

# CLINICAL FEATURES AND RISK FACTORS FOR HIV ENCEPHALOPATHY IN CHILDREN

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**Abstract.** A prospective cohort study was conducted to determine the incidence of progressive encephalopathy (PE) and its associated clinical manifestations amongst a cohort of HIV infected children attending the HIV/AIDS clinic of the Pediatric Institute, Kuala Lumpur Hospital, Malaysia. Neurological and neurobehavioral assessments were performed in 55 children with HIV over a 24-month study period. Parameters assessed were physical and neurological assessments, CD4 counts, CD4 percentages, RNA viral loads and an IQ assessment at four monthly intervals. PE was diagnosed when patient developed at least one of the definitive criteria for PE based on the Consensus of Pediatric Neurology / Psychology Working Group, AIDS Clinical Trial 1996. The incidence of encephalopathy was 18.2% ( $n=10$ ) in 2002. All the patients had hepatosplenomegaly, lymphadenopathy, abnormal deep tendon reflexes and five had impairment in brain growth. The CD4 counts and CD4 percentages were more likely to be associated with PE compared to the non-PE group.

## INTRODUCTION

Human immunodeficiency virus (HIV) infection is a major cause of mortality and morbidity amongst children worldwide, with over five million women and 700,000 children having been infected since the start of the pandemic more than two decades ago (WHO, 2003). The first reported case in Malaysia was in 1986, and since then the number of new infections, especially amongst women and children, has increased over the years. Since 1998, a prophylactic strategy against vertical transmission has been implemented in all infected mothers and babies with HIV in Malay-

sia. The protocol of zidovudine given to infected mothers during antenatal screening and continued for the first six weeks in the newborns of infected mothers (Center for Disease Control and Prevention, 1992; Ministry of Health, 2001). In the same year, triple drug therapy was also made available free to all pediatric patients, and treatment was instituted according to the regimen outlined in the Malaysian HIV pediatric guidelines (Ministry of Health, 2001).

Pediatric acquired immunodeficiency syndrome (AIDS), is caused by HIV type 1 (HIV-1), a human retrovirus of the lentivirus group. The four recognised human retroviruses belong to two distinct groups, namely the human T lymphocyte retroviruses (HLV-1 and HTLV-2) and the human immunodeficiency viruses (HIV-1 and HIV-2). The HIV-1 subtype is known to be a common causative agent for HIV in humans (Epstein and Gendelman, 1993;

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Fauci, 1996). Neurological manifestations in children infected with HIV may manifest as "HIV-1 associated progressive encephalopathy (PE)", which has similar features to "AIDS dementia complex (ADC)" in adults (Belman *et al*, 1988; Simpson and Tagliati, 1994; Cooper *et al*, 1998). It is known that PE affects children in three distinct courses: the rapid progressors, the sub-acute (slow) group and those with a static neurological course (Mintz, 1996; Ojukwu and Epstein, 1998). They may present with developmental regression, microcephaly, behavioral disorders, pyramidal tract or cerebellar signs. As with adult patients, PE may occur in children in the absence of opportunistic infections or with central nervous system (CNS) malignancies.

As pediatric HIV cases in Malaysia are on the rise, it is likely that PE may cause a major health problem for health care providers in the near future. However, there is surprisingly little data regarding this condition. This prospective cohort study was the first, to our knowledge, attempting to describe the incidence of PE amongst children with HIV in Malaysia and the factors associated with this condition.

## MATERIALS AND METHODS

### Subject enrolment

This was a prospective cohort study of HIV-infected children attending the HIV clinic at the Institute of Pediatrics, Hospital of Kuala Lumpur, Malaysia. It was carried out over a period of two years (January 2001 to December 2002). Universal random sampling was used to recruit patients for this study. HIV infection in the study population was defined by the presence of 2 or more polymerase chain reaction (PCR) tests for HIV in children below 18 months and a positive serology on particle agglutination test for those above 18 months (Ministry of Health, 2001). All HIV infected children who attended the clinic during the study period were invited to participate in this study.

A thorough explanation was given to the main caregivers before verbal informed consent was obtained. Patients were excluded from the study if: the patient was more than 18 years old, refused to participate or had been diagnosed with HIV encephalopathy prior to the study. This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Kebangsaan Malaysia.

### Study design

Study assessments were conducted during recruitment for baseline and four monthly thereafter. Parameters assessed during the baseline and four monthly intervals were: physical examination, neurological assessment, CD4 count, CD4 percentage and RNA viral load. All these parameters were performed routinely at each visit. All clinical examinations were performed by pediatricians. The patients were referred to a neurology team in the Pediatric Institute if the need arose.

For I/Q assessment, the "Griffith Mental Development" was used for children < 72 months of age, whereas the older children were assessed using the "Wechsler Intelligence Scale for Children-Third Edition". A diagnosis of mental retardation or development delay was given to children who scored < 80 on their respective scale. Both of these tests were performed by a qualified clinical psychologist. Assessment was limited to a maximum of three sessions as only one clinical psychologist was available during the study period.

### Definition

The definition of HIV encephalopathy was based on the Consensus of Pediatric Neurology / Psychology Working Group, AIDS Clinical Trial, Washington 1996 (Working Group of the American Academy of Neurology, 1991). Definitive diagnosis requires at least one of the following to be present for at least two months in the absence of a concurrent illness other than HIV infection: (1) failure to attain or loss

of developmental milestones, or a loss of intellectual ability, verified by a standard developmental scale or neuropsychological tests; (2) impaired brain growth, or acquired microcephaly demonstrated by head circumference measurement, or brain atrophy demonstrated by computed tomography or magnetic resonance imaging, with serial imaging required for children less than two years of age; and (3) acquired symmetric motor deficit manifested by: paresis, hyperreflexia, hypertonia, and/or pathologic reflexes, ataxia or gait disturbances. For the purpose of this analysis, the onset of encephalopathy was defined as significant neurological deterioration, a loss of previously documented neurological changes, or two consecutive abnormal findings during the visits.

#### Statistical analysis

Data was summarized and analyzed with the Statistical Package for the Social Sciences (SPSS), version 11.5. Descriptive analysis was used for categorical data such as age, sex, ethnic group, mode of transmission and modalities of treatment. Comparison of categorical data was by chi-square test. Fisher's exact test was performed for small expected values less than 5. Independence *t*-test was used to assess continuous/numerical data. A *p*-value of <0.05 was considered as significant.

## RESULTS

#### Demographic characteristic of HIV patients

As of December 2002, a total of 86 HIV positive children were registered with the Pediatric HIV clinic. Of these, 19 children (22.7%) had died of HIV/AIDS complications, six cases (7.1%) were referred to other centers for further follow-up and another six cases (7.1%) had defaulted on follow-up. The remaining 55 children were the total cases available for analysis. Forty-four of the 55 patients (80%) were recruited at the onset of the study while the

remaining 15 were recruited during follow-up.

The median age of this cohort of children was 3.56 years (SD  $\pm$  3.0 years) with the youngest being four months old and the oldest being twelve years old. Pertaining to racial distribution, Malays constituted 54.6% of cases ((30/55), followed closely by Chinese (41.8%, 23/55), and 3.6% (2/55) were Indians. Data on route of transmission showed that almost all were infected through vertical transmission (94.5%, 52/55), with the remaining two children being infected via blood transfusion (3.8%, 2/55). We were unable to identify the source of infection for the final case as she was adopted. Thirty-six of the 55 (64.4%) infected mothers/babies had received the AZT (zidovudine) prophylaxis during pregnancy, whereas 12 mothers (21.8%) were not given prophylaxis during their pregnancy. The remaining seven (12.8%) were unsure of their status as they were abandoned or adopted.

#### Incidence of progressive encephalopathy (PE) among children with HIV

In this study the incidence of PE was 18.2% (n=10). The mean age was 24 months, with the youngest being four months old and the oldest being 48 months old. The majority of children (7/10) were more than 12 months old when first diagnosed with PE. Six of the children were adopted, however there was no documentation of the reasons for adoption and the age when the children were adopted. Almost all of the children were infected via vertical transmission. Only one was reported to be infected via blood transmission. In regard to parental status, 6/10 (60%) had both parents infected with HIV. All these children were referred from other hospitals to the Pediatric Institute for further management.

#### Clinical manifestations of children with PE

All children with PE demonstrated hepatomegaly, lymphadenopathy and splenomegaly during the follow-up. Other physical findings were as in Table 1. Neurological

Table 1  
Physical findings of 10 patients diagnosed with PE attending the HIV / AIDS Clinic,  
Pediatric Institute, Kuala Lumpur.

Physical findings	Number (n = 10)	Percentage (%)
Lymphadenopathy	10	100
Hepatomegaly	10	100
Splenomegaly	10	100
Dermatitis	3	30
Parotitis	3	30
Recurrent respiratory symptoms	1	10
Anemia (< 8g /dl)	4	40
Neutropenia (1,000 /mm <sup>3</sup> )	1	10
Thrombocytopenia (<100,000 mm <sup>3</sup> )	1	10
Persistent oropharyngeal candidiasis (thrush)	6	60
Diarrhea (recurrent or chronic)	3	30
Abnormal tendon reflexes	10	100
Impairment of brain growth	5	50

Table 2  
Comparison of laboratory parameters between PE and non-PE children attending the  
HIV/AIDS clinic, Pediatrics Institute, Kuala Lumpur.

Variable	PE (n=10)	Non-PE (n=45)	p-value
CD4 counts	350 ± 160.2	1,027.0 ± 689.5	0.009
CD4 percentages	10.3 ± 3.4	25.4 ± 6.5	0.0001
RNA viral load	313,042.2 ± 83,782.3	139,434 ± 3,086.3	0.09

manifestations of patients with PE revealed that all children diagnosed with PE had abnormal deep tendon reflexes and five (50%) had impairment of brain growth. These children demonstrated static brain growth in serial head circumference measurements for at least two consecutive visits. None of the children presented with development delay or impairment in cognitive abilities. Laboratory parameters showed that children with PE had lower CD4 counts, CD4 percentages and higher RNA viral loads (Table 2). Comparison with non-PE patients showed significant differences in CD4 counts and CD4 percentages.

The frequency of attendances to I/Q assessment sessions varied from none (17/55,

30.9%) to three sessions. The overall attendance rate was recorded as 69.1% (38/55). Almost three-quarters of the participants (28/38) attended three sessions, six (6/38 15.8 %) attended two and the remaining four (4/38, 11%) attended only one session during the study period (Table 3). During follow-up, all the patients were on Highly Active Anti -Retroviral Therapy (HAART) treatment, 70% were on triple therapy and the remaining patients (30%) were on dual therapy. The treatment included mandatory Zidovudine or Stavudine therapies.

## DISCUSSION

The overall profile of our cohort of HIV patients followed the HIV infection trend in

Table 3  
Descriptive analysis of I/Q assessment.

I/Q (Score)	Visit one	Visit two	Visit three
112-120	0	0	0
105-112	0	0	0
91-105	22 (57.9%)	23 (60.5%)	22 (57.9%)
81-90	16 (42.1%)	15 (34.5%)	16 (42.1%)
70-80	0	0	0

children worldwide. Our findings of high perinatal transmission (94.5%) concurred with other studies (Working Group of the American Academy, 1991; Msellati *et al*, 1993). Whilst perinatal transmission remains the single greatest route for transmission of HIV in children, the literature elaborates on maternal risk factors for perinatal transmission which include: drug abusers and heterosexual partners with risk factors for HIV infection. Intravenous drug use (IVDU) remains the major route of transmission for HIV in Malaysia in 2001 (76.1%) (Ministry of Health, 2001). Given the fact there is a rising trend of unprotected heterosexual acts among adults in Malaysia which involves the transmission of HIV to unprotected women, we postulate this trend may be a contributing factor to the high perinatal transmission of HIV in our population (Ministry of Health, 2004).

In this study, the incidence of PE amongst the cohort of HIV infected children at our center was 18.2%. Similar studies looking at the incidence of PE have resulted in equivocal findings (Zuckerman *et al*, 1998; Fragoso *et al*, 1999; Mintz, 1999; Gurbindo *et al*, 1999; Chase *et al*, 2000; Pearson *et al*, 2000). Although the incidence varies from 8% to 50%, the overall trend appears to have been decreasing over the past twenty years. Our incidence agrees with this decreasing trend. This low incidence may be attributable to two major factors. The combination of Pediatric AIDS Clinical Trial Group (PACTG) regimen given

during the antenatal period and the availability of triple anti-retroviral therapy to pediatric HIV patients in Malaysia may have contributed to the lower incidence of PE. Second, it is widely believed that combination therapy with either AZT or d4T penetrates the blood brain barrier thus arresting the replication of the virus. This process diminishes the viral dissemination to the central nervous system therefore delaying the occurrence of the encephalopathy (Belman *et al*, 1988).

Although the number of patients in our study is too small to clarify the effects of treatment, the characteristics of HIV infected children with PE highlight the main features of the neurological manifestation in these children. The PE patients in our cohort had hyperreflexia and half of them had demonstrable brain atrophy. This is not surprising, since literature reviews reveal this disease has a variable, non-linear course. It is generally believed that each patient may have a different course, which may include spontaneous improvement or stabilization (Chase *et al*, 2000). Therefore, it is not uncommon for HIV infected children with PE to present with variable manifestation of cognitive, motor and behavioral impairment throughout the course of the illness. The physical manifestations of PE patients, such as the presence of lymphadenopathy, splenomegaly and hepatomegaly were comparable to those observed in Thailand (Chearskul *et al*, 2002). Although these features are non-specific, researchers have suggested the presence of

these HIV associated signs may be useful in deciding upon further management of these patients, in particular, the decision regarding initiation of anti-retroviral therapy (Chearskul *et al*, 2002; Asnake and Amsalu, 2005).

The CD4 counts and CD percentages showed a significant association with encephalopathy amongst the patients we studied. Our findings are in concordance with a study by Gurbindo *et al* (1999) who demonstrated that low CD4 counts and percentages were strong early predictive markers for PE in HIV children. However viral load failed to show any significant association with PE in our study, although the viral load was quantitatively higher in the PE group compared to the non-PE group. A possible explanation for this finding is that several of the RNA samples were either missing or rejected by the machine as there were technical flaws during the collection stage.

In our study, only 69.1% of the patients attended the I/Q assessment sessions, with attendances varying from one to three assessments during the course of the study. Therefore, a comparison of mean I/Q scores to level of neuropsychological functioning was impossible due to the small sample size and heterogeneous distribution of the assessment sessions. Although our study failed to demonstrate any significant findings from I/Q assessment testing, previous studies have highlighted the association between intellectual ability and PE. Pearson *et al* (2000) demonstrated that children with the lower neuropsychological functioning (I/Q score) were at risk for developing PE. On the other hand, Chase *et al* (2000) found no significant association between global intellectual ability and the status of HIV progression amongst subjects studied up to eight year after the onset of HIV. One possible explanation for the scores demonstrated in our study is the cohort of patients in this study may not have yet shown any declined in global intellectual functioning due to

the relatively short period of observation.

As this was the first study in Malaysia looking at neurological manifestations of children with HIV, our study had several limitations. We were unable to perform a neuro-imaging study in our population as this modality was not easily accessible at the center. The limitation of sampling could not be avoided as children with HIV in Malaysia are still under diagnosed, therefore the small sample size may represent the possibility that children with HIV are under represented in Malaysia. We believe the number studied represent the tip of iceberg of HIV among children in this country. Furthermore, this study was carried out at an Infectious Disease Clinic in the Kuala Lumpur Hospital; thus our findings cannot be extrapolated to the whole country.

In conclusion, the incidence of PE amongst children with HIV in Kuala Lumpur was 18.2%. Hepatosplenomegaly and lymphadenopathy were the commonest physical findings amongst those who were diagnosed with PE. Hyperreflexia and brain atrophy were the neurological manifestations associated with PE in our cohort of patients. Lower CD4 counts and percentages were associated with PE in HIV infected children. We believe the findings represent only the tip of the iceberg of HIV infected children in Malaysia.

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