming growth factor-beta and basic fibroblast growth factor, on renal structures. Treatment modalities available locally include corticosteroids, angiotensin-converting enzyme (ACE) inhibitors and where possible antiretroviral agents. The demographics of the HIV/AIDS epidemic indicate that the risk pool for HIVAN will continue to rise, and with it the prevalence of renal failure.

Renal manifestations are an important component of HIV disease, and renal disease contributes significantly to morbidity and mortality in patients with HIV.

Of the South African population of 47 million an estimated 6.5 million people are infected by HIV, although the prevalence is not universally agreed upon.[1]

Data from the USA suggest that 10% of HIV-infected patients will develop HIV renal disease at some stage of their infection (although usually late in the course of the disease). From these data it is estimated that in the South African context 650 000 people may well suffer from HIV renal disease – frightening figures indeed. Furthermore, South Africa is part of the developing world, so most patients with HIV and renal disease have limited or no access to antiretroviral and renal replacement therapy (including dialysis). Although such therapies are not curative, they may slow disease progression and even prolong survival.[2]

EPIDEMIOLOGY

In the USA over 85% of cases of HIVAN occur in African-Americans, and it is the third leading cause of end-stage renal disease (ESRD) in blacks aged 20 - 64 years.[3]

In South Africa the majority of patients with HIVAN are black, although this may simply reflect the high prevalence of HIV in this population group in general. However, in a study from Cape Town Bates *et al.*[4] described 5 patients of mixed race in a cohort of 22 biopsy-proven HIVAN cases. Interestingly, patients with family members with renal disease appear to have a higher risk of developing HIVAN. It is possible that an inherited susceptibility to renal failure is present in many blacks with HIV infection who subsequently develop nephropathy.[5]

RISK FACTORS FOR HIVAN

The clinical determinants of HIVAN are heterogeneous, although commonly described risk factors for its development include black ethnic group, male gender, injected drug use, a low CD4 count and a high viral load.

PATHOGENESIS

Although the exact pathogenesis is not completely understood, two distinct features appear to be of importance:

- molecular mechanisms related to genetic predisposition, and
- HIV itself.

Patients who are homozygous for a deletion mutation in the CCR5 co-receptor appear to be protected from HIV infection.[6] It has been demonstrated that HIV-1 mRNA is expressed in human renal epithelium and this transgenic

expression results in cellular proliferation and is likely to play a key role in the pathogenesis of HIVAN.[7] The presence of HIV-1 mRNA further suggests localised replication of HIV-1 in the kidney and the existence of a renal viral reservoir.[8] Furthermore, upregulation of transforming growth factor-beta (TGF-β) may cause loss of nephron structure and sclerosis.[9]

PATHOLOGY

Although the classic pathological feature of HIVAN is the collapsing form of focal and segmental glomerulosclerosis, the affected glomeruli contain hypertrophied visceral epithelial cells, large cytoplasmic vacuoles and numerous protein resorption droplets. Such distortion results in an increase in kidney size by up to 25%. Glomerular endothelial cells classically contain tubuloreticular inclusions, the interstitium is oedematous with T-cell infiltration, and Bowman's capsule can be dilated.[10] Importantly, a spectrum of other histological lesions are associated with HIV infections. Lesions such as mesangiocapillary glomerulonephritis (GN), post-infectious GN, membranous GN, amyloid AA, and IgA nephropathy make up to one-third of the diagnoses in renal biopsy series, including those in South African patients.[4,11,12]

CLINICAL PRESENTATION AND RISK FACTORS FOR HIVAN

Although HIVAN may be the presenting manifestation of AIDS, it usually occurs after a prolonged period of viral infection often associated with high levels of HIV viraemia.[13] Cases have been described in which HIVAN has occurred before HIV antibody seroconversion.[14]

Patients typically present with nephrotic range proteinuria and unrelenting progression to renal failure. Peripheral oedema and hypertension are uncommon, although patients with malignant hypertension have been described.[15] Besides proteinuria urinalysis is bland, although in the uncommon proliferative GNs found in HIV the sediment may contain red blood cell casts. Unfortunately the correlation between clinical presentation and underlying HIV renal pathology is poor and true diagnosis is only possible on biopsy.

FACTORS PREDISPOSING TO PROGRESSION

Strong associations exist between increasing HIV RNA level and decreasing CD4 lymphocyte count and the presence of proteinuria and occurrence of renal failure. Furthermore the presence of coinfection with hepatitis C increases the chance of progression.[16]

EVALUATION OF HIV-INFECTED PATIENTS WITH RENAL DYSFUNCTION

Even among patients with normal kidney function, the presence of proteinuria indicates early glomerular disease. Although no clinical practice guidelines exist for the evaluation of HIV-infected patients with renal dysfunction, considering the high incidence of HIVAN in such patients, it would be appropriate to perform a simple urinalysis at their initial visit. Annual follow-up examinations of individuals in high-risk groups (see above) may be justified. Proteinuria should be quantified with a protein/creatine ratio performed on a spot urine sample, serological tests for coinfection with hepatitis B and C and syphilis should be done, and CD4 and HIV RNA levels should be measured if facilities are available. Renal biopsy is warranted and indicated in patients with significant proteinuria (> 0.5 g/24 h) or progression of renal failure, and when a definitive histological diagnosis will alter therapy.

ACUTE RENAL FAILURE IN HIV

Acute renal failure is well described in patients with HIV, and possible causes are listed in Table I. Underlying glomerular disease and disturbances in renal tubular function predispose these patients to haemodynamic and nephrotoxic insults. Prerenal azotaemia is the commonest cause, although direct damage to the renal tubules from nephrotoxic medications occurs frequently in hospitalised patients. Tubulointerstitial nephritis as a result of allergic reactions to medications is also well described. Importantly, crystalluria and nephrolithiasis occur in relation to drugs used to treat HIV directly and those used to treat associated infections.

TABLE I. ACUTE RENAL FAILURE IN HIV – POSSIBLE CAUSES

Glomerular diseases
- HIVAN
- Membranoproliferative glomerulonephritis

Acute tubular necrosis
- Hypotension and sepsis
- Antibiotics: Aminoglycosides; amphotericin B
- Antivirals: Pentamidine; foscarnet; cidofovir; acyclovir

Haemolytic uraemic syndrome

Acute interstitial nephritis
- Trimethoprim-sulphamethoxazole
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Rifampicin and isoniazid (INH)

Renal obstruction (crystalluria and nephrolithiasis)
- Sulfadiazine; indinavir; acyclovir

HIV-positive patients presenting with acute renal failure have a similar outcome to those who are not infected, so HIV should NOT be an exclusion criterion when deciding on acute renal failure therapy in such patients.

TREATMENT

In the South African context there are few options for the majority of patients with HIV and renal disease, particularly HIVAN. Although there are no randomised clinical trials, angiotensin-converting enzyme (ACE) inhibitors have shown promise in the therapy of HIV and kidney disease and are available in this country. Interestingly, ACE inhibitors appear to mediate their effect in HIVAN via mechanisms other than altered renal haemodynamics. By inhibiting the angiotensin-II-mediated rise in TGF-β (present in the kidneys of patients with HIVAN), ACE inhibitors may slow the formation of sclerosis in the kidney and thus slow the progression of renal failure.[17]

The proteinuria-decreasing effects of ACE inhibitors have long been recognised, and it seems logical to prescribe an ACE inhibitor for patients with HIVAN.

Logic would seem to dictate that corticosteroids should not be used in a patient with HIV. However, their use is definitely advocated in HIV patients with nephropathies to which they are known to respond, e.g. minimal-change GN and aggressive interstitial nephritis related to concomitant drug use. Their place in direct therapy is more controversial. Observational studies have shown improved survival in some patients, although relapses are common and when they are used for prolonged periods there is a risk of infection.[18,19] They should therefore be used judiciously, while closely monitoring clinical response, and ideally with the backing of a histological diagnosis. Common sense would suggest the addition of preventive antibiotics such as INH and trimethoprim-sulphamethoxazole (Bactrim), although these drugs cause renal problems in their own right.

Antiretroviral therapy has been shown to slow the progression of HIVAN, whether it consists of monotherapy with zidovudine, protease inhibitors or highly active antiretroviral therapy (HAART).[13,20,21] Patients who received HAART have been found to maintain stable renal function, whereas patients who did not required dialysis or died with advanced renal failure. Monotherapy for HIV could induce resistance and is not recommended, although with the possibility that HAART will become more readily available in South Africa, the treatment of HIVAN should be optimised. Many of these drugs are renally cleared, so caution is required when prescribing them to patients already in renal failure. Furthermore, little information is available on HAART medications and their clearance by dialysis. Stavudine and nevirapine accumulate in renal failure and

are cleared by haemodialysis, whereas Saquinavir is poorly removed and adjustment of the dose is needed.

HIV patients are excluded from State-funded long-term dialysis programmes in South Africa, and although this raises ethical issues, the grounds for such a ruling may not be unfounded, particularly with regard to a resource as scarce as dialysis. Patients who do receive dialysis have a poor prognosis, with 50% mortality within the first year, although this may improve if they receive HAART.[22] Infection and thrombosis are more common than in patients without HIV infection, and the risk an HIV-positive patient poses to staff and other patients should not be forgotten. Peritoneal dialysis has similar problems in the way of infection, and the fact that virus replicates in peritoneal dialysis fluid may worsen the patient's systemic viral load.

CONCLUSION

As therapy for HIV becomes more readily available in South Africa it is to be hoped that the prevalence of HIVAN and renal disease related to this epidemic will decrease. Currently available therapy is far from adequate, and without HAART many patients will die of the renal illness.

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