REVIEW ARTICLE

Pediatric HIV Infection

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ABSTRACT

HIV infection by maternal transmission is increasing in the world due to the increase in infected women who are not receiving appropriate antiretroviral therapy. Prognosis of HIV infection in children is poor because the newborn has an immature immune system. Early diagnosis and therapy are needed to avoid the development of AIDS. New therapies are becoming available but prevention of infection, through maternal therapy during pregnancy, is the most effective measure in avoiding this infection through this transmission route.

Keywords: Anti Retroviral Agents; Antigens, CD4; HIV; Vertical Transmission

INTRODUCTION

The number of HIV infected people is increasing worldwide:\textsuperscript{1,2} In 2003, 5 million new cases, of whom half were women under 30 years of age, were added to the infected population. Less than 15\% of HIV-infected people have access to therapy. This situation leads to an increase in mother-to-child-transmission (MTCT) which has very poor prognosis: 800,000 new cases and 600,000 deaths were reported in 2003.

Available effective prevention measures\textsuperscript{3,4} include therapy applied during pregnancy, at delivery and in the post-partum period;\textsuperscript{5} nevertheless, infections in children are increasing and mortality remains very high\textsuperscript{6} if no antiretroviral therapy is applied.

Many questions are yet to be resolved regarding susceptibility to infection including measures for immune protection in different populations and different situations.\textsuperscript{7} However, it has been very clearly demonstrated that viral load at delivery (and, as a direct relationship, CD4 number and maternal status) are predictive of viral transmission.\textsuperscript{8} Furthermore, the very good results obtained with antiretroviral therapy (AR) in pregnant women with low viral load at delivery confirm that viral transmission is almost nil.\textsuperscript{9,10}

Factors which contribute to the poor prognosis of MTCT of HIV infection, include:

- Immaturity of the newborn’s immune system and more so if they are premature or the infection occurs intrauterino.\textsuperscript{11}
- Lack of immunologic memory, thus, each contact with any infectious agent will lead to an immune response that will, as a consequence, give rise to viral replication and shedding, thereby infecting new CD4 cells. Viral load in children is always higher than in infected adults and is more difficult to control.\textsuperscript{12}

Our Experience

In our hospital, a 350-bed pediatric hospital (NHS and University hospital), we have diagnosed, treated and followed around 100 infected children and 500 children born of HIV-positive mothers since 1984. Two clear-cut periods can be distinguished: the first between our first case and the beginning of triple therapy with anti-proteases in 1997, and the second since then.

In the first period we had many more cases with severe forms of presentation and very short mean life span.\textsuperscript{13} The first patient was referred to our Unit with suspected congenital immunodeficiency (SCID). He had disseminated CMV infection and hypogammaglobulinemia. Although we ruled out a SCID after immunological evaluation, and HIV had been very
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recently described, no definitive diagnosis could be made until antigen detection tests became available (1 year after he died). Other cases of hypogammaglobulinemia have been reported, but HIV infection in the mothers had previously been diagnosed.

Two main patterns of disease presentation were observed:

Pattern 1: when symptoms began before the age of 6 months, with P. Carinii, CMV or other opportunistic infections, life expectancy was very short and death before 2 years of age was the most common outcome.

Pattern 2: when the patients presented with lymphoid proliferation, bacterial infections, etc and were diagnosed late, prognosis was better. The oldest surviving patient infected by MTCT and with good clinical status was born in 1981.

We considered these two patterns to correspond to intrauterine pattern or perinatal infection pattern. Other authors refer to a bi-modal distribution.

A recent meta-analysis on prognosis revealed similar data and emphasized the relationship between CD4’s and viral load. Prognosis is clearly worse with the same CD4 number if the child is under 2 years of age.

Diagnosis of Infection and Immunodeficiency Status

A- Diagnosis of HIV infection:

In the early years of the epidemic, infected newborns and infants were diagnosed using the coculture techniques and detection of p24 in supernatants, with a very high predictive value mainly in those who were asymptomatic with good CD4 levels. In children older than 12 months, serology and viral load by molecular biology techniques are the currently used diagnostic tests with high sensitivity and specificity. Other less expensive methods have been described but their use depends on the socio-economic circumstances in each country.

B- Diagnosis of immunodeficiency:

Blood cell count, lymphocyte subsets, mainly CD4 number considering age difference, Ig levels and, when possible, lymphocyte activation markers, complete the picture of the situation in each patient and aid the decision of the best anti-retroviral (AR) protocol.

The CDC classification is not often used when therapy is initiated, and controls and therapeutic decisions are based on CD4 numbers and viral load.

Other immunological markers have been investigated to ascertain the different susceptibility to this infection in the population, and very interesting results have been obtained. Among them, mutations in the CCR5 co-receptor correlate with a less severe disease and provide new insights into the pathogenesis of this disease.

HLA genotyping also shows interesting correlation with progression and severity of the infection.

Eradication of MTCT

Several measures are to be implemented in order to decrease very significantly the incidence of MTCT:

a) Therapy during pregnancy and at delivery:

Control of viral load during gestation must be accompanied by serology, detection of other infections such as CMV, toxoplasmosis, tuberculosis, etc. Therapy protocols vary if the pregnant woman is already on AR therapy or is not., and recommendations have been published. The wide use of Zidovudine (protocol 076) in the last months of pregnancy, during labor and in the first weeks of the newborn’s life has led to a clear reduction in MTCT. However, a greater reduction is achieved if combinations with three drugs are implemented (up to 0.6% in Spain last year).

b) Caesarean section:

It has been shown to decrease transmission of the infection by avoiding the entry of blood cells from the mother into the fetus’s blood during labor and delivery.

c) Avoiding breastfeeding:

The risk of HIV transmission to infants through breast milk outweighs the dangers associated with other nursing methods.

Adverse Effects of AR Therapy During Pregnancy

A few cases of neurologic syndrome associated with persistent mitochondrial dysfunction in children born to seropositive mothers and exposed to antiretrovirals have been described. Obviously, different drugs are being studied with a view to avoiding this toxicity, but the percentage of this adverse effect
versus the high number of non-infected newborns, thanks to these preventive measures, advocates the use of these protocols.

**Treatment of HIV Infection**

Treatment protocols of HIV infection have changed enormously in the last 10 years, and major advances have been made in the management of pediatric HIV patients in the last 2 years,27 thanks not only to the advent of new drugs (that are aiding therapy of other viral infections) but also to the information derived from many research studies on AR drugs.

Prior to AR therapy, we observed that children with late presentation of HIV infection and who had mainly bacterial infections benefited from gamma-globulin therapy28 since immune stimulation was decreased and thus, as we now know, viral replication. This treatment, together with treatment of demonstrated infections (*P. carinii*, CMV, bacterial infections, etc) and infection prevention (prophylactic antibiotics in cases with low CD4 numbers) were the only measures available. Zidovudine therapy (we treated our first pediatric patient in 1987) produced a significant improvement in disease progression and particularly neurologic manifestations. However, the following protocols with two AR drugs and, as a complete change in the history of this disease, triple therapy with one or two protease inhibitors, also called HAART29,30, have led to effective control of viral replication, and therefore CD4 cell destruction and thus have nearly stopped the evolution to AIDS with quite good quality of life in the large majority of patients.

The combination of two nucleoside analogues with one protease inhibitor is the standard protocol to begin therapy in a newly diagnosed child with low CD4 cells and high viral load: if the child is under 12 m. of age with CD4<25-30% and viral load >10^6 and after 12 months when viral load is over 250,000 RNA particles. Monotherapy is not useful, thus many other combinations can be used.

**Follow-up**

Thymic dysfunction and involution are markers of immunodeficiency and rapid progression in infected children. The use of T-cell receptor excision cycles (TRECs) in treated children as a measure of new thymic emigrants (Cells that emigrate /go out from the thymus to the periphery) has confirmed the main role of these new T cells (naive cells). Immune restoration,31 with this method, following potent AR therapy, has been clearly demonstrated.

Patients who have access to HAART therapy are now considered to have a chronic HIV infection and although a complete clearing of the virus has never been achieved, they can lead a normal life. Although a few reports exist on malignancies in children, mainly lymphomas32 in patients with severe immunodepression and high viral load, overall life expectancy is very high and intercurrent diseases are very rare.

It is also true that some problems derived from HAART exist:

- Medication must be taken rigorously. Adherence must be complete; if not, the risk of resistant virus33 is very high.
- There are also adverse effects of therapy (gastrointestinal, pancreatic, lipid metabolism, etc).
- There are other infections after long periods on AR therapy (mycobacteria, bacteria resistant to antibiotics, etc) but most are related to viral-resistant strains and the difficulty in controlling viral load.

**New Perspectives**

New AR drugs are under investigation34 and some new ways to avoid infection are already in use. Anti-fusion drugs to avoid the attachment of viral particles to the cell are showing promising results.

Therapeutic vaccines35 to be used in infected subjects to increase their immune response are under investigation and would be a means of keeping the virus under control. A preventive vaccine is proving very elusive36,37 although much research is being devoted to it.

However, prevention continues to be the best way of avoiding infection and its consequences.

**CONCLUSION**

This very important global health and population problem is leading to the loss of a whole generation of young people, which will make it very difficult for many countries to develop economically owing to the loss of work forces in coming decades.

With respect to MTCT, it is now clear that the adequate treatment and control of pregnant women are the only way to improve the overall situation: fewer infected babies and healthier mothers. From the
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financial point of view, it is less expensive to treat the mothers during pregnancy and to avoid MTCT than to treat the infected children for the rest of their lives. However, in epidemics such as HIV infection, political decisions are essential to define health policy in each country.

REFERENCES