Resolution of Organ-Specific Complications of Human Immunodeficiency Virus Infection in Children with Use of Highly Active Antiretroviral Therapy

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Opportunistic infections are a major source of morbidity and mortality in children and adults infected with human immunodeficiency virus (HIV). In addition, organ-specific complications of HIV infection, such as cardiomyopathy, nephropathy, encephalopathy, and others, contribute substantially to the morbidity and mortality associated with HIV infection. Highly active antiretroviral therapy (HAART) has produced a dramatic decline in the incidence of opportunistic infections among patients with HIV infection. Nevertheless, there is very little information concerning the value of HAART for organ-specific complications of HIV infection. In this report, we describe 3 children with HIV infection in whom the dominant clinical manifestations were cardiomyopathy, red cell aplasia, and nephropathy. HAART produced a decrease in the HIV ribonucleic acid level, an increase in the CD4 cell count, and resolution of the organ-specific complications in all patients. These cases add to our knowledge concerning the benefits of HAART for children with HIV infection.

The hallmark of HIV infection in children is increased susceptibility to infection with common pathogens and opportunistic organisms. In addition, HIV infection is associated with a variety of organ-specific complications, including cardiomyopathy, nephropathy, hematologic abnormalities, encephalopathy, and others [1].

Highly active antiretroviral therapy (HAART) has changed the clinical course and the prognosis of HIV infection. HAART decreases plasma HIV RNA levels, increases CD4 cell counts, and leads to restoration of immunologic function [2, 3]. Accordingly, there has been a decrease in the incidence of opportunistic infections among patients with HIV infection and a resultant decline in morbidity and mortality [4]. Moreover, with the use of HAART, established opportunistic infections have been cured [5–9], and prophylaxis can safely be discontinued for some patients [10–13]. It is likely that the restoration of immunologic function by use of HAART has other benefits in addition to the treatment and prevention of opportunistic infections. Nevertheless, there is very little information concerning the effect of HAART on noninfectious complications of HIV infection.

In the present report, we describe 3 children with HIV infection that was complicated by cardiomyopathy, red cell aplasia, or nephropathy. With HAART, these organ-specific complications of HIV infection resolved completely.

CASE REPORTS

Case 1. This patient had perinatally acquired HIV infection diagnosed at 9 weeks of age, when he pre-
sented with *Pneumocystis carinii* pneumonia. He was treated with zidovudine. At 7 months of age, the patient was found to have tachycardia and a prominent gallop by cardiac auscultation. A chest radiograph showed cardiomegaly. An echocardiogram showed dilated cardiomyopathy with a diminished left ventricular shortening fraction of 28%. By 9 months of age, cardiomegaly had progressed, and the left ventricular shortening fraction had declined to 15%. The serum selenium level was normal. Treatment with digoxin and furosemide was initiated. Zidovudine therapy was discontinued, and treatment with didanosine was started. He was hospitalized at 12 months of age for treatment of acute pulmonary edema. A chest radiograph showed massive cardiomegaly, and the left ventricular shortening fraction was 12%. Pulmonary edema improved with positive pressure ventilation and iv administration of digoxin and furosemide.

During the ensuing 2 years, the patient was admitted to the hospital on numerous occasions for treatment of pulmonary edema. On each occasion, he had dilated cardiomyopathy with very poor left ventricular function according to echocardiographic evaluation. Between episodes of acute deterioration, the patient had frequent cough and wheezing. Even slight exertion during play resulted in shortness of breath. During this period, there was a steady decline in the CD4 cell count (figure 1) and a persistent elevation of the plasma HIV RNA level (figure 2).

When the patient was 3.5 years of age, zidovudine, lamivudine, and ritonavir therapy was started. At that time, the left ventricular shortening fraction was 12%. The CD4 cell count was 344 cells/$\mu$L (9%), and the HIV RNA level was 493,241 copies/mL. Within 3 months, the CD4 cell count had increased to 644 cells/$\mu$L (19%), and the virus load had decreased to 418 copies/mL; by 6 months after therapy, the CD4 cell count was 1175 cells/$\mu$L (29%), and the HIV RNA level was <400 copies/mL. The left ventricular shortening fraction had increased to 25%. A gallop rhythm was no longer audible, but the heart size remained enlarged. The patient had no cough, wheezing, or shortness of breath. His exercise tolerance was normal. Digoxin and furosemide therapy was discontinued 9 months after HAART was started.

One year later, a chest radiograph revealed that the heart size was still slightly large, but echocardiography revealed normal cardiac function with a shortening fraction of 33%. At 5.5 years of age, the patient remained asymptomatic with normal cardiac function. The CD4 cell count was normal at 1400 cells/$\mu$L (32%; figure 1), and the HIV RNA level was 206 copies/mL (figure 2).

**Case 2.** This patient had perinatally acquired HIV infection diagnosed at 5 months of age, when she presented with *P. carinii* pneumonia. She was treated with zidovudine. The patient was well until she was 12 months of age when she presented with lethargy and poor appetite. Results of physical examination were normal except for extreme pallor. Laboratory studies revealed the following values: WBC count, 13,000 cells/$\mu$L; hemoglobin, 3 g/dL; hematocrit, 10%; platelet count, 230,000 cells/$\mu$L; and reticulocyte count, 0. Coombs' test results were negative. Examination of bone marrow showed increased numbers of lymphocytes and plasma cells. The erythroid elements were decreased, but erythroid maturation appeared normal. There were no giant pronormoblasts. The serum erythropoietin level was markedly elevated at 960 mU/mL (normal range, 3–19 mU/mL). The CD4 cell count was 658 cells/$\mu$L (14%). The patient received packed RBC transfusions for treatment of anemia.

Parvovirus B19 infection was considered a likely cause of red cell aplasia, and the patient received a total of 3 g of iv Ig/kg over several ensuing days. Intravenous Ig therapy had no effect.
on anemia. Subsequent testing of a serum sample sent for analysis before iv Ig administration revealed no IgM or IgG antibody to parvovirus B19, and the results of PCR assay of the serum sample were likewise negative for parvovirus B19 DNA. Zidovudine therapy was discontinued, and the patient was treated with didanosine.

During the ensuing 18 months, the patient remained anemic (hemoglobin concentrations ranging from 5 g/dL to 7.5 g/dL) and reticulocytopenic (reticulocyte counts ranging from 0 to 2%). She required packed RBC transfusions every 2–3 weeks. When the patient was 2.5 years of age, zidovudine, lamivudine, and ritonavir treatment was started. At that time, the CD4 cell count was 630 cells/μL (18%), and the HIV RNA level was 195,000 copies/mL. Within 2 months, the reticulocyte count was 2.6%; within 4 months, the reticulocyte count was 5%, and RBC transfusions were no longer necessary. One month after the final transfusion, the hemoglobin level was 10.5 g/dL, and the reticulocyte count was 3.8%. With HAART, there was a dramatic and sustained increase in the CD4 cell count (figure 1) and a modest but sustained decline in the HIV RNA level (figure 2).

The patient did not require further transfusions in the ensuing 2.5 years. The hemoglobin concentrations remained normal (range, 11.5–13 g/dL). The results of successive tests for IgM and IgG antibody to parvovirus B19 were negative at 2 and 5 years of age. The CD4 cell counts ranged from 1800 to 2400 cells/μL (26%–30%), and the HIV RNA levels ranged from 15,000 to 20,000 copies/mL. At 5.5 years of age, the patient remained asymptomatic with normal health and normal growth and development.

Case 3. Patient 3 had perinatally acquired HIV infection diagnosed at 4 months of age. She was treated with zidovudine. The patient was well until she reached 21 months of age, at which time she presented with lethargy and shortness of breath. Physical examination revealed generalized edema involving the face, abdomen, and extremities. The blood pressure was 133/76 mm Hg. Laboratory studies revealed the following values: blood urea nitrogen, 8 mg/dL; serum creatinine, 0.3 mg/dL; serum albumin, 1.3 g/dL; and cholesterol, 322 mg/dL. Urinalysis showed grade 3+ protein. A timed urine collection had 3.9 g of protein per 24 h. The CD4 cell count was 1400 cells/μL (37%).

The patient was treated with iv albumin and furosemide, and anasarca resolved. She was also treated with prednisone, and didanosine was added to zidovudine therapy. Prednisone treatment was continued in varying doses for the next 9 months. When the patient was 3.5 years of age, the CD4 cell count was 506 cells/μL (35%), and the HIV RNA level was 80,000 copies/mL. A timed urine collection had 1000 mg of protein per 24 h. Ritonavir was added to treatment with zidovudine and didanosine. Within 12 months, proteinuria had disappeared completely, and urinary protein excretion became normal. Within 2 months of initiation of HAART, the CD4 cell count increased to 666 cells/μL (31%), and the HIV RNA level decreased to <400 copies/mL. With use of HAART, there was a sustained increase in the CD4 cell count (figure 1), and there was a dramatic and sustained reduction in the HIV RNA level (figure 2). Three years after HAART was initiated, the CD4 cell count was 847 cells/μL (43%), and the HIV RNA level was <50 copies/mL. At 6.5 years of age, the patient remained asymptomatic. She had normal renal function and no proteinuria.

DISCUSSION

This report describes 3 children with HIV infection in whom the dominant clinical manifestations were dilated cardiomyopathy, chronic red cell aplasia, and nephropathy. To date, the major benefit of HAART has been a decline in morbidity and mortality due to opportunistic infections [4]. Although there is very little information concerning the value of HAART for patients with organ-specific complications, the present report suggests that a variety of noninfectious complications of HIV infection are amenable to HAART.

Patient 1 had dilated cardiomyopathy as the major complication of his HIV infection. Dilated cardiomyopathy has been described in 20%–40% of adults with HIV infection [14] and in 10%–20% of children with HIV infection [15–17]. The mean age at diagnosis of cardiomyopathy in children is 18–24 months [15, 16], but symptomatic cardiomyopathy may occur in children who are as young as 6 months of age [15]. HIV-associated cardiomyopathy is a progressive condition, and survival beyond 12 months after infection is unusual in children with symptomatic cardiomyopathy [16, 18].

In recent years, the pathophysiology of HIV cardiomyopathy has become better understood. It is clear that most patients with dilated cardiomyopathy have preceding or concomitant myocarditis [19, 20]. By means of a variety of techniques, HIV sequences are found in myocardial cells in 50%–75% of patients with dilated cardiomyopathy [19, 20]. Thus, dilated cardiomyopathy appears to be the end result of myocarditis due to direct infection of myocardial cells by HIV.

Patient 1 had clinical, echocardiographic, and radiographic resolution of dilated cardiomyopathy after initiation of HAART. In addition, HAART resulted in a dramatic and sustained increase in the CD4 cell count, and the HIV RNA level became very low. To my knowledge, this child is the first patient in whom dilated cardiomyopathy resolved by use of HAART has been reported.

Patient 2 had chronic red cell aplasia as the major complication of her HIV infection. Pure red cell aplasia is an uncommon complication of HIV infection. Parvovirus B19 infection has been described in some patients with HIV infection complicated by red cell aplasia, and such patients may respond to
iv Ig therapy [21, 22]. However, Mylonakis et al. [23] described an adult patient with HIV infection and parvovirus B19–induced red cell aplasia that did not respond to iv Ig therapy. Red cell aplasia resolved only after the initiation of HAART. Patient 2 had no serological or histologic evidence of parvovirus B19 infection.

HAART was associated with resolution of red cell aplasia in patient 2. Moreover, patient 2 had a marked and sustained increase in the CD4 cell count, but there was only a modest decline in the HIV RNA level. Other investigators have reported an increase in CD4 cell counts without sustained suppression of HIV RNA levels with HAART [24, 25]. This response may indicate that HAART is effective in improving and maintaining immunologic function and slowing disease progression independent of the effects on plasma HIV RNA levels.

Thrombocytopenia is a much more common complication of HIV infection than is red cell aplasia. Zidovudine monotherapy may improve HIV-associated thrombocytopenia, but platelet counts rarely return to normal [26]. Recently, Carbonara et al. [27] reported complete resolution of thrombocytopenia in 7 of 9 patients who received HAART.

Patient 3 had HIV nephropathy that was manifested by nephrotic syndrome as the major complication of her HIV infection. Although edema and massive proteinuria resolved with prednisone therapy, the patient continued to have abnormal urinary protein excretion for >2 years after presentation. All features of nephropathy resolved within 12 months of initiation of HAART.

Nephropathy is a frequent complication of HIV infection. It has been described in ~30% of adults with HIV infection [18, 28] and in 10%–25% of children with HIV infection [29, 30]. Nephropathy is usually a late complication of HIV infection in children. The average age at diagnosis of HIV nephropathy is ~3 years [28, 29], but renal disease may be the presenting feature of HIV infection in some children [15]. HIV nephropathy is a progressive disease that ultimately leads to renal failure and early death [29, 30].

Although corticosteroids and cyclosporine have been reported to be beneficial therapy for some patients, there is no universal effective treatment of HIV nephropathy [18]. Iifu et al. [31] reported that zidovudine monotherapy prevented the progression to end-stage renal disease in adults with HIV nephropathy, but there is little, if any, evidence that such therapy will reverse established renal disease. To date, only 1 adult [32] and 1 child [33] have been described as having HIV nephropathy that resolved with HAART. With HAART, nephropathy in patient 3 completely resolved. In addition, she had a sustained increase in the CD4 cell count and a dramatic reduction in the HIV RNA level. Patient 3 may therefore be added to the short but growing list of patients in whom HAART has cured HIV nephropathy.

Restoration of immunologic function with HAART has produced a dramatic reduction in morbidity and mortality due to opportunistic infections in patients with HIV infection [4]. The present report expands the benefits of the use of HAART for HIV infection. The patients in this report indicate that HAART is associated with resolution of previously untreatable and often fatal organ-specific complications of HIV infection.

References

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