Factors responsible for mother to child transmission (MTCT) of HIV-1 – a review

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Abstract. – Many factors have been identified to influence the risk of mother to child transmission (MTCT) of HIV. Chief amongst these is high maternal viral load (mVL), measured at delivery, has been described as the strongest risk factor for both in utero (IU) and intrapartum (IP) transmission. Similarly, CD4+ T cell count and clinical stage of infection are also the confirmed significant predictors of transmission. Correspondingly, higher mVL in the genital tract has also been independently associated with a higher risk of MTCT of HIV-1. So, the present review article would put light on various aspects of factors responsible for MTCT of HIV in pediatric patients.

Key Words: HIV, Pediatrics, MTCT, Maternal viral load.

Introduction

The transmission of a disease including AIDS is dependent on the biologic properties of the virus, its concentration in the exposed body fluid, and the nature of the host susceptibility both at the cellular as well as immunological levels. Furthermore, it has been reported that a strong genetic bottleneck occurs during mother to child transmission (MTCT) of HIV-1. This is evident through population diversity and phylogenetic pattern analysis of the HIV-1 subtype C envelope glycoprotein, where a single viral variant appeared to be responsible for infection in the infants. As a result, the newly transmitted viruses were less diverse and harbored significantly less glycosylated envelope. This suggested that viruses with the restricted glycosylation in envelope glycoprotein appeared to be preferentially transmitted during HIV-1 subtype C perinatal transmission. In utero (IU) transmitters were more likely to transmit single or multiple major maternal viral variants; whereas, intrapartum (IP) transmitters were more likely to transmit minor HIV-1 variants, indicating that different selective pressures might be involved in determining the pattern of maternal HIV-1 variant transmission. Similarly, in another study, viral sequences from the blood and cervico-vaginal fluid from HIV-1 transmitting mothers were compared to those in their infants. This showed the presence of more than one HIV-1 variant in the neonate’s plasma that derived from the maternal blood and vaginal compartment. This suggested that more than one episode of transmission with more than one viral strain from different maternal compartments occurred, which included both cell-free and cell-associated maternal virus. Other reports have also suggested that the HIV-1 subtype influences MTCT. In a Tanzanian study, subtype C was found to be preferentially transmitted IU when compared to subtypes A and D; while in Kenyan women, MTCT was more common among mothers infected with subtype D compared with subtype A. However, these findings have not been observed in other population groups.

Host/Genetic Factors

Host factors could be broadly divided into innate as well as adaptive immune parameters. Innate factors include the chemokines and chemokine receptors. The chemokines CCL3 (macrophage inflammatory protein1α, MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES, regulated on activation, normal T cell expressed and secreted) are natural ligands for CCR5 and therefore chemokine receptor-ligand interactions represent a barrier to HIV-1 binding to its co-receptor. Both qualitative and quantitative traits in either chemokine receptors or ligands have been described to influence susceptibility to HIV-1 MTCT.

A well-known genetic factor that has received considerable attention over the last decade is the CCR5 locus and its CCR5-D32 (rs333) allele. The
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32-bp deletion within the coding region of the CCR5 gene generates a premature stop codon that forms a truncated protein that is not expressed on the cell surface. In this manner, CCR5-D32 homozygosity has been found to confer near complete resistance to sexual transmission of HIV-1 infection by R5-type HIV-1 isolates, as well as protection against MTCT. Also, individuals with at least one copy of CCR5-D32 exhibit an improved resistance about wild-type individuals. However, if heterozygotes do become infected, they have reduced HIV-1 VL with slowed progression to AIDS by an additional 2-3 years. Additionally, other CCR5 single nucleotide polymorphisms (SNPs) have also been associated with protection against HIV-1 transmission in adults and with delayed progression to AIDS. The authors proposed that protection might be due to reduced expression of the CCR5 receptor but was dependent on a delicate ratio of virus to the receptor. Conversely, high expression of CC chemokines (the natural ligands for CCR5) in EU infants has suggested that chemokines might have a role in mediating inhibition of MTCT. In fact, copy number variation (CNV) in CCL3L1 and CCL4L2 chemokine genes has been linked to HIV-1 susceptibility. Further, possession of a lower copy number of CCL3L1 (relative to population mean) is associated with increased risk of HIV-1 infection. CCL3L1 gene copy number is also associated with CCL3 production and with vertical transmission. Moreover, high CCL3L1 gene copies in the infant, but not maternal, were associated with reduced HIV transmission. Conversely, MTCT was greatest if mother and infant both had low CCL3L or CCL4L copy numbers. Recently, two CCL3 haplotypes (Hap-A1 and Hap-A3) were noticed to influence MTCT. The authors reported that Hap-A1 in infants (which also associated with higher CCL3L copy number) is associated with protection from IU HIV-1 infection. On the other hand, Hap-A3 in mothers is also associated with increased risk of IP transmission. These works highlight the importance of understanding the gene content and gene copy number in disease susceptibility and/or resistance.

Immune Factors

Both humoral and cellular immune responses have been found to play an important part in influencing MTCT with regard to adaptive immune factors. Several studies have correlated the presence of neutralizing antibodies (nAbs) in maternal serum with protection from MTCT of HIV-1. Maternal anti-p24 and anti-gpl20 antibodies were inversely associated with vertical transmission rates. Whilst in another paper, IU-transmitting mothers were significantly less likely to have autologous NABS to their own HIV-1 strains at delivery compared to non-transmitting mothers. Furthermore, both heteroduplex and phylogenetic analyses showed that there was selective MTCT outgrowth of maternal autologous neutralization escape HIV-1 variants. This showed maternal autologous NABS could exert powerful protective and selective effects in perinatal HIV-1 transmission. With regards to cellular immune responses, a number of researches have identified HIV-1 specific CD4+ and CD8+ T cell responses in HIV-1 exposed but uninfected individuals. Further, these specific responses are a correlate of immune protection from HIV-1 infection. These HIV-1 specific responses have been observed and characterized in the Pumwani Kenyan cohort of sex workers both at systemic and mucosal levels. The detection of HIV-1 specific CTLs in ESN individuals thus seems to indicate that HIV-1 has managed to initially infect the host, but that its further propagation has been contained by immune mechanisms and completely eliminated. Also, specific HLA genes have also been implicated in risk of MTCT. One study found that mothers with HLA-B variants (B*13:02, B*35:01, B*35:03, B*44:02, B*50:01) transmitted HIV-1 to their infant even in the context of low VL, whereas mothers with other variants (B*49:01, B*53:01) did not transmit the virus despite high VL. Furthermore, since the infant shares at least half of his or her HLA genes with the mother, both cell-free and cell-associated HIV-1 virions of maternal origin display maternal HLA. Then, fetal/newborn anti-HLA antibodies or alloreactive T cell responses could potentially protect against infection from the mother, if there is some degree of HLA discordance between mother and child. Indeed, mother-infant HLA concordance has been associated with increased risk of MTCT. So, infants whose HLA-matched their mothers might be less able to recognize HIV-1 that has evolved to evade maternal immune responses via HLA-mediated selection. Furthermore, children who were homozygous or who shared both alleles with their mothers at more than one HLA class I locus were more likely to progress to AIDS or death than other children. This suggested that the level of mother-infant concordance may compromise the child’s capacity to control HIV-1 replication when the virus is acquired from the mother.
Obstetric Factors
Several obstetric factors such as preterm delivery, prolonged membrane rupture and the use of invasive procedures (amniocentesis) have been associated with MTCT. However, elective caesarean section before the onset of labor and rupture of the amniotic sac reduced markedly the risk of MTCT. This is likely due to the avoidance of micro transfusions of maternal blood to the fetus during labor contractions and of direct contact of the fetus’s skin and mucosal membranes with infected secretions or blood in the maternal genital canal. Furthermore, in addition to elective caesarean section, if ART was provided antepartum, intrapartum, and post-partum, the risk of MTCT was reduced even further.

Prevention of MTCT
With increasing knowledge about the underlying mechanisms of MTCT has come an increased emphasis on the search for interventions to prevent or reduce the risk of transmission. Consequently, the WHO has promoted a comprehensive approach that includes four PMTCT components: (1) primary prevention of HIV-1 infection, (2) prevention of unintended pregnancies among HIV-1 infected women, (3) prevention of HIV-1 transmission from HIV-1 infected mothers to their infants and (4) care, treatment and support for HIV-1 infected mothers, their children and families. Most important has been the administration of ART to mothers and their infants. It is estimated that in the absence of ART, 25% of infants infected with HIV-1 progress rapidly to AIDS or death within the first year of life. However, effective ART has reduced the rate MTCT to 2.7%, and where infants are infected, ART has transformed pediatric HIV-1 into a chronic disease.
ART could reduce MTCT in one or more of the following ways: (1) by reducing viral replication and thus lowering plasma VL in pregnant women, (2) through pre-exposure prophylaxis (PrEP) of babies by crossing the placenta, (3) through post-exposure prophylaxis (PEP) of babies after delivery and (4) through reducing transmission via breast-feeding.

Antiretroviral Drugs
In the early 1990s, few ART options for HIV-1 infection existed, and ART largely consisted of monotherapy with zidovudine (ZDV), a nucleoside analog initially called azidothymidine (3’-azido-3’-deoxythymidine) or AZT. Initial HIV-1 treatment with AZT led to a sense of excitement in the medical field arising from the possibility that perhaps HIV-1 could be controlled, but it soon became clear that monotherapy was inadequate for long-term viral suppression as HIV-1 with its high rate of replication, the low fidelity of reverse transcription and capacity for recombination lead to an elevated genetic diversity and the development of drug-resistant strains. As such treatment evolved over the years to dual therapy and combination therapy, also known as highly active antiretroviral therapy (HAART). To date, six distinct classes have been classified according to their effect on HIV-1 replication: (1) nucleoside reverse transcriptase inhibitors (NRTIs), (2) nucleotide reverse transcriptase inhibitors (NtRTIs), (3) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (4) protease inhibitors (PIs), (5) entry inhibitors (EIs) and (6) integrase inhibitors (INIs), of which the INIs represent the most recent antiviral drug class.

Conclusions
Various factors are responsible for the MTCT of HIV-1. The thorough study, as well as understanding of these factors, would definitely result in better management/preventive avenues in the near future.

Conflict of interest
The authors declare no conflicts of interest.

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