RENAL CONSEQUENCES IN HIV INFECTED CHILDREN

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Abstract

Background and Aim: Renal dysfunction is seen after years of HIV infection in adults but the true prevalence of childhood HIV nephropathy is unknown. HAART has been beneficial not only for long term patient survival but also to slow down the process of renal involvement and rapid progression to end stage renal disease. HIV infection can have a renal impact conditioned by the induced immunodeficiency (autoimmunity, infection) or by its highly aggressive therapeutical approach. The aim was to study the renal involvement of long term HIV infection in 91 children and adolescents. *Materials and Methods:* The study lot comprised 91 HIV patients (6 weeks-19 years old) admitted in the period of September 2008 - February 2009. All were previously diagnosed cases in different HIV stages. 70.32% of patients have been on HAART (2 NRTI + 1 PI) and rest on double or single anti retroviral drugs. *Results:* 32.96% of patients were hypertensive (16.66% borderline, 66.66% stage1, 10.12% stage 2, and 6.66% stage 3). Hematuria in Addis cell count was present in 8.79% and proteinuria was found in 5.49% patients all in stage C2 and C3. On 24 hr urine samples we found 25.57% having high chloride levels, 6.59 with natriuria. Urinary levels of potassium and calcium were within normal range. Metabolic acidosis was found in 31.86%. 8.79% had hyperkalemia and 5.49% had hypernatremia in stage C2 and C3. 2.19% had low creatinine clearance (in stage C2). Urinary tract infection (UTI) was diagnosed in 13.18% (91.66% with E.Coli & 8.33% with Proteus); associated mild hydronephrosis in 5.49% and renal calculi in 3.29% of patients have been identified. 27.47% had a high viral load at the time of study. *Conclusion:* Renal involvement in HIV positive children is a frequent finding. Hence, measuring early urinary biomarkers can help in early detection of kidney disease and to prevent ESRD in HIV-infected children. Metabolic acidosis and hyperkalemia were positive findings without any evidence of kidney damage seen in our patients. The presence of proteinuria in only 5.49% patients was suggestive of none having severe glomerular lesions. There is evidence that HAART treatment has a beneficial effect on kidney disease progression as the same can be seen in our patients. We can conclude that the impact of long term HIV infection in our study lot affects the renal function, but on a slow velocity.

Key words: HIV, nephropathy, children.

Introduction

HIV infection/AIDS is a global pandemic, with cases reported virtually from every country. In Romania we were confronted HIV/AIDS being is one of the world's most devastating diseases; nearly 25 million people have died worldwide, since 5th June 1981, since the first case was diagnosed by Dr. M. Gottlieb (from UCLA). The current estimates of the number of persons living with HIV infection worldwide are over 42 million. Though children represent only 6% out of it, they accounted for 18% of the 3 million AIDS deaths approximately every year. Only 4% out of the one million people now on antiretroviral treatment are children. Unlike adults where more than 90% of the time HIV infection occurs through sexual route, in children 95% of cases occur due to Vertical Transmission from their infected parents. Among the various organs which are involved with the progression of HIV infection, kidney is also a part of it. Hence, HIV-associated nephropathy (HIVAN) is a type of kidney disease that occurs in patients who are infected with the human immunodeficiency virus (HIV). In 1984, clinicians in New York and Miami reported HIV-infected patients with heavy proteinuria (often > 10 gm/day) and rapid progression to end-stage renal disease (ESRD) occurring within 1-2 years. Nephropathy associated with human immunodeficiency virus type 1 (HIV-1), is generally seen after years of HIV-1 infection, although in few cases early onset have been described (1). Associated AIDS is found in majority of patients with early-onset HIV associated nephropathy (2). Nearly 5 to 15 % of patients having well-controlled HIV-1 infection and an undetectable viral load in blood may have histologic stigmata of HIV-associated nephropathy (5). However, in these patients, actual AIDS had occurred in the course of the disease, which was not the same in our study group. A paper from NEJM 2005 suggested that HIV-associated nephropathy (HIVAN) can occur at any stage of HIV-1 infection (4). Attempts to estimate the number of HIV-infected or AIDS patients who have developed the HIV nephropathy are hindered by the fact that diagnosis of nephropathy in an HIV-infected patient does not lead to the diagnosis of AIDS; this diagnosis is made only when the HIV antibodies plus certain unusual infections occur. Appropriate accurate diagnosis based on HIV antibody detection until the age of 15 months is generally difficult and hence needs special additional parameters. (6) Striking similarities are encountered between patients having HIV associated or

AIDS associated nephropathy. These nephropathies are labeled as HIVAN, HIVN, AIDSN, AIDSAN, HAN, etc., but HIVAN and HIVN (7) are most frequently used. Varying components are described and the most significant include: proteinuria with nephrotic syndrome (NS), azotemia, normal blood pressure, enlarged kidneys, rapid progression to end-stage renal disease (ESRD), and not do not clearly respond to any treatment (8).

The virus

HIV1 is a retrovirus, which carries RNA as their genetic material and hence reverses the usual flow of genetic information within the host cells in order to reproduce (4, 20). Studying the infected Tcell has helped us in understanding the association between HIV-1 and host factors. The HIV1 virus induces a productive infection of the Tcells mainly by the process of membrane fusion (mediated by its envelope protein *gp120*, *gp41* or *Env*) (26). The fusion of HIV-1 to the cell membranes is usually triggered by the interaction of *gp120* with two cellular components: CD4 and a coreceptor belonging to the chemokine receptor family. Once inside the cells, the retrovirus RNA is copied using a reverse transcriptase enzyme into a complementary single strand of DNA. In the cytoplasm, this single-stranded retroviral DNA is then copied into double-stranded retroviral DNA and the retroviral DNA migrates into the host cell nucleus and becomes inserted into the host cell DNA as a provirus. At this stage, HIV-1 can remain in a latent form without producing any viral protein or may start to produce new copies of HIV RNA immediately. The process of HIV-1 replication starts when the cell's RNA polymerase becomes activated by DNA sequences located in two DNA regions near the ends of the provirus, named long terminal repeats. Within the host cell, proviral DNA, when activated, produces new strands of HIV RNA. Some of the RNA strands behave like mRNA producing proteins essential for the production of HIV-1, while others become encased within the viral core proteins to become the new viruses. The HIV genome contains at least nine recognizable genes that produce at least 15 individual proteins (26, 27). These proteins are divided into three classes: 3 major structural proteins named Gag, Pol, and Env; 2 regulatory proteins Tat (regulator transactivator protein) and Rev (differential regulator of expression of virus protein); 4 necessary accessory proteins - Nef (auxiliary protein), Vif (virus infectivity factor), Vpu (virus protein U), and Vpr (virus protein R). The gag gene is involved in making the nucleocapsid and it has the ability to direct the formation of virus-like particles. The pol gene codes for HIV enzymes that are necessary for viral replication; these include the protease, the virus associated polymerase - reverse transcriptase, and endonuclease – integrase (27). The remaining six HIV genes produce proteins essential for viral replication (tat and rev) and proteins that perform accessory functions that enhance replication and infectivity (nef, vif, vpu, and vpr). The HIV-1 genes env, vpr, tat and nef have been linked to the pathogenesis of HIVAN. Very little is known about renal co-factors that might affect the function of these proteins in the kidney or whether these proteins are produced in relevant quantities by human renal cells.

The epidemiological data

Despite HIVAN being a known complication of HIV infection in children, information on the prevalence, patient characteristics, and course of HIVAN with ESRD has not been reported for the United State ESRD population. Soon after HIVAN was described in adults, children with perinatal HIV infection were reported to develop collapsing FSGS similar to adults. Ahuja et al in 2004 analyzed data from the standard analysis files as of October 2001 of the United States Renal Data System (USRDS). (21) The incidence and prognosis of HIVAN in children with HIV infection was expected to be similar to adults, but from the 7,732 patients with HIVAN who received dialysis in the United States, only 0.78% was younger than 21 years. The fact that HIVAN occurs in end-stage AIDS could have attenuated the effect of HIV stage of infection on survival showed in Ahuja analysis (24, 25).

Under-reporting of cases of HIVAN could be an important factor contributing to the low prevalence seen in children, as routine screening of all ESRD patients for HIV infection is not a practice. In recent years the lower number of children with HIVAN who have ESRD is more likely due to a decrease in perinatal transmission due to an increase in the number of caesarian sections in HIV-infected mothers and the use of antiretroviral drugs during pregnancy, in US. (23) We tried to search in our patients the underlying etiology whether it is due to primary renal disease or it is due to HIV infection induced or it is an outcome of HIV treatment. While information on antiretroviral therapy in children with HIVAN and ESRD was not available, improved survival after 1996 is consistent with the initial researcher's observations that HAART improves survival of ESRD patients with HIV. (24) The rate of biopsy in HIV-infected children is different from that of adults, which could have potentially underestimated the prevalence of HIVAN in children. So, the HIVAN and ESRD in children predominantly occur in blacks and the survival of the children is better than that of adults with HIVAN. Obviously, future studies are required to determine changing trends of incidence and prevalence of HIVAN in children in the HAART era.

Essential findings in HIV nephropathy - proteinuria and enlarged kidneys

HIVAN is caused by direct infection of the renal cells with the HIV-1 virus and leads to renal damage through the viral gene products. It could also be caused by changes in the release of cytokines during HIV infection. An up-regulation of renal heparan sulfate proteoglycans seemed to play a relevant role in this process, by increasing the recruitment of heparin-binding growth factors, chemokines, HIV-infected cells, and viral proteins. These changes enhance the infectivity of HIV-1 in the kidney and induce injury and proliferation of intrinsic renal cells. HIVAN usually occurs only in advanced disease states and approximately 80% of patients with HIVAN have a CD4

count of less than 200. Despite being a cause of chronic renal failure, kidney sizes are usually normal or large. Proteinuria seems to be the earliest finding which should raise suspicion of HIVAN and initiate efforts to distinguish HIVAN-related signs/symptoms from those of idiopathic NS. All the non-renal conditions associated with hypoproteinemia and edema may be found in HIV-infected/ AIDS patients: liver disease, intestinal protein losses, and malnutrition. For distinguishing HIVAN from other conditions, HIVAN requires identification of an excessive amount of total protein or albumin excreted in the urine per 24 h or determination of a high albumin to creatinine ratio in a spot sample (9, 10) with guidelines as follows: 24-h excretion of total protein >100 mg/m2 in a child. Gross proteinuria is defined as >~1 g/m2 per 24 h in a child. (11) Urine albumin/creatinine ratio normally is <0.2 mg/mg in neonates and 0.1 in older children and in the NS usually exceed 5 mg/mg (12). Using Albustix - levels of > + found on more than one occasion are abnormal; persistent readings of > ++ are compatible with gross proteinuria (9). Although clearly present, levels of albuminuria have not been reported in patients with HIV infection/AIDS; thus, in these patients, abnormal albuminuria levels are defined less clearly than abnormal proteinuria levels.

In pediatrics a unique opportunity is available for prospective early identification of children born to HIV-positive mothers; this early identification by their group may account for the marked increase in our rate of identification of patients with HIVAN (12). Numerous technical difficulties get in the way of the accuracy of timed urine collections from infants and children, especially when they are ill. Although the random urine protein/creatinine ratio (Upr/UCr) has previously been shown to accurately reflect daily proteinuria in both adult and pediatric patients (9, 14, 15, 16), a primary concern was the possible overestimation of proteinuria by low creatinine excretion in malnourished patients with low muscle mass. Both Haycock (17) and Schwartz (18) have warned against the errors inbuilt in the assay for PCr. The preferable assessment of proteinuria in any population is the measurement of daily excretion. This may be facilitated by estimating daily urine volume. In the event that body measurements are unavailable, random Upr/UCr closely approximates daily proteinuria. An Upr/UCr <0.2 reflects normal proteinuria of <0.1 g/m2 per day and a ratio >2.0 is consistent with nephrotic proteinuria >1.0 g/m2 per day. (19)

Enlarged kidneys are also constantly found among patients with HIVN at both early and late stages; this characteristic may differentiate patients with HIVN from those with other proliferative renal disorders in which the kidneys are enlarged initially but shrink later on. It is important to remember that the finding of enlarged kidneys by ultrasound does not make the diagnosis of HIVAN. The enlargement may be the reason for requesting the determination of anti-HIV antibodies but the diagnosis of HIV infection must not be made until the other usual criteria are fulfilled (13, 20). The abnormal anatomical findings in the kidneys have consisted of engorged and enlarged organs which can be recognized on the outer and on the cut surfaces; weight and other measurements (width, length, etc.) have confirmed these findings. For all ages, normal tables for weight and size should be consulted for greater accuracy.

The histology

The true prevalence of childhood HIVAN is unknown, since in many pediatric centers renal biopsies have not been performed regularly in all HIV-infected patients with proteinuria [7, 28-33]. In the early years of the AIDS epidemic, based on histology and/or clinical criteria, Strauss et al. and others [30,31,32,33] reported a prevalence of childhood HIVAN of approximately 10%–15%, in populations with a majority of HIV-infected African American children (95%).The following clinical findings not typical of HIVAN were used to suspect the presence of other renal diseases: macroscopic hematuria; microscopic hematuria without proteinuria; high blood urea nitrogen and serum creatinine levels without significant proteinuria; hematuria and/or proteinuria in Caucasian or Hispanic HIV-infected children. Nevertheless, a renal biopsy is the only definitive way of making the diagnosis of HIVAN. One of the features considered characteristic of HIVAN is the presence of focal collapsing glomerulopathy associated with renal enlargement. These changes contrast with the small fibrotic kidneys typically seen in patients with chronic renal diseases of other etiology. In 1994, using the HIV-Tg26 mouse line, they (41) provided the first evidence that: the characteristic renal enlargement of HIVAN was due to an increased proliferation of RTEc; the expression of HIV-1 genes in RTEc was associated with the development of multicystic lesions; the renal accumulation of bFGF/FGF-2 was at least partially responsible for these changes. Subsequent studies confirmed and expanded their initial findings, both in HIV-Tg mice and children with HIVAN [34-38]. In 1999, a landmark paper by Barisoni et al. (38) reported that a dysregulated podocyte phenotype was associated with the proliferation of podocytes and development of HIV-collapsing glomerulopathy and other forms of collapsing FSGS. Under these circumstances, podocytes lose markers of cell differentiation, such as synaptopodin, podocalyxin, and Wilms tumor antigen (WT-1), and proliferate. Synaptopodin, normally found only in mature podocytes, is lost in HIV-associated nephropathy, (1,3) and the podocytes undergo proliferation. The combination of collapsing FSGS and extensive renal tubular injury was initially thought to be specific to HIVAN. However, today we know that under certain circumstances both adults and children not infected with HIV-1 can develop similar lesions. Thus, it is tempting to speculate that other infectious agents may be involved in the pathogenesis of collapsing FSGS. Several studies have investigated the role of Mycoplasma fermentans, the polyomaviurs simian virus 40, and parvovirus B19 with inconclusive results (39, 40, 41]. Several reviews have been written describing the progress made in the treatment of HIVAN during the last 20 years [42-47]. Most previous studies were performed before the HAART era and excluded children. It should be noted that HIVAN is a typical late manifestation of AIDS and, as

such, the outcome of the renal disease will be affected by the presence of other AIDS-related illnesses (encephalopathy etc). Secondly, it is known that HIV-infected children who are not properly treated with anti-retroviral drugs or do not respond to HAART usually die of other reasons before developing ESRD. Thus, the treatment of childhood HIVAN should be planned in close collaboration with other physicians with experience in the treatment of pediatric AIDS, and the treatment of the HIV-1 infection should be a priority over the treatment of the renal disease.

The prognosis of childhood HIVAN depends on the presence of other AIDS-related conditions more than the nature of the primary renal diagnosis. These factors include the response of the child to anti-retroviral therapy, the stage of HIV-1 infection/AIDS, the nutritional status, and the severity of other AIDS-associated illnesses at the time of diagnosis (48). HIV-infected children typically developed proteinuria or azotemia approximately 2–5 years after the onset of HIV infection. The mean duration from the onset of proteinuria to the development of ESRD in children with HIVAN varied from 8 months to up to 3 years, depending on the geographical location and the presence of other AIDS-associated illness. The prognosis of HIVAN in children on dialysis prior to the introduction of HAART was very poor, and depended on the overall clinical status of the HIV infection (30-33).

Our study

We started our study assuming whether the HIV infection can have a renal impact conditioned by the induced immunodeficiency (autoimmunity, infection) or by its highly aggressive therapeutical approach. The main aim was to study the renal involvement of long term HIV infection. Our cohort is 91 children and adolescents having age between 6 weeks and 19 years. (48 females and 43 males) admitted in the period of September 2008 to February 2009 in our HIV department were analyzed. All were previously diagnosed and registered cases of our hospital. The HIV stages noted were as follows : B1-23.07%, B2-8.79%, C1-38.46%, C2-21.97% & C3-4.39%; 70.32% of patients have been on HAART (2 NRTI + 1 PI) and rest on double or single anti retroviral drugs. No mortality was seen in our study period. All of them were from were from Timis, Arad and Caras-Severin counties, all three from the Western part of Romania. Monitoring the blood pressure, measuring the serum and urine electrolytes, analyzing the 24 hour urine specimens and taking into account the blood gas analysis were our main concerns. Results obtained were as follows: 32.96% of patients were hypertensive. Out of which 16.66% were having borderline, and the majority 66.66% were in stage1 of hypertension. 10.12% were in stage 2, and the rest 6.66% were having stage 3. Hematuria in Addis cell count was present in 8.79% and proteinuria was found in 5.49% patients all in stage C2 and C3 of HIV. On 24 hr urine samples we found 25.57% having high chloride levels, 6.59 with natriuria. Urinary levels of potassium and calcium were within normal range. Metabolic acidosis was found in 31.86%. 8.79% had hyperkalemia and 5.49% had hypernatremia in stage C2 and C3 of the disease. 2.19% had low creatinine clearance (in stage C2). Urinary tract infection (UTI) was diagnosed in 13.18%, among these majority i.e. 91.66%, E.Coli was the culprit found and in rest 8.33% Proteus was the causative bacteria. Abdominal ultrasound revealed associated mild hydronephrosis in 5.49% children and renal calculi in 3.29%. From all, 27.47% had a high viral load during the study period. Among these 91 children 48 were adolescents suffering from HIV infection for more than 10 year. The above mentioned laboratory picture was found more frequently in these 48 patients, then in children having less than 10 years since diagnosis, which leads us to understand that renal changes appear generally after a long term HIV infection. Hence from our study we were able to conclude that renal involvement in HIV positive children is a frequent finding. Therefore, measuring urinary biomarkers can help in early detection of kidney disease and also in preventing ESRD in HIV-infected children. Metabolic acidosis and hyperkalemia were positive findings without any evidence of kidney damage seen in our patients. The presence of proteinuria in only 5.49% patients was suggestive of none having severe glomerular lesions. Since UTI is present in similar percentage of normal sexually active adolescent population it cannot be concluded that presence of UTI found in our study lot is due to HIV associated decreased immunity. There is evidence that HAART treatment has proved to have beneficial effect not only in HIV treatment but also on kidney disease prevention and the same can be seen in our patients. We can conclude that the impact of long term HIV infection in our study lot affects the renal function, but on a slow pace. Early detection and careful clinical follow-up of children with HIVAN may reduce the incidence of renal complications and improve their quality of life.

Conclusions

Renal involvement in HIV positive children is a frequent finding. Hence, measuring early urinary biomarkers can help in early detection of kidney disease and to prevent ESRD in HIV-infected children. There is evidence that HAART treatment has a beneficial effect on kidney disease progression as the same can be seen in our patients. We can conclude that the impact of long term HIV infection in our study lot affects the renal function, but on a slow velocity. The prevention of HIVAN should be our first priority. The early identification of HIV-1-infected pregnant women and prevention of the vertical transmission of HIV-1 continues to be a health challenge throughout the world. Almost 20 years after the first cases of HIVAN were described; we continue to see children who are newly diagnosed with AIDS and HIVAN in the emergency room. Highly active anti-retroviral therapy (HAART) appears to be the most promising treatment to prevent the progression of childhood HIVAN. Moreover, the diagnosis of HIV-1 infection/AIDS in a child could be the first indication of the HIV-1-positive status of the mother. We are hopeful that during the next years, better education, prevention, and treatment programs will lead to the eradication of this fatal childhood disease.

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