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MINIREVIEW

Proteinuria in paediatric patients with human immunodeficiency virus infection

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Abstract

In human immunodeficiency virus (HIV)-infected people kidney disease is as an important cause of morbidity and mortality. Clinical features of kidney damage in HIV-infected patients range from asymptomatic microalbuminuria to nephrotic syndrome. The lack of specific clinical features despite the presence of heavy proteinuria may mask the renal involvement. Indeed, it is important in HIV patients to monitor renal function to early discover a possible kidney injury. After the introduction of antiretroviral therapy, mortality and morbidity associated to HIV-infection have shown a substantial reduction, although a variety of side effects for long-term use of highly active antiretroviral therapy, including renal toxicity, has emerged. Among more than 20 currently available antiretroviral agents, many of them can occasionally cause reversible or irreversible nephrotoxicity. At now, three antiretroviral agents, *i.e.*, indinavir, atazanavir and tenofovir disoproxil fumarate have a well established association with direct nephrotoxicity. This review focuses on major causes of proteinuria and other pathological findings related to kidney disease in HIV-infected children and adolescents.

Key words: Human immunodeficiency virus-infection; Nephropathy; Proteinuria; Antiretroviral therapy; Children

Core tip: Higly active antiretroviral therapy has decreased the mortality and morbidity of human immunodeficiency virus (HIV)-infected adults and children, too. Many of the antiviral drug used can cause side effects and in particular renal toxicity. A monitoring of renal function is useful for the management of HIV-infected patients.

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INTRODUCTION

In human immunodeficiency virus (HIV)-infected people kidney disease has recently emerged as an important cause of morbidity and mortality. HIV, can cause severe kidney disease directly, including acute kidney injuries, thrombotic microangiopathies, HIV-associated nephropathy (HIV-AN), and HIV immune complex kidney disease (HIV-ICK). Likewise, many co-morbidity, such as tuberculosis, opportunistic and bacterial infections and sexually transmitted infections can cause a variety of kidney disorders that may affect the outcome of HIV infection. Rao *et al*[1] divided the HIV-1-associated renal parenchymal diseases in four groups: (1) acute tubular dysfunction with electrolytes abnormalities and/or renal failure caused by infections and nephrotoxic drugs; (2) HIV glomerulophaties related to immunological abnormalities; (3) HIV-associated thrombotic microangiopathies; and (4) HIV-AN.

Before highly active antiretroviral treatment (HAART), an association of renal impairment with faster progres-

sion to acquired immunodeficiency syndrome and death in HIV-infected people was demonstrated[2]. Hence, in the United States approximately 40% of all HIV-infected children presented renal complications. Among them, 10%-15% developed a renal disease named HIV-AN[3,4]. HIV-AN has been described as a clinical and renal histological syndrome characterized by heavy proteinuria and rapid progression to end-stage kidney disease[5,6]. Histopathological findings include collapsing glomerulopathy, global or focal glomerulosclerosis, microcystic transformation of renal tubules, interstitial inflammation and hyperplasia of podocytes[7]. A genetic predisposition was supposed on the demonstration of the unique susceptibility of African-Americans to the development of this disease, although the responsible genes have not yet been identified[8,9]. The finding of HIV-AN in children provided strong evidence that HIV-1 per se was capable of inducing renal disease independently of other confounding variables that are present in HIV-infected adults (such as heroin abuse)[10].

Clinical features of kidney damage in HIV-infected patients range from asymptomatic microalbuminuria to full-blown nephrotic syndrome[11]. Children with HIV-related kidney disease may also develop acute kidney injury, thrombotic microangiopathies (including atypical forms of haemolytic uraemic syndrome) and some may progress to chronic kidney disease (CKD)[4]. The most common presentation is nephrotic syndrome, followed by anasarca and moderate range proteinuria. Edema and hypertension, in accordance with reports from adults, are rare in children with kidney disease[5]. The lack of clinical features despite the presence of heavy proteinuria may mask the renal involvement. Indeed, it is important in HIV-infected patients to monitor renal function to early discover a possible kidney injury.

After the introduction of antiretroviral therapy, mortality and morbidity associated to HIV-infection have shown a substantial reduction, although a variety of side effects for long-term use of HAART, including renal toxicity, has emerged[12,13].

Among more than 20 currently available antiretroviral agents, many of them can occasionally cause reversible or irreversible nephrotoxicity. Many of the nucleoside reverse transcriptase inhibitors, particularly older agents like didanosine, have been implicated as a cause of type B lactic acidosis, but this acid-base imbalance is not, strictly speaking, renal toxicity. Only three antiretroviral agents, *i.e.*, indinavir, atazanavir (ATV) and tenofovir disoproxil fumarate (TDF) have a well established association with direct nephrotoxicity.

Indinavir is an antiretroviral agent belonging to the protease inhibitor class. It was among the first agents used as a part of potent combination HAART and the most commonly protease inhibitor used in 1996, but nowadays, because of its inconvenient dosing, meal restrictions and nephrolithiasis, it is only rarely prescribed. Indinavir notoriously causes renal and urologic toxicity mediated by tubular crystallization[14,15]. Guidelines recommend that patients receiving indinavir drink at least 1.5 L of water a day and that periodic urinalysis and monitoring of serum creatinine concentration be performed.

ATV is a newer antiretroviral agent belonging to the protease inhibitor class characterized by an excellent tolerability and a potent efficacy in controlling HIV infection. It is poorly soluble in urine and easily precipitating at alkaline pH. In contrast to indinavir, clinically significant crystalluria and associated interstitial nephritis were not observed in patients treated with ATV, whereas several reports described ATV nephrolithiasis[16,17]. Two recent publications estimated the relation between CKD and antiretroviral drug use in HIV-positive patients. Mocroft *et al*[18] analysed a cohort of 225 subjects showing that 3.3% persons progressed to CKD during 21 482 persons-year follow-up, thus resulting in CKD incidence of 1.05 per 100 person-year follow up. After adjusting for traditional risk factor associated with CKD and other confounding variables, increasing cumulative exposure to ATV (IRR 1.21, 95%CI: 1.09-1.34) and lopinavir/r were associated with a significant increased risk rate of CKD. Dauchy *et al*[19] in the Aquitaine cohort demonstrated that the use of ATV is associated with an increased risk of proximal renal tubular dysfunction (1.28 per year of exposure). Lastly Rockwood examinated the development of renal stones in a cohort of HIV-infected individuals attending the Chelsea and Westminster Hospital Foundation Trust exposed to different antiretrovirals. The rate of development of renal stones in the ATV/r group (n = 1206) compared with efavirenz-lopinavir/r-darunavir/r combined group (n = 4449) was 7.3 per 1000 patients years of antiretroviral therapy exposure (95%CI: 4.7-10.8). Thus ATV/r renal stones should be considered as a potential comorbidity[20].

TDF is a nucleotide reverse transcriptase inhibitor. It is currently widely used due to its excellent properties, combining good potency, tolerability and convenience, either as a single agent or co-formulated with emtricitabine or with emtricitabine plus efavirenz[21]. TDF showed a relatively good safety profile in registrational clinical trials, but subsequently a number of reports have alerted about cases of tubular damage and occasionally of renal insufficiency in patients treated with TDF[22-24]. The pathogenesis of renal damage caused by TDF remains unclear[25,26]. Reviews of reported cases of TDF-associated nephrotoxicity suggest that it mostly manifests as proximal tubular injury with associated reduction in glomerular filtration rate (GFR). Patients often develop glycosuria, tubular proteinuria, lowered serum phosphate and increased serum creatinine. Some patients may develop frank Fanconi's syndrome or reduced bone mineral density. Thus, it is important to early and accurately diagnose TDF-associated nephrotoxicity[27]. If many data are available for adult patients, the renal safety of TDF in HIV-infected children and adolescents has not been well documented. Although sporadic cases of renal toxicity have been reported in HIV-infected children treated with TDF, a report describes renal safety outcome after 96 wk of use of tenofovir in HIV-infected children and

adolescents. The findings suggest that 96-wk use of TDF is not associated with any impairment of glomerular and tubular renal function in children with normal renal function at baseline[28]. According to another 60 mo follow-up study in HIV-infected children, adolescents and young adults treated with TDF, this antiretroviral drug has an excellent renal safety profile[29]. It stands to reason that TDF renal safety needs to be further evaluated in children, in particular in those who may be at higher risk as a result of pre-existing renal disease and concomitant use of nephrotoxic drugs. Moreover, given the need for long-term exposure to antiretroviral therapy in HIV pediatric patients, the renal safety of TDF could be better defined by longer observational studies.

Early detection and treatment of potentially serious kidney problems are especially critical for people living with HIV, since many of these cases are reversible or their evolution can be slowed if recognized in time[30,31].

NEPHROPATHY AND DIAGNOSTIC TESTS

With the exception of the rather dramatic clinical presentations seen with a severe or complete loss of kidney function, many kidney disorders are asymptomatic or the symptoms are non-specific, such as fatigue, loss of appetite, nausea, headache, *etc*. For this reason, many kidney disorders can only be recognized with laboratory tests. The biomarkers currently used to detect kidney injury or monitor kidney function have limited sensitivity or dubious accuracy and have not been well studied in HIV-infected people, according to a recent review by Post *et al*[32]. Other markers, which may provide a better and earlier indication of specific forms of kidney damage, including tenofovir-related proximal tubule damage, are being investigated.

HIV-infected people can present with the classic clinical features of the nephrotic syndrome, such as heavy proteinuria, edema and hypoalbuminemia. The renal disease may also be clinically manifested by persistent and isolated proteinuria[4]. CKD is determined by the presence of kidney damage, indicated by albuminuria or proteinuria, or GFR below 60 mL/min per 1.73 m^2 for $\geqslant$ 3 mo[33]. Kidney disease and GFR are directly correlated, and the latter typically decreases before the onset of symptoms of kidney failure[34]. Several equations to calculate GFR exist. The Cockcroft-Gault equation, which uses the 24-h urine creatinine clearance as indirect reference method, was the first and most attractive formula validated in adults. However, the need of body weight in the equation has greatly limited its practicability for widely use in renal medicine. Subsequently, the modification of diet in renal disease (MDRD) equation adjusted for four variables (age, gender, serum creatinine and ethnicity) was validated by Levey *et al*[35]. In addition, the same author recommended that the constant factor used in the original equation should be re-expressed using a new constant, if creatinine measurement is standardized against Isotope Dilution-Mass Spectrometry (reference method). Extensive evaluation of the MDRD study equation shows good performance in population with lower levels of eGFR but variable performance in those with higher levels[36]. To overcome the above mentioned pitfalls, the MDRD equation was revisited again by its original author[37] and modified into a new equation: the CKD epidemiology collaboration (CKD-EPI) equation. Therefore, it was suggested to replace the MDRD equation with CKD-EPI in clinical use in adults.

In children over 12 years of age, the Cockcroft-Gault equation is the most frequently used. For children under 12 years of age, Schwartz formula enables to calculate GFR using length in place of weight[38]. Although these equations are used in clinical practice as well as in several studies conducted in HIV-infected children and adults to evaluate GFR, none of them have been really validated in these cohorts of patients[27].

The diagnosis of kidney injury may include albuminuria and proteinuria testing. Proteinuria is believed to be the earliest and most consistent clinical finding for the diagnosis of HIV-AN[39,40]. Han *et al*[11] have reported the presence of microalbuminuria as an early marker of HIV-AN in adults. Urine albumin-to creatinine ratios (ACR) or protein-to-creatinine ratios (PCR) are reproducible measurements of proteinuria. Micro and macroalbuminuria are defined by ACRs > 30 mg/g and > 300 mg/g, respectively, while significant proteinuria is defined by a PCR > 200 mg/g. While albuminuria is more specific to glomerular injury (such as is seen in HIV-AN), proteinuria, that predominately includes albumin with other proteins, can be an indicator of either a glomerular or tubular defect. The most widely available tests that screen for proteinuria and albuminuria are urine dipstick test. However, a recent study has demonstrated that the sensitivity of dipstick test, may be affected by urinary concentration[41]. So dipstick tests may miss about one out of five people with kidney disease, and positive dipstick test results for proteinuria may have to be confirmed by other lab tests. Dipstick test has been efficiently used by Ray *et al*[3] in association with other tests to diagnose HIV-AN through the following criteria: (1) persistent proteinuria, defined as an albustix reading above 1+ or a urinary protein-to-creatinine clearance ratio more than 0.1 for more than 2 mo in the absence of acute infection episodes; (2) abnormal microscopic examination of the urinary sediment under similar conditions, which in some cases included the presence of urine microcysts; (3) presence of enlarged echogenic kidneys detected by renal ultrasonography in at least two different studies performed 2 mo apart; and (4) black race and clinical history consistent with the typical diagnosis of HIV-AN (*i.e.*, nephrotic-range proteinuria without significant oedema and/or severe hypertension). Nephrotic range proteinuria has been defined by Ramsuran *et al*[42] as a PCR of $\geqslant$ 2.0 and by Chaparro *et al*[43] as a PCR of > 1.0.

Proteinuria in children is an important prognostic factor for HIV-associated renal disease, and it needs to be assessed in follow-up to diagnose concurrent potentially progressive renal disease. As much as one third of the

Table 1 Features of proteinuria in different human immunodeficiency virus-associated kidney diseases in children

Type of proteinuria	Laboratory findings	Clinical findings
Glomerular proteinuria	Proteinuria: Urine protein to creatinine ratio > 200 mg/g Microalbuminuria: Urine albumine to creatinine ratio > 30 mg/g Macroalbuminuria: Urine albumine to creatinine ratio > 300 mg/g	HIV associated nephropathy
Tubular proteinuria	Proteinuria: Urine protein to creatinine ratio > 200 mg/g Urine albumine to creatinine ratio < 30 mg/g	Infections or atazanavir use
	Proteinuria: Urine protein to creatinine ratio > 200 mg/g Urine albumine to creatinine ratio < 30 mg/g Glycosuria with normal glycemia Increased fraction excretion of phosphorus Reduced fraction excretion of uric acid	Fanconi syndrome associated with tenofovir use

HIV: Human immunodeficiency virus.

population may present proteinuria, but no more than 10% generally have a real nephropathy, defined as nephrotic-range proteinuria, which may benefit of HAART or angiotensin blockade therapy. Surveillance of quantitative proteinuria in conjunction with imaging and chemical indicators of renal dysfunction is very much warranted. It seems reasonable to propose nephrotic range proteinuria as a major criterion for defining the clinical nephropathy in children and would be a clear indication for renal biopsy and initiation of HAART in naive patients[44,45]. Biopsy diagnosis can reveal the typical histological features of minimal change nephrotic syndrome, mesangioproliferative glomerular lesions, and "lupus-like" renal lesions[3,10,39,46,47]. Other patients show renal changes consistent with the diagnosis of HIV-AN or HIV-ICK[47]. Thus, performing a renal biopsy is the only way to establish a definitive diagnosis.

People with kidney disease localized in the renal tubule such as Fanconi's syndrome may have mild proteinuria composed of other proteins but rarely of albumin. The presence of renal tubular disorders in HIV-infected African American and Venezuelan patients has been recognized through hypercalciuria with a potential for nephrocalcinosis, and less frequently with crystalluria, hyperchloremia, and metabolic acidosis[3,10,39]. Tubular disorders may induce sodium, potassium, and phosphate wasting states. Elevated fractional urinary excretion of phosphate is perhaps an earlier marker of proximal tubular dysfunction and might be useful in monitoring for TDF toxicity.

Besides proteinuria, there are a number of other biomarkers that could potentially be more specific for tubular inflammation or damage and that may serve as earlier and better indications of which patients are likely to experience tenofovir-associated toxicity. Post *et al*[32] note that since the proximal tubule is supposed to reabsorb substances such as low molecular weight proteins, increased excretion of these in the urine could indicate tubular dysfunction[48,49]. Tests for these markers are not yet affordable or widely available and research into the use of these substances as biomarkers for renal tubule disorders is still in its infancy. Therefore it would be worth underline that a urine high PCR in conjunction with a normal or low urine albumine-to-creatinine ratio may identify patients with renal tubular disorders[50]. Thus, the assessment of these markers may be very useful to discover the proximal tubular dysfunction induced by TDF exposure.

In the meantime, studies using these markers as evidence of kidney damage should be interpreted with caution.

Table 1 is provided to summarize the different features of proteinuria in different HIV-associated kidney diseases in children.

CONCLUSION

A prompt diagnosis of nephrotoxicity due to antiretroviral therapy in HIV-infected patients allows to take rapid steps to mitigate damage to the kidney. It is also important to distinguish it from other causes of HIV-associated renal diseases. The collaboration with a nephrologists, the close monitoring of renal function and the biopsy in case of progressive renal disease allow to establish an accurate diagnosis.

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