Renal Diseases in HIV Infection

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Citation

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Abstract

BACKGROUND

Even before HIV was established as the causative agent of AIDS, a distinct renal syndrome was reported in patients with AIDS and nephrotic syndrome. It was initially thought that the kidney involvement was not a major complication of HIV infection. However, in due course a broad spectrum of renal disease has been reported in patients with AIDS. Diverse forms of renal pathology and clinical syndromes have been reported in medical literature. Kidney is not only known to be affected by HIV infection, but is also proven to be a reservoir for HIV. HIV infection per se and pharmacologic agents used in HIV treatment and prophylaxis and treatment of opportunistic infections have been increasingly recognized to contribute to HIV associated renal diseases. The clinical course of HIV associated nephropathy (HIVAN), if untreated, is that of rapid progression. Highly active anti retroviral therapy (HAART) has been shown to delay the progression of end stage renal disease. HAART has also been shown to reverse renal failure in some patients. The importance of HAART in treatment of HIV associated renal disease cannot be overemphasized. In the following article, we will review the renal involvement in HIV infection and explore available treatment options.

HISTORICAL PERSPECTIVE

Rao et al, in 1984 described focal and segmental glomerulosclerosis in nine patients with AIDS and nephrotic syndrome [1]. The changes were similar to heroine-induced nephropathy. However, unlike heroine associated nephropathy, the progression to end stage renal disease in these patients was much more rampant. This drew attention towards HIV and it's association with nephropathy. This report antedates the establishment of HIV as the causative agent of AIDS. In the same year Pardo et al reported a variety of glomerular changes seen at autopsy in patients with AIDS [2]. This offered further insight into the association of HIV and nephropathy and also broadened the pathology to include mesangial proliferation. Since then, many reports have validated renal involvement in HIV infected population and a wide spectrum of renal syndromes has been reported [3,4]. Several retrospective studies, case control studies, case reports and experiments on animal models have enhanced our understanding of HIV associated renal diseases.

SPECTRUM OF RENAL DISEASES

A wide spectrum of renal syndromes has been associated with HIV infection. While renal failure and HIV infection can coexist and the former may not be due to the latter, certain histologic changes are thought to be characteristic of HIV associated nephropathy. Renal failure in HIV infected patients may present as an acute (ARF) and as chronic renal insufficiency (CRI). Although several renal diseases are similar in both HIV infected patients and non-HIV infected populations, the prognosis is generally worse in the former [5,12]. Certain renal diseases are exclusive to HIV infected population.

ACUTE RENAL FAILURE

ARF in HIV infected population happens by and large for the same reasons as in non-HIV infected patients, barring ARF due to the use of anti retroviral (ARV) agents or prophylactic treatment for various opportunistic infections. Acute deterioration in renal failure may be thought of as prerenal, intrinsic to renal tissue and postrenal. The fundamental etiology and mechanisms involved in acute renal injury in HIV patients are generally the same as in non-HIV patients. Certain causes of acute renal injury, however, are exclusive to HIV infected patients [5]. In overwhelming number of patients with ARF, prerenal etiology is noted.

Prerenal causes of ARF include hypovolemic states due to profuse vomiting, diarrhea and infections; sepsis, excessive

and life threatening bleeding. Diarrhea is commoner in HIV infected patients and significant fluid loss may ensue. Due to suppressed immunity, HIV patients are typically more prone to infections and sepsis. This predisposes them to ARF. Third spacing of fluid and hypoalbuminemia (due to disease state or anorexia) are also other causes that may lead to prerenal ARF. The prognosis of renal failure in patients with HIV infection is generally worse than non-HIV infected patients.

Intrinsic ARF in HIV infected patients may be due to hypovolemia, sepsis, shock and use of nephrotoxic agents for therapeutic and diagnostic purposes. These causes generally lead to acute tubular necrosis. Commonly implicated drugs include: Pentamidine, foscarnet, amphotericin B, aminoglycoside antibiotics and radiocontrast material for diagnostic work up. Several other nephrotoxic agents predominantly cause renal failure secondary to allergic interstitial nephritis. Such agents include: TMP/SMX, rifampin, cephalosporins and phenytoin. Protease inhibitors, particularly Indinavir, have been associated with crystalluria and renal failure.

Rhabdomyolysis, azotemia, use of NSAIDs, hemolytic uremic syndrome (HUS) and thrombocytopenic purpura (TTP) are the other causes of ARF. Statin use for hyperlipidemia secondary to HAART has been reported to cause rhabdomyolysis. Concomitant use of gemfibrozil also has been reported to cause rhabdomyolysis [6,7,8]

Postrenal acute failure may be either due to external or distal obstruction. Intrinsic obstruction may also lead to postrenal ARF. Outflow obstruction, retroperitoneal fibrosis and crystalluria may contribute to post renal ARF. Indinavir, sulfadiazine and acyclovir have been implicated in crystalluria [9,10,11]

CHRONIC RENAL INSUFFICIENCY

Chronic renal damage by HIV leads to diverse histo-pathology. Large number of pathologic findings has been reported in HIV infected patients. Of the various causes of chronic renal insufficiency, the three variants that have received most attention include: Focal segmental glomerulosclerosis, often referred as Classic HIV associated nephropathy; Immune complex renal disease; and Microangiopathic renal disease [41]. The first lesion to be described, focal segmental glomerulosclerosis [1] also remains the most frequently seen in HIV infected kidney.

Focal glomerulosclerosis is the classical manifestation of HIV associated nephropathy. Such a lesion is predominantly seen in young African American men. There appears to be a positive correlation between FGS and intravenous drug use. Low socioeconomic status has also been reported to be associated with this variant. If left untreated, the course of focal segmental glomerulosclerosis is rapidly progressive [43].

Immune complex renal disease is also a common syndrome in HIV infected patients and presents itself as glomerulonephritis. Reports from Europe suggest that there is higher prevalence of HIV associated glomerulonephritis as compared to HIV associated FGS. In Hispanic population and American population of European descent, immune mediated nephritis is thought to be commoner than FGS. Such a distribution points towards genetic basis of renal syndromes in HIV infected patients [13,14,15,16,41].

Microangiopathies associated with HIIV infection have been increasingly reported in medical literature. These may present as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. This form of nephropathy is commoner in Caucasians as compared to Hispanics or African Americas. Also the prognosis of microangiopathies in HIV infected patients is worse than that in a non-infected person.

The following table offers an overview of HIV related renal diseases.

Figure 1

Table 1

Overview of HIV Related Renal Diseases

Acute Renal Failure

Prerenal
- Hypovolemia (Diarrhea, vomiting, bleeding,third spacing, pancreatitis)
- Sepsis (Multiple etiologies)
- Hypoalbuminemia (Severe malnutrition, cirrhosis)

Intrinsic Renal
- Acute Tubular Necrosis (Aminoglycosides, amphotericin B, foscarnet, Pentamidine, contrast based dyes, rhabdomyolysis, statins)
- Allergic Interstitial Nephritis (Protease inhibitors, trimethoprim/ sulfamethaxazole, cephalosporins, Phenytoin)
- Crystal deposition (Protease inhibitors, sulfadiazine, acyclovir)

Post Renal
- External Obstruction (Tumor, prostate hyperplasia, urethral obstruction, retroperitoneal fibrosis)
- Internal Obstruction (Crystal deposition, blood clots, tumor lysis)

Chronic Renal Failure

Focal Glomerulosclerosis (Classic HIVAN)

Immune Complex Disease
- IgA Nephropathy
- Mixed sclerotic immune complex nephropathy
- Proliferative glomerulonephritis

Microangiopathies
- Hemolytic Uremic Syndrome
- Thrombotic thrombocytopenic purpura

PATHOGENESIS

Renal involvement in HIV infected patient is not clearly understood. While the basis of acute renal failure is better understood and is by and large similar to non-HIV infected patients; the pathogenesis of chronic nephropathies (FGS, Immune complex disease and microangiopathies) remains somewhat obscure. However with recent research and observations, a clearer picture is emerging. It is helpful to highlight several important observations and consolidate various evidence. Viral activity and replication have been demonstrated in the renal tissue. Tubular cells, glomerular epithelia, endothelial and mesangial cells have been shown to demonstrate viral activity and/or replication. Increasingly, direct cellular injury by the virus is being recognized as the basis of HIVAN [17,18,19,20,21]. Cellular entry by HIV is not clearly understood. Mesangial cell membranes have been shown to have CD4 coreceptors CXCR5 and CCR5. This partly explains mesangial cell infection [21]. These coreceptors are thought to facilitate cellular entry. How endothelial and epithelial cells are infected, needs to be further explored. While FGS variant is predominantly seen in African Americans, immune complex renal disease is commoner in Europeans [13,14,15,16]. Such an ethnic distribution also suggests genetic basis. Genetic factors influencing renal disease pattern has also been studied in animal models. Increased level of cellular death by apoptosis has been observed in HIV infected renal cells [22,23,24,41]. Continued presence and replication of HIV in the glomerular epithelial cells, despite undetectable viral load, points towards the role of kidney as reservoir of HIV [19,40]. All these observations allow us to come up with a composite picture of pathogenesis of HIV associated nephropathy.

Hence, direct HIV infection of renal cells with subsequent proliferation and cellular apoptosis, alongwith activation of cell-mediated immunity, in genetically predisposed patient may be considered as the basis of HIVAN.

MANAGEMENT

The pharmacologic armamentarium for the treatment of HIV associated renal diseases includes ACE inhibitors, antiretroviral therapy and corticosteroids. Discontinuing the offending agents may be prudent in some instances. However, before stopping these potentially nephrotoxic agents, one must weigh the risks, alternatives and benefits. It may not always be possible to discontinue certain medicines, even if they are strongly thought to be contributing to nephropathy.

Experience with angiotensin converting enzyme inhibitors (ACE inhibitors) has been promising. They have been shown to reduce proteinuria and delay end stage renal disease (ESRD). The mechanism of action of ACE inhibitors in altering the disease course is similar to its action in non-HIV patients with diabetes. ACE inhibitors have been shown to improve renal function and delay progression of renal failure. Preventive role of ACE inhibitors has also been reported in mice models. Many practitioners have started incorporating ACE inhibitors alongwith antiretroviral treatment, in the patients who are at an increased risk of developing nephropathies [28,29,30].

There is some evidence that suggests the beneficial role of corticosteroids in HIV associated renal disease. While improvement of renal function has been observed in some studies, with the use of corticosteroids, their use has not been associated with an improvement of overall mortality despite improved renal survival. Concomitant use of steroids with HAART has recently shown improve renal function and decrease in morbidity. Therapy with corticosteroids is also associated with increased opportunistic infections. Systemic Mycobacterium avium intracellulare (MAC), invasive aspergillosis, Toxoplasma encephalitis and sepsis have been reported. In view of immunosuppression and reports of life threatening opportunistic infections, caution should be exercised in using steroids in HIV infected patients in an attempt to avert or delay renal damage. [31,32,33,34].

The importance of HAART in HIV associated renal disease is increasingly being recognized. The incidence of HIVAN appears to have declined ever since HAART was introduced. Exceptional recovery of renal function has been reported and discontinuation of maintenance hemodialysis has been successfully achieved in some patients, after initiation of HAART [36,38]. The role of HAART in preventing HIV associated renal disease has been repeatedly and consistently observed. Dramatic reversals of renal failure have been reported. HAART remains the mainstay of treatment for HIVAN. Concomitant use of ACE inhibitors and/or corticosteroids should be driven by risks versus benefits and scientific evidence. [35,36,37,38,39]

Renal transplant in patients successfully treated with highly active antiretrovirals and with undetectable viral load is promising. Large studies are not yet available, however initial results in graft recipients reflect high percentage of graft survival rates [41,42]

Optimum strategy for treatment of HIV associated renal disease needs to be established. Some authors recommend a semiannual screening for proteinuria in patients who are thought to be at an increased risk of developing HIV associated nephropathy. Such at risk patient population includes young African American men and active IV drug users [43].

SUMMARY

We have come a long way in understanding HIV infection and the involvement of various organ systems. Over the years, we have developed a better comprehension regarding the mechanism of cellular entry of HIV. Renal involvement by HIV is now understood to be 'at least' a direct infection by the virus. It is not entirely clear how the HIV enters the glomerulus, but renal tissue is established to be a reservoir of HIV [40]. HAART has shown enormous promise in halting and reverting HIV associated nephropathies. Therefore, HAART remains the mainstay of treatment for HIVAN. Of the six million people who need treatment for HIV infection; only a small fraction (about 40K) is receiving it. The WHO/UNAIDS initiative of treating three million patients by the year 2005 seems to be very promising [44,45]. Cellular entry by HIV, impact of renal reservoir in terms of disease course and progression, feasibility and success of renal transplants remain major avenues that need to be better understood.

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