

Perinatally Acquired Human Immunodeficiency Virus Infection in Children in Hong Kong: The Experience of One Centre

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Abstract

To date, almost 1500 people infected with the human immunodeficiency virus have been reported in Hong Kong. The number of children infected perinatally is relatively small: 11 children have been identified and reported. We review our experience in caring for 8 of these children at Queen Mary Hospital since January 1996. Five children originally thought to be healthy were diagnosed because a parent tested HIV positive. Three children presented an AIDS defining illness. Only 2 of the presumed asymptomatic children had normal absolute CD4 counts and percentages. All 8 children had high HIV viral load at the time of diagnosis. They were treated with highly active anti-retroviral therapy (HAART) with favourable response. Except for 2 patients, all have achieved a sustained viral suppression to an undetectable level. One patient died of lymphoma despite an undetectable viral load. Five children were diagnosed because a parent tested HIV positive. Three children presented with symptoms suggestive of HIV infection. Other aspects of care including cost as well as some of the difficulties in caring for these children are highlighted. The need for a policy for universal screening of pregnant women in order to benefit from the effective antiretroviral regimen for reducing perinatal transmission of HIV is also discussed.

Key words

Perinatal human immunodeficiency virus infection

Introduction

Since the beginning of the AIDS epidemics around two decades ago, human immunodeficiency virus (HIV) has infected nearly four million children worldwide. Three quarters of them already died. The number of children infected with HIV in Hong Kong is very small when compared to the global figures. Children can be infected perinatally, by transfusion of blood products, sharing of needles or through sex. In Hong Kong where all the blood products are regularly screened, almost all the new cases of HIV infection in children are due to perinatal transmission. The number of young women infected with HIV in Hong Kong has continued to rise from a male to female ratio of 24:1 in 1990 to 3.6:1 in 1999. More than three quarters of the infected females were between the

child-bearing years of 20 to 39 years of age. Similarly, there is a rise in the number of children diagnosed of HIV infection in the recent few years.

Objectives

The objectives of this review is to examine the characteristics of Hong Kong children perinatally infected with HIV with reference to the age of presentation, severity of disease at initial presentation, the complexity of care, and their response to anti-retroviral treatment. In addition, we want to examine the circumstances under which the diagnosis was made and whether there was any missed opportunity to interrupt transmission and prevent infection altogether.

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Methods

A retrospective chart review was conducted of all the HIV infected children followed in the HIV clinic at Queen Mary Hospital from January 1996 to April 2000. Inclusion criteria included the absence of other risk factors like transfusion and a history or documentation of maternal

HIV infection. Haemophiliac patients infected with HIV through blood products were excluded.

Results

In addition to the 10 cases of perinatal HIV infection in Hong Kong reported up till the end of March 2000 according to the statistics from the Department of Health, one more child was diagnosed and referred to Queen Mary Hospital in March 2000.¹ Eight of these children were referred to Queen Mary Hospital either for diagnosis or for care. There was a trend of more children being diagnosed in more rapid succession: the first referral to our hospital was in November, 1996. It was not until 1998 that two more children were referred, with four more in 1999 and one in the first quarter of 2000. This may be due to an increase of awareness or reflect a genuine increase in incidence. Detailed information on these children is tabulated in Tables 1 and 2.

Presentation at Time of Diagnosis

Patient 1 was diagnosed at 18 months because her asymptomatic father underwent HIV testing and was found positive. When the mother also subsequently tested positive, the child was tested. She had in fact been assessed by a paediatrician at one year of age for adenopathy but was diagnosed of reactive lymphadenopathy because she was thriving very well and there were no other findings. The mother of Patient 2 was diagnosed when she presented with fever of unknown origin a few weeks post-partum but the child was initially thought to be uninfected. She was finally diagnosed at 5 ½ months when she presented with *Pneumocystis carinii* pneumonia (PCP). She also had *Streptococcus viridans* meningitis, failure to thrive and already had developmental delay at the time. Patient 3 was tested when she presented at 18 months with prolonged fever and cough and was found to have hepatomegaly and multiple infections that included tuberculosis, Epstein-Barr Virus (EBV) infection and recurrent pseudomonas thigh abscess. Patient 4 was tested for HIV when he presented at almost five years of age with disseminated *Penicillium marneffei* infection at the same time that his father presented to another hospital with cerebral toxoplasmosis. Both father and son tested positive for HIV infection essentially at the same time. The mothers of patients 3 and 4 were subsequently tested after the diagnosis of the children and found to be positive for HIV. Patient 5 and 6 are brother and sister and were diagnosed at the same time when their mother presented with PCP and subsequently tested positive. They had been considered to be a bit thin, but otherwise perfectly healthy by the parents but upon examination were found to have

generalized lymphadenopathy and failure to thrive. The mother of Patient 7 had died in Burma almost a year ago of a disease that the father suspected was Acquired Immunodeficiency Syndrome (AIDS). The father but not the child had HIV testing because he assumed antenatal HIV screening was routinely performed in Hong Kong. It was when he realized that this was not the case that he brought the child for testing. The child whom he thought was perfectly healthy actually had failure to thrive, being less than the third percentile for both height and weight. Patient 8 was referred to us in March 2000 at three months of age. His mother actually presented late for antenatal care at 35 weeks gestation. HIV testing was done as part of a pilot study of prenatal screening but she went into premature labour before she could be given antenatal zidovudine (AZT) chemoprophylaxis. However, intrapartum intravenous AZT was administered and the infant received AZT after birth and trimethoprim/sulfamethaxazole (TMP/SMX) prophylaxis was started at about one month of age. His HIV RNA viral load was <69 copies/ml on day 3 of life. Unfortunately, that rose to 1.3×10^6 copies/ml at one month of age and he was infected. The undetectable viral load during the first few days of life suggests peripartum transmission.²

Five children were diagnosed because a parent tested HIV positive. Although none of these children were totally asymptomatic or entirely normal on examination, their manifestations like lymphadenopathy and failure to thrive were minor and nonspecific enough that they had been thought to be healthy by their caregivers and even doctors. Three children presented with symptoms suggestive of HIV infection. Not counting the child who presented at the same time as his father, two of these three children were the first members of their families to present with HIV infection. Their diagnosis led to the diagnosis of HIV infection in the parents. All three patients who presented with symptoms were severely affected (C category of CDC classification), or in other words, had an AIDS defining illness at the time of diagnosis. Of the five children who were thought to be asymptomatic, four had generalized adenopathy and two had failure to thrive upon referral. One child (Patient 6) was in fact symptomatic with failure to thrive, generalized adenopathy and hepatomegaly. He also had a very low CD4 count of 103/ μ L (5%) for his age. He was severely immunosuppressed and at great risk of developing opportunistic infections had he not been diagnosed and treated. In general, CD4 counts are higher in children and gradually decrease to the adult level at 6 years of age. Almost all of these children had moderate to severe immune suppression according to the 1994 CDC Pediatric HIV Classification.³ Only two children (patients 1 and 8) had normal absolute CD4 count and percentage. Four children had extremely low CD4 counts with a

Table 1 Epidemiologic data and baseline conditions of the perinatally infected children

Patient	Sex/age	Age & date of diagnosis	Ethnicity (father/mother)	Reason of HIV testing	Manifestations at time of diagnosis	Baseline HIV load (RNA copies/mL)	Baseline CD4 (%), CD4/CD8 ratio	CDC classification
1.	F/4y11m	18m/Nov, 96	British/Filipino	Father tested positive	Multiple occipital, cervical, axillary lymphadenopathy	4x10 ⁵	2267 (36%), ratio 1.42	B1
2.	F/2y5m	5.5m/April, 98	Filipino/Filipino	Symptomatic	PCP, Strep. Viridans meningitis Hepatitis, FTT, Developmental delay and cerebral atrophy	5x10 ⁵	94/μL (21.7%), ratio 0.74	C3
3.	F/2y5m	18m/June, 98	Chinese/Chinese	Symptomatic	Pancytopenia, Hemophagocytic syndrome, EBV infection, PulmonaryTB, Recurrent pseudomonas thigh abscess, FTT, Developmental regression and progressive multifocal leukoencephalopathy (PML)	2.3x10 ⁵	756/μL (29.6%), ratio 0.6	C2
4.	M/4y11m	4y10m/ March, 99	Chinese/Chinese	Symptomatic	Disseminated Penicillium marneffei infection, FTT	2.4x10 ⁵	17/μL (1.9%), ratio 0.05	C3
5.	F/3y9m	2y10m/May, 99	Chinese/Chinese	Mother tested positive	Cervical and axillary lymphadenopathy, Thrombocytopenia	1.7x10 ⁵	430/μL (23.5%), ratio 0.74	B3
6.	M/5y11m	5y2m/May, 99	Chinese/Chinese	Mother tested positive	FTT Cervical, axillary lymphadenopathy, Hepatomegaly	1.1x10 ⁵	103/μL (5%), ratio 0.11	A3
7.	M/3y6m	3y/Oct, 99	Chinese/Burmese	Mother died of AIDS	FTT Cervical, axillary, inguinal lymphadenopathy, Anemia	5x10 ⁵	66/μL (6.3%), ratio 0.13	B3
8.	M/4m	3m/March,00	Thai/Thai	Mother tested positive	Occipital and cervical lymphadenopathy Hepatomegaly, slightly deranged transaminases	1.3x10 ⁶	2284/μL (26.8%), ratio 1.06	B1

Table 2 Treatment regimen, disease progression and response to therapy

Patient	Complications	Most recent antiretroviral regimen	Additional therapy /prophylaxis	Most recent HIV load (RNA copies/mL)	Most recent CD4 (%), CD4/CD8 ratio	Current status
1.	Herpes zoster twice	d4T, 3TC, Nevirapine		3.4x10 ³	1932/μL (41.2%), ratio 1.3	Well
2.		d4T, 3TC, Nelfinavir	TMP/SMX	2.9x10 ³	3323 (43.2%), ratio 1.75	Thriving, Spastic diplegic, Expressive speech delay
3.	Anaphylactic reaction to Nevirapine, Allergic to d4T	AZT, 3TC, Nelfinavir	TMP/SMX, monthly IVIG, INH, rifampin, pyridoxine	Undetectable	1578/μL (43.9%), ratio 1.14	Died of EBV associated T/NK lymphoma
4.	Admitted thrice to supervise administration of medication	AZT, 3TC, Ritonivir	TMP/SMX, itraconazole, monthly IVIG	Undetectable	513/μL (22.8%), ratio 0.69	Thriving
5.	Thrombocytopenia (Plt 55 x 10 ⁹ /L), treated with IVIG 500 mg/kg x 3d	d4T, 3TC, Nelfinavir	TMP/SMX, monthly IVIG	Undetectable	805/μL (39.8%), ratio 1.36	Well
6.		d4T, 3TC, Nelfinavir	TMP/SMX, monthly IVIG	Undetectable	459/μL (20.8%), ratio 0.44	Gaining weight
7.	Lobar pneumonia	AZT, 3TC, Ritonavir	TMP/SMX	Undetectable	204/μL (17.3%), ratio 0.46	Gaining weight
8.		d4T, 3TC, Nelfinavir	TMP/SMX	Undetectable	Not repeated yet	Gaining weight

d4T=stavudine; 3TC=lamivudine; AZT=Zidovudine; TMP/SMX=trimethoprim/sulfamethaxazole; IVIG=intravenous immunoglobulin

percentage below 10% and two children had moderate immunosuppression. All of them had a high HIV viral load on presentation.

Treatment and Response

Except for patient 1 who was diagnosed in 1996 before the introduction of highly active antiretroviral therapy (HAART), all the children were started on three antiretroviral agents that usually comprise of two nucleotide reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) or a nonnucleotide reverse transcriptase inhibitor (NNRTI). The rationale for two NRTIs and a PI is to attempt to attain maximal suppression of viral replication. This approach has proven successful in selected studies where reduction to undetectable levels of HIV RNA was achieved in children.⁴⁻⁶ Patients 1, 2, 3, 5 and 6 have already experienced at least one therapeutic failure after an initial virologic and clinical response, requiring a change of antiretroviral regimen. This viral rebound and subsequently treatment failure happen when antiretroviral resistance emerges if HIV is not suppressed to an undetectable level and active replication continues at a high level favouring resistance gene mutation. The HIV viral load assay was performed by the Department of Health Virology Laboratory at Queen Mary Hospital. The level of detection of the assay varies between 69 and 500 RNA copies/ml. Using the Roche DNA kit, a viral load of <500 copies/ml is considered undetectable in the literature. Our patients have responded remarkably well to antiretroviral therapy, despite after failing an initial regimen in some. Six children can be considered to have undetectable viral load. The response to antiretroviral treatment can be very brisk: patients 4, 7 and 8 had a decrease of viral load to an undetectable level in four to six weeks after therapy. Some patients had a more gradual decrease and their viral load became undetectable over four to six months. In general, the improvement of cellular immunity as reflected by the response of CD4 lymphocyte count lags behind that of HIV viral load.

Patient 1 was initially started on AZT and didanosine (ddI) but was changed to stavudine (d4T), lamivudine (3TC) and nevirapine when her viral load remained relatively high and treatment recommendations changed to include three drugs. An NNRTI (nevirapine) instead of a PI (e.g. ritonavir) was used because the mother refused to let the child take a PI for fear of one of its side effects: lipodystrophy. This redistribution of body fat commonly manifested as development of a long thin face together with truncal obesity was first described in PI recipients but later also found in NRTI recipients. However the mother had received a PI earlier herself and found this side effect totally unacceptable. There will have to be ongoing discussion with the parents and if the patient fails current therapy, a regimen that includes a PI will have to

be used.

Monthly intravenous immunoglobulin (IVIG) infusion is given to four patients according to established recommendations. IVIG therapy is recommended for children with humoral immunodeficiency manifested as: (1) hypogammaglobulinemia (IgG <250 mg/dL); (2) recurrent, serious bacterial infection; (3) children who fail to form antibodies to common antigens; (4) treatment of parvovirus B19 infection; (5) treatment of thrombocytopenia. These four children had humoral immune defects as evidenced by having defective functional antibodies despite having a normal level of IgG. They were unable to form adequate antibodies to common antigens like tetanus or measles after routine vaccination. All the children with initial abnormal CD4 counts were put on TMP/SMX prophylaxis for PCP.

Course of Illness

In general, despite the majority of children were rather advanced in their HIV disease at the time of diagnosis and some even had serious manifestation of their immunosuppressive states, they have done remarkably well. There was no serious recurrent infection. Patient 1 had developed two episodes of uncomplicated herpes zoster that responded to short courses of acyclovir. Patient 2 presented with AIDS defining illnesses and despite a good response to HAART, already had neurologic damage. She progressed to develop spastic diplegia and expressive speech delay that are classic neurologic manifestations of HIV infected children. She has, however, remained infection-free and is growing well and is about to start attending an early training centre. Patient 3 had died despite a low HIV viral load. She died of EBV associated NK/T cell lymphoma which had never been previously reported in HIV infected individuals.⁷ Despite the rarity of her malignancy, malignancy is common in HIV infected adults and children. Kaposi's sarcoma is rare in children but non-Hodgkin's lymphoma of B lymphocyte lineage is common and is an AIDS defining illness. Patient 4 recovered from the disseminated *Penicillium marneffeii* infection and is now taking life-long itraconazole suppressive therapy. His HIV viral load decreased five logs to undetectable after one month of HAART. Patient 5 developed HIV-associated thrombocytopenia soon after diagnosis that promptly resolved after IVIG for three days. She and her brother (patient 6) were initially put on AZT, ddI and nevirapine (an NNRTI) to which they had an initial response. Their HIV viral load decreased by two logs. However, five months later, they had a viral rebound and their regimen was changed to 3TC, d4T and nelfinavir (a PI). With that regimen, their HIV viral load became undetectable. Patient 7 was noted to have fever and cough during one follow-up session and found to have a lobar pneumonia. He was treated with a course of amoxicillin/clavulanate as

outpatient and recovered with no complication. Patient 8 also experienced a remarkable response to HAART and his HIV viral load also became undetectable.

Psychosocial Issues

Psychological counselling is offered to all the family members of a newly diagnosed child. Some parents refused the offer while a small number went for an initial session. In general this service has not been heavily utilized by this small group of patients and their families. Despite ongoing encouragement to let caregivers know of the children's diagnosis so as to care for the child better, secrecy is a big problem with parents. In most families, only the parents know the child's diagnosis and the secret is kept even from grandparents who live with the family. With the availability of more effective antiretroviral agents, HIV infection has been converted to a chronic disease in some patients. These children are encouraged to have as normal a lifestyle as possible and except for the two younger children, all of them attend school. One child will be starting early training. However, despite repeated counselling, only the parents of the child who is starting school has disclosed the diagnosis to school authorities.

Discussion

There are many challenges in taking care of HIV infected children. The issues and problems that arise from an HIV infected child include both medical and social. When a perinatally infected child is identified, there is at least one infected parent in the family. Dealing with the shock, anger, guilt, blame and feeling of isolation and secrecy can be a difficult and long process. As the children grow older, their diagnosis will have to be disclosed to them. There is no arbitrary age of disclosure. The appropriate time should be determined jointly with the parents and when the child is deemed mature enough. A step-wise approach may be used. As they grow older, they will question their need for taking medication and frequent clinic attendance and blood draws. At this point, the child may be told that he/she has a problem with fighting infection and therefore need special care and medication. Clinical psychologist referral for the child should also be made at this point. Later when he/she becomes more sophisticated to ask for the reason for this immune problem, the actual diagnosis should be given with full support from the family and clinical psychologist.

With the development of antiretroviral agents, particularly the protease inhibitors, HIV therapy has become more effective. However, it may not be possible to fully suppress the viral load of all patients. When viral replication is not fully suppressed, mutation will occur with viral replication and when resistance develops to one

drug, it may also develop resistance to a whole class of drugs and limit the usefulness of drugs of the same class. The principle of treating HIV is analogous to that of treating tuberculosis in that adding only one new drug to a failing regimen is contraindicated. However, the current practice of changing the whole treatment regimen when clinical failure is encountered will quickly exhaust available choices for a particular patient. There is a need for the development of genotypic and phenotypic resistance testing in Hong Kong so as to guide physicians in selecting an agent. With information on the genotypic and phenotypic resistance of the HIV isolate from a patient, resistance is known for specific drugs.

In addition to problem with resistance, the availability of antiretroviral agents to children is more limited than in adults. Usually much less is known concerning the pharmacokinetics, pharmacodynamics, efficacy and side effects of newer antiretroviral agents use in pediatrics since studies in children lag behind that of adults. Sometimes the only dosage recommendation available is that used in ongoing studies. The ability to successfully deliver uninterrupted treatment to children poses a challenge to parents, caregivers and clinicians. Many antiretroviral agents do not have pediatric formulations, and others have very poor palatability. An example is ritonavir that was only available in liquid form for a period of time due to manufacturing problem and the liquid form tastes bad. Patient 4 had to be hospitalized for the administration of ritonavir. This five years old child refused to take the medicine, making it a 2-hour struggle each time this twice a day medication was administered and this became impossible for the family. It took three hospitalizations to train the child to take his medication.

Nonadherence to therapy is taken very seriously since intermittent drug exposure that fails to fully suppress viral replication encourages drug resistance and treatment failure is likely. One of the pre-requisites of starting HAART is the long-term commitment of the family to comply with a complex regimen that usually involves many drugs. Special attention is also given to vomiting of drugs. Parents of our patients are instructed to call immediately if the child does not tolerate the medication at any time. With the exception of patient 4, our children and their families have done very well with no problems. A recent study on adherence to HAART in HIV infected children in the US showed that the level of adherence was only 58%, with adherence defined as filling $\geq 75\%$ of all prescribed antiretrovirals.⁸ This did not account for prescription filled but not given to the patients. This same study also reported that only 35% of patients were able to maintain an undetectable viral load, much less than that reported in adults, but comparable to other small reports of HAART in children. The good adherence of our group of children may partially explain why viral suppression

can be achieved and maintained in 75% of our patients despite their having multiple problems at presentation. While suppression below the level of detection by the 4th to 6th month of therapy is the goal for many physicians treating HIV-infected patients, it is realized that this may not be feasible when some patients had a very advanced disease at baseline. In fact, only a third of HIV infected patients in the US have achieved this goal and this response is supposed to be even more difficult to achieve in children who in general respond less well to antiretroviral agents. It is expensive to care for an HIV infected child both in terms of manpower and drug cost. The cost of antiretroviral agents, monthly IVIG and various primary prophylaxis and lifelong maintenance therapy calculate out to cost on average \$80,000 to treat one child for a year. As the number of patient escalates, it becomes prohibitive for one department or hospital to shoulder all the cost. There should be ongoing discussion on whether there should be a policy for referral and central budgeting.

All of these children were diagnosed only when either one, or both, parent was found to be HIV positive or when they themselves presented with an AIDS-defining illness. Except for one infant whose mother was diagnosed immediately before delivery, all had a high HIV viral load with immunosuppression at the time of diagnosis. This late diagnosis indicates that there are probably more asymptomatic HIV infected children in Hong Kong who are not yet diagnosed. In addition, with very effective chemoprophylaxis, perinatal transmission of this fatal illness can be avoided to a large extent. The first chemoprophylaxis with antepartum, intrapartum and postnatal zidovudine reduced vertical HIV transmission rate from 25.5% in the control group to 8.3% in the prophylaxis group.⁹ Since then studies using short course and different antiretroviral agents provided to pregnant women near or at labour and delivery have shown that reduction of perinatal HIV transmission rates are also feasible.¹⁰⁻¹² Increased surveillance and antiretroviral treatment of HIV-infected pregnant women have contributed to a declining perinatal HIV transmission rate in North America and western Europe.¹³ Chemoprophylaxis is only possible if the infected pregnant woman can be diagnosed. HIV testing with prompt return of results therefore should be offered to all pregnant women. One quarter of the families in this study was diagnosed of HIV infection only after their children presented with symptomatic HIV infection. They were shocked to know of the diagnosis because they had not considered themselves at high risk for HIV infection. Selectively offering antenatal screening to the "high risk" group, whether by perception of the patients or their doctors, will inevitably miss some infected mothers. Universal screening of pregnant women as a strategy to reduce perinatal transmission of HIV in Hong Kong should be discussed and considered as a matter of urgency.

Conclusion

In conclusion, we have presented our experience and highlighted some difficulties in caring for children perinatally infected with HIV in Hong Kong. As seen in our group of children, HIV infection is a hidden problem in Hong Kong. Considering the high cost of medication as well as laboratory and manpower resources, there is a need to explore for a "best care" model in providing quality care to these children. With an effective antiretroviral regimen available for reducing perinatal transmission of HIV, a policy for universal screening of pregnant women is a pressing need.

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