The Clinical Course of Human Immunodeficiency Virus Infection in Genetically Identical Children

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Human immunodeficiency virus (HIV) infection in children is associated with diverse clinical manifestations and highly variable rates of progression. There is little information concerning the clinical course of HIV infection in genetically identical children. We review the cases of identical triplets who were infected with HIV at 1 day of age via a blood transfusion from a common unit of contaminated blood. The subsequent clinical manifestations of HIV infection in the triplets were remarkably uniform. Moreover, the patients' CD4 cell counts declined at similar rates. These patients enhance our understanding of the role of viral and host factors in determining the clinical progression of HIV infection.

HIV infection acquired during the perinatal period is associated with extremely diverse clinical manifestations. Some children with HIV infection experience the early onset of opportunistic infections, rapidly progressive disease, and early death, while others have delayed symptoms and prolonged survival [1].

Although our current understanding is incomplete, a number of important factors that influence the clinical course of HIV infection have been identified. These include the timing and source of HIV infection, the biological properties of the virus, and the genetic constitution and immune response of the host [2]. The relative importance of any single determinant is very difficult to investigate because it is virtually impossible to control for the other factors influencing the course of HIV infection.

See the editorial response by Pizzo on pages 975–6.

In rare, unfortunate instances, HIV infection in children provides insight into the factors determining disease progression. This occurs when genetically identical children are infected with HIV from the same source at the same time. To date, however, little if any information concerning the clinical course of HIV infection in identical hosts has been available. Previous reports of HIV infection in twins focused on concordance of infection and provided little information concerning the clinical manifestations of HIV infection in twin pairs [3–6]. This report describes the clinical manifestations of transfusion-acquired HIV infection in identical triplets.

Patients and Methods

The patients were identical triplets born on 2 July 1984 after a 27-week gestation. On the first day of life, each received a 20-mL transfusion of packed RBCs from a common unit of blood. The triplets were found to have HIV infection in September 1985, at 15 months of age. The donor of the blood was later found to be infected with HIV [7]. No information concerning the subsequent clinical course of the donor is available.

Serum antibody to HIV was measured by EIA and by western blotting. Serum HIV p24 antigen was measured by EIA. Human leukocyte antigen (HLA) typing was performed on peripheral blood mononuclear cells with use of standard microcytotoxicity methods. Zygosity testing was performed by the University of Virginia DNA Laboratory (Charlottesville, VA). Pst I–digested peripheral blood DNA was separated by agarose gel electrophoresis, hybridized with one multilocus probe (DNF24) and three single-locus probes (D17S79, D4S163, and D7S21), and then examined by Southern analysis.

Results

All patients had serum antibody to HIV, as measured by enzyme immunoassay and western blotting. Moreover, all three children's tests for p24 antigen were positive. Their mother was HIV-seronegative.

The patients were identical at the HLA A, B, and C loci. HLA DR typing was not performed. The triplets were judged to be monozygous by DNA analysis.

Case Reports

Patient 1

This patient was the 1,000-g firstborn of identical female triplets. HIV infection was confirmed at 15 months of age,
after one sister (patient 3) was found to have HIV-associated thrombocytopenia. CD4 cell counts are shown in figure 1.

Persistent cervical adenopathy was first apparent at 4 years of age, but she had no other signs or symptoms attributable to the HIV infection. Zidovudine therapy and trimethoprim-sulfamethoxazole prophylaxis were instituted at 5 years of age.

At 6 1/2 years of age, she and her sisters developed chickenpox. The patient had severe varicella-zoster virus (VZV) infection, complicated by pneumonitis. She was treated with acyclovir and recovered.

At 7 years of age the patient acutely lost vision in the left eye. Ophthalmologic examination revealed acute retinal necrosis characteristic of varicella retinitis. Detachment of the left retina ensued, and she was blind in the left eye thereafter. Concomitant with the retinal necrosis, cutaneous varicella reappeared. The lesions persisted despite acyclovir therapy. VZV isolated from the lesions was resistant to acyclovir. Intravenous foscamet therapy resulted in control but not total clearing of the varicella.

At 7 1/2 years of age the patient developed fever, chills, and night sweats and lost weight. Blood cultures were positive for Mycobacterium avium. Therapy with clarithromycin provided symptomatic relief, but her blood cultures remained positive for M. avium until her death.

At 8 years of age she developed left hemiparesis. Examination of the CSF yielded normal results. MRI of the brain revealed cerebral atrophy and multifocal leukoencephalopathy. Progressive neurological deterioration ensued, and the patient died at 8 1/2 years of age. The patient’s clinical manifestations are summarized in table 1.

Patient 2

This patient was the 910-g second-born of the identical female triplets. HIV infection was confirmed at 15 months of age, after one sister (patient 3) was found to have HIV-associated thrombocytopenia. CD4 cell counts are shown in figure 1.

The patient had no symptoms referable to her HIV infection until 4 years of age. At that time she developed immune-mediated thrombocytopenia. Therapy with prednisone and intravenous immunoglobulin was marginally beneficial; the platelet counts remained <100 × 10^9/L (<100,000/mm^3). Several months later she had a splenectomy, after which the thrombocytopenia resolved. Zidovudine therapy and trimethoprim-sulfamethoxazole prophylaxis were instituted at age 5 years.

The patient had uncomplicated chickenpox at 6 1/2 years of age. At 9 years of age cutaneous varicella recurred. Her condition partially responded to acyclovir therapy, but the VZV infection persisted to varying degrees until her death 2 years later.

At age 10 years the patient developed disseminated M. avium infection manifested by fever, diarrhea, and weight loss. Treatment with clarithromycin and ethambutol relieved the symptoms, but blood cultures remained persistently positive for M. avium.

At age 10 1/2 years, the patient developed bilateral varicella retinitis. Bilateral retinal detachment ensued, and she was left totally blind. Shortly thereafter, the patient developed progressive neurological deterioration manifested by right hemiparesis and loss of cognitive function. No diagnostic studies were performed to determine the etiology of her encephalopathy, and she died at 11 years of age. The patient’s clinical manifestations are summarized in table 1.

Patient 3

The patient was the 880-g third-born of the identical female triplets. At 8 months of age she developed immune-mediated thrombocytopenia. Prednisone therapy was started, and the platelet counts returned to normal in 1 month. The development of thrombocytopenia during infancy prompted testing for HIV, and HIV infection was diagnosed at 15 months of age [8]. CD4 cell counts are shown in figure 1.
She remained asymptomatic until 3 years of age, when thrombocytopenia recurred. The patient received prednisone and intravenous immunoglobulin, but the platelet counts remained $< 100 \times 10^9/L < 100,000/mm^3$. Zidovudine therapy and trimethoprim-sulfamethoxazole prophylaxis were instituted at 5 years of age. Shortly thereafter the platelet count increased, and she had no further problems with thrombocytopenia.

The patient had uncomplicated chickenpox at 6 1/2 years of age. Six months later, varicella recurred. She was treated with acyclovir, which cleared the lesions, but 3 months later VZV infection recurred. Acyclovir-resistant varicella was recovered from the lesions, and she was treated with intravenous foscarnet for 3 weeks, followed by daily intravenous foscarnet therapy.

At 9 years of age she developed bilateral varicella retinitis. Bilateral retinal detachment ensued, and she was left blind. Three months later, the patient developed encephalopathy manifested by seizures, left hemiparesis, and loss of cognitive ability. She had progressive neurological deterioration and died at 9 1/2 years of age. The patient’s clinical manifestations are summarized in table 1.

Discussion

This report represents the first detailed description of the clinical course of HIV infection in genetically identical children. The patients in this report were identical triplets who were infected with HIV at 1 day of age via a common unit of contaminated blood. The children exhibited remarkably uniform clinical manifestations of HIV infection.

Many factors influence the clinical manifestations of HIV infection in any given patient. These include the timing and source of HIV infection, the biological properties of the virus, and the genetic constitution and immune response of the host [2]. The circumstances surrounding the HIV infection in the patients in this report allow insight into the viral and host factors that influence disease progression.

The age at acquisition of HIV infection is a major determinant of the subsequent clinical course of disease in children. The course of vertically acquired HIV infection varies widely, depending on the timing of transmission of HIV from the mother to the fetus or newborn. HIV infection acquired in utero is often more rapidly progressive than infection acquired at or around the time of birth [9, 10]. Similarly, the clinical course of transfusion-acquired HIV infection is influenced by the age of the recipient of the contaminated blood [11, 12]. The patients in this report were all infected with HIV at precisely the same time.

A number of recent studies have convincingly demonstrated that the HIV viral load is a powerful predictor of the subsequent clinical course [13]. Sensitive, quantitative assays for measuring viral load were not available for the vast majority of time during which the patients in this report were alive. Unfortunately, serial plasma samples were not available for retrospective testing.

The source of HIV infection and the biological properties of the virus play critical roles in determining the subsequent clinical course of the disease. HIV has an extremely high level of genetic variability, owing to the error-prone reverse transcriptase [2]. Over time, distinct but related HIV strains arise within an individual; these strains are termed quasispecies [2, 14]. Within an individual and between individuals, HIV quasispecies may vary considerably with respect to any number of biological properties, including virulence [2]. Clearly, two patients infected with different HIV strains from different sources would be expected to manifest different clinical courses.

A number of HIV quasispecies undoubtedly existed in the donor of the blood that infected the triplets. It is certain, however, that the patients were exposed to exactly the same strain or strains of HIV at the time of their transfusion. Recent compelling evidence indicates that the development of HIV quasispecies represents adaptive evolution of the virus under natural selection governed by the immunologic environment [15, 16]. Since the patients were genetically identical, one would predict uniform evolution of quasispecies and hence similar clinical manifestations. Unfortunately, we have no direct information pertaining to HIV genotypes in the patients.

The genetic constitution of the host is clearly a critical determinant of the clinical course of HIV infection—that is, the immunologic response to HIV infection is genetically influenced to a great extent. Some genetically determined HLA alleles are associated with increased susceptibility to HIV infection and more rapid progression to AIDS, while others are associated with resistance to infection or prolonged survival [17].

HLA molecules are critically important in shaping the host’s T cell repertoire. In fact, HLA-identical, monozygous individuals have very similar T cell receptor repertoires [18, 19] and concordant immune responses [20]. Thus, one would predict that the triplets would have uniform immune responses to their HIV infection. Indeed, they had very similar declines in CD4 cell counts over time, coincident with their similar clinical courses.

In summary, this report describes the clinical features of HIV infection in genetically identical children. Triplets with similar immune systems, infected at exactly the same time with the same strains of HIV, had nearly identical clinical courses. These patients enhance our understanding of the factors governing the clinical course of HIV infection.

References

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