Slow progression of paediatric HIV disease: Selective adaptation or a chance phenomenon?

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Abstract

Background: Disease progression in human immunodeficiency virus / Acquired immunodeficiency syndrome (HIV/AIDS) is affected by several factors both external and internal to the human hosts. In the European Caucasian populations, the chemokine-cell receptor variant CCR5 "Delta 32" is a the genetic determinant of HIV disease progression that is believed to have been selected for in the general population by exposure to antigens closely interlinked to HIV like Yersinia pestis or smallpox virus. Among African populations, it is possible that this selection will be induced by HIV over time.

Aim: To present two cases of mother-to-child transmitted HIV highlighting the possible increasing prevalence of slow disease progression.

Methods: Clinical case reports of slow progression of pediatric HIV

Introduction

Human immunodeficiency virus (HIV) disease progression in humans is affected by a number of factors, both exogenous and endogenous. Infants born with or who acquire HIV from their mothers form an ideal population for observing determinants of HIV disease progression in humans. Within sub-Saharan Africa, poverty, orphanage with its associated socio-economic stresses and a high prevalence of opportunistic infectious pathogens may be some of the exogenous factors contributing to fast disease progression in infants who were born with, or acquired HIV perinatally. Recent studies have however identified and elucidated other endogenous determinants of disease progression in HIV. While most cases of mother-to-child transmitted (MTCT) HIV within the sub-Saharan setting have been observed to die within 3-6 years after birth if no highly active antiretroviral therapy (HAART) is instituted, a number of discrepancies exist in this pattern of HIV disease progression. We present here two cases of MTCT HIV who were observed to survive into their late teens without prior use of HAART as a succinct to further examining the possible factors for slow progression of disease.

Case Reports

Case 1

An 18-year-old girl was admitted in the later quarter of 2002 via ward 4B to Intensive Care Unit (ICU),
New Mulago Hospital (Uganda) with a diagnosis of HIV encephalopathy. Her sero-status (HIV +ve) had been known since age 7 years, both by Enzyme Linked Immuno-absorbent Linked Assays (ELIZA) and Polymerase Chain Reaction (PCR). Her father had succumbed to acquired immunodeficiency syndrome (AIDS) in 1992 (10 years preceding this admission). The mother was HIV +ve, not on antiretroviral therapy (ART), and yet well and alive (10 to 18 years following presumed contraction). ART was only initiated in this case after discussing the prognosis with the mother. The past medical history indicated previous repeated upper respiratory tract infections (URT), but this was the first major hospitalization. The CD4 cell counts was 180 cells/μL but the viral loads were not done.

Case 2

A 16 year old girl was admitted in coma with polyneuritis and hemiparesis to Ward 4B, Mulago Hospital Uganda between March and April 2004. Toxoplasmosis was suspected on admission. Along the way, the diagnosis was changed from central nervous system (CNS) toxoplasmosis to possible tuberculous meningitis following a negative serum and cerebral spinal fluid (CSF) screen for toxo-titres, and a highly marked CSF lymphocytosis, turbid CSF despite a negative Ziehl-Neelsen (ZN) stain for acid fast bacilli (AFB). CD4 cell counts were 110 cells/μL but the viral loads were not done. She was HIV +ve, her mother had died with AIDS 10 years previously, but the father was alive. He too was HIV +ve but had not progressed to AIDS, presumably 10-16 years after contraction despite not being on HAART.

Discussion

In both cases, facilities were not readily available to conduct histo-immuno-genetic assays for some of the factors associated with slow progression of HIV disease such as chemokine-cell receptor gene (CCR5) variant "Delta 32 [ CCR5 "Delta 32"] 11-15, histocompatibility complex (MHC) genotype 7-10, other chemokine receptors CCR5 11-15, CCR2 12-13, and CX3CR1 16, the chemokine-receptor ligands (CCL5-RANTES) 17, CCL2 (MCP1) 18-20, CCL3L1 (MIP1P) 21 and CXCL12 (SDF-1) 22, the cytokine IL10 23, a killer immunoglobulin receptor gene, APOBEC3G 24 and HIV subtyping. We assumed that the surviving parent had acquired HIV infection from the late partner, although this was unreliable history, especially given the discordance that assails primary HIV infection among a section of married couples with a history of unprotected extramarital sexual intercourse.

These two cases serve to illustrate the fact that although most cases of mother-to-child transmitted (MTCT) human immunodeficiency virus (HIV) succumb to AIDS-related illnesses within 3-6 years after birth, of late, some discrepancy in disease progression have been observed occur and some patients survive into the late teens despite not being on highly active antiretroviral therapy. The question this raises is whether this progression is a matter of chance, a consequence of a more health friendly exogenous environment or there is an on-going selective adaptation for the endogenous factors that determine HIV disease progression within the sub-Saharan setting as has been noted elsewhere 5,6. Interaction with clinicians at various paediatric HIV treatment centres in Uganda such as Mild May, Entebbe Road, Joint Clinical Research Centre (JRC), Mango, The AIDS Support Organization (TASO), Mulago, and the Paediatric Infectious Disease Clinic (PIDC), Makerere, offered undocumented support to our observations.

For instance, individuals who are homozygous for a 32-bp deletion in the chemokine-cell receptor gene (CCR5) are highly resistant to infection by HIV-1 3,4. This CCR5 "Delta 32" variant became established in Europe centuries ago, perhaps under selective pressure from some other pathogen such as Yersinia pestis 5 or smallpox 6. Because of non-permissive conditions, it was not possible to do genotyping for the CCR5 "Delta 32" variant, as well as a full bacteriology and virology screen to rule out previous infections with such pathogens in both cases presented. However, our observation underlines the need to search for the possibility of such endemic pathogens within the sub-Saharan
setting that may select for such protective endogenous factors. It is also likely that the selection in this setting for this variant will occur under the pressure of HIV itself, given that over 70% of cases of HIV occur here as per The Joint United Nations Programme on HIV/AIDS (UNAIDS) progress reports over 1999 to 2006. It is worth noting the slow progression history of HIV disease in the surviving biological parent of both cases. Case 1 had a mother who was HIV+ve but well and not yet on HAART about 18 years after presumed contraction (provided her current HIV strain was acquired from the late father). Similarly, case 2 had a surviving father who was HIV+ve but well and not yet on HAART about 16 years after presumed contraction. It was also interesting to note that both patients reported were females. These additional observations have led us to question, if an endogenous protective factor was involved, if or not this factor is genetically transmitted through a sex-linked Mendelian style inheritance (X-linked recessive trait expressed in the heterozygous form in females).

Additional human genetic variants reported to influence HIV-1 transmission, viral replication, and/or disease progression include those of the major histocompatibility complex (MHC) genes, as well as other variants, in the chemokine receptors CCR5, CCR2, and CX3CR1, the chemokine-receptor ligands CCL5-RANTES, CCL2 (MCP1), CCL3L1 (MIP1P), and CXCL12 (SDF-1), the cytokine IL10, a killer immunoglobulin receptor (KIR) gene, and APOBEC3G. Just as HIV evolves within the human body to escape selective pressure from MHC genes, the human genome is also under selective pressure from microbes. In sub-Saharan Africa, where HIV is highly endemic, genetic factors that delay HIV disease progression such as certain human leucocytes antigen (HLA) types will likely become somewhat enriched in the population, whereas those which promote rapid progression to AIDS will decline.

Conclusion

A more in-depth immunologic and genetic approach is called for to establish the current baseline prevalence and to further examine the possibility of adaptive selection for immunologic protectors of HIV disease progression within the sub-Saharan setting.

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