Cardiac manifestations in HIV-infected Thai children

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(Accepted January 2004)

Summary Cardiac complications contribute significantly to morbidity and mortality in HIV-infected children. There have been few reports of cardiac manifestations in HIV-infected children in developing countries. The aims of this study were to evaluate the clinical manifestations and echocardiographic findings in Thai children with HIV infection and determine the clinical predictors of left ventricular dysfunction and pulmonary hypertension. We retrospectively reviewed the medical records of 27 infants infected with HIV perinatally who presented with cardiovascular problems at a tertiary care hospital between 1995 and 2000. The mean age at initial cardiac evaluation was 36 months (range 8–65). Signs and symptoms included dyspnoea in all cases, oedema in 12 (44%), finger clubbing in 11 (41%), cyanosis in 6 (22%) and S3 gallop in 8 (30%). Echocardiographic abnormalities included pericardial effusion in 12 (44%), right ventricular dilatation in 12 (44%), pulmonary hypertension in 11 (41%), diminished left ventricular fractional shortening in 10 (37%), left ventricular dilatation in 9 (33%) and combined ventricular dilatation in 2 (7%). Left ventricular dysfunction did not correlate with HIV CDC classification, age, nutritional status or clinical signs and symptoms.

Introduction

Many cardiac abnormalities in HIV-infected children have been reported to contribute to morbidity and mortality, and to increase with advancing HIV infection. The various types of cardiac complication include cardiomyopathy, congestive heart failure, myocarditis, myocardial infarction, arrhythmias, pericarditis and pulmonary hypertension.

The incidence of cardiac involvement reported in HIV-infected children varies according to the method of surveillance employed. In children who had undergone cardiac evaluation, complications ranged from 1.2% to 93%.1–3 Data on the prevalence of cardiac manifestations in HIV-infected children in developing countries are limited. Nkrumah et al. reported that over 70% of HIV-infected Zimbabwean children presenting with respiratory distress had echocardiographic abnormalities.4

Studies from Zimbabwe and Thailand reported high incidences of pulmonary hypertension — 48% and 75%, respectively.5,6 Pericardial effusion is also an important feature of HIV-associated heart disease and occurred in 60% of the Zimbabwean series. Impaired left ventricular systolic function seems to be less common.5

The purpose of this study was to study the cardiovascular manifestations and echocardiographic findings in HIV-infected children in Thailand and to determine the predictors of left ventricular dysfunction and pulmonary hypertension in these children.
Materials and Methods

Study population

In Chiang Mai University Hospital between January 1995 and December 2000, 27 of 772 symptomatic infants perinatally infected with HIV were referred for cardiac evaluation because of respiratory distress and cardiomegaly discovered during chest radiograph. All diagnoses of symptomatic HIV infection were made according to the Centers for Disease Control 1994 revised criteria for AIDS.7

Measurements

Each child underwent non-invasive evaluation at the time of initial consultation and before beginning anticongestive therapy. Evaluation included physical examination, ECG, chest X-ray and echocardiography. M-mode, two-dimensional and Doppler echocardiographic studies were recorded. Left ventricular systolic function was determined by calculating the fractional shortening (FS) as follows:

\[ \% \text{LVFS} = \frac{\text{LVDD} - \text{LVSD}}{\text{LVDD}} \times 100\]

LVDD, left ventricular end-diastolic dimension;
LVSD, left ventricular end-systolic dimension.

The normal range of fractional shortening is 28–44%.8 Children with left ventricular fractional shortening (LVFS) <28% were classified as having LV dysfunction or diminished LV function. Estimation of the pulmonary artery systolic pressure was derived from measuring a tricuspid regurgitant jet using Bernoulli’s equation.9 A fixed value of right atrial pressure, 5 or 10 mmHg, was added to the transtricuspid pressure gradient to yield systolic right ventricular pressure (SRVP). SRVP was approximated to be systolic pulmonary pressure (SPAP) in the absence of pulmonary stenosis. Pulmonary hypertension was defined as SPAP > 30 mmHg at rest.9

Statistical analysis

Clinical and demographic data are expressed as frequencies and means with standard deviations, as appropriate. The \( \chi^2 \) test was used to determine the significance of selected variables and Fisher’s exact test to compare the different subgroups of patients; \( p \leq 0.05 \) was considered to be statistically significant. Analyses were performed using SPSS for Windows, version 11 (SPSS Inc., Chicago.).

Results

Patients’ characteristics

Twenty-seven (3.5%) of 772 children diagnosed with HIV during the study period had symptomatic cardiac manifestations. The median age at initial evaluation was 36 months (range 8–65). There were 12 boys and 15 girls. According to the latest CDC classification,7 four (15%) children were in category B and 23 (85%) in category C. Sixteen (59%) had a weight-for-age <3rd centile. Haematocrits ranged from 12% to 47% [mean (SD) 27% (8)]. Of the 27 cases, 23 (85%) had intercurrent infections. Pneumonia occurred in 17 (63%), sepsis in five (18%), diarrhoea in three (11%), cytomegalovirus infection in two (7%) and fever of unidentified cause in two (7%).

Clinical features with relevance to cardiac disease

Clinical features suggestive of cardiac involvement are shown in Table 1. All cases had dyspnoea and hepatomegaly.

Radiographic features and ECG characteristics

Cardiomegaly was detected in all children on chest X-ray (cardiothoracic ratio >50% in children and >57% in infants <2 years of age10). Eighteen (66%) had evidence of alveolar infiltration and ten (37%) had
diffuse reticulonodular infiltration. Twelve-lead ECG recordings were obtained from 23 children. Twelve (52%) had evidence of right axis deviation and right ventricular hypertrophy (RVH). Only one child had left ventricular hypertrophy (LVH). Nine (39%) had non-specific ST-T changes, associated in one of them with LVH. Low QRS voltage in the limb leads was noted in two children (9%).

Echocardiographic findings

Echocardiograms were abnormal in all children. The common echocardiographic findings were pericardial effusion, RV dilatation, pulmonary hypertension and LV dysfunction and dilatation (Table 2). Most of the cases with pericardial effusion had a small amount of pericardial fluid, and pericardiocentesis had not been attempted. The one case who presented with massive pericardial effusion with cardiac tamponade was found to have tuberculosis. A silent patent ductus arteriosus (diameter 1.5 mm) was found unexpectedly in one child who had an FS of 27% and mild LV dilatation.

Table 3 shows the baseline clinical characteristics and status of LVFS. Diminished LVFS was detected in ten cases and enhanced LVFS in eight. There was no significant relationship between age, clinical signs, history of recurrent pulmonary infections, CDC classification, nutritional status, anaemia or encephalopathy and LV dysfunction. Children with LV dilatation or combined ventricular dilatation were significantly associated with decreased LVFS ($p < 0.001$).

Of the 27 cases, 19 had a measurable tricuspid regurgitation gradient, eleven of whom were classified as pulmonary hypertension because SPAP was $> 30$ mmHg and the other eight as normal pulmonary pressure because SPAP was $< 30$ mmHg. The remaining eight without a measurable tricuspid regurgitation gradient were assigned to the normal pulmonary pressure group because there was no clinical or echocardiographic evidence of pulmonary hypertension. In children with pulmonary hypertension, the average pulmonary artery systolic pressure was 56 mmHg (range 36–86). Children with pulmonary hypertension were significantly associated with RVH on ECG ($p = 0.002$) and RV dilatation on echocardiogram ($p = 0.02$). Acute pneumonia significantly increased the risk of pulmonary hypertension in these cases ($p = 0.04$) (Table 4). Six of the children with pulmonary hypertension had underlying lymphocytic interstitial pneumonitis (LIP).

Management

Only one child was on antiretroviral therapy (zidovudine) but compliance was poor. All cases received supportive and symptomatic treatment for congestive heart failure. Medication included digoxin, diuretics and enalapril. Intravenous dobutamine was commonly given to children with acute, severe congestive heart failure.

### TABLE 1. Clinical features.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Patients, n (%)</th>
<th>Total = 27</th>
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<tbody>
<tr>
<td>Dyspnoea</td>
<td>27 (100)</td>
<td></td>
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<tr>
<td>Hepatomegaly</td>
<td>27 (100)</td>
<td></td>
</tr>
<tr>
<td>Oedema/puffy face</td>
<td>12 (44)</td>
<td></td>
</tr>
<tr>
<td>Clubbing of fingers</td>
<td>12 (44)</td>
<td></td>
</tr>
<tr>
<td>S, gallop</td>
<td>8 (30)</td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td>6 (22)</td>
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</table>

### TABLE 2. Echocardiographic features.

<table>
<thead>
<tr>
<th>Echocardiographic features</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Chamber enlargement</td>
<td>23 (85)</td>
</tr>
<tr>
<td>RV dilatation</td>
<td>12 (44)</td>
</tr>
<tr>
<td>LV dilatation</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Combined ventricular dilatation</td>
<td>2 (7)</td>
</tr>
<tr>
<td>LV fractional shortening</td>
<td></td>
</tr>
<tr>
<td>Diminished (&lt;28%)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Normal (28–44%)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Enhanced (&gt;44%)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Silent ductus arteriosus</td>
<td>1 (3.5)</td>
</tr>
</tbody>
</table>
This study found echocardiographic abnormalities in all HIV-infected children with symptomatic cardiac manifestations and cardiomegaly. Symptoms and signs of cardiac dysfunction in HIV-infected children are difficult to distinguish from
Cardiac manifestations of HIV

Tachycardia might be caused by fever and anaemia. Hepatomegaly and splenomegaly are seen in chronic HIV infection. In addition, HIV-induced nephrotic syndrome could be attributed to oedema and congestion. Clinicians should maintain a high degree of suspicion of cardiovascular abnormalities in HIV-infected children, and patients with pulmonary symptoms not responsive to conventional therapy should undergo cardiac evaluation.

LVFS is the simplest and most widely used measurement of left ventricular function. This index depends on ventricular pre-load, after-load and contractility. There are two patterns of abnormal left ventricular function in HIV-infected children: hyperdynamic left ventricular performance or enhanced LVFS and LV dysfunction or diminished LVFS. Enhanced LVFS was seen in eight (30%) of our subjects. This appeared to be common in early HIV infection in children and was often associated with autonomic instability, e.g. exaggerated heart rate and blood pressure. These cardiovascular effects might be manifestations of an autonomic neuropathy. Left ventricular dysfunction has been described in several large studies of HIV-infected children. Reported incidences range from 9% to 65%, depending on the manner of ascertainment.

Our 37% prevalence of LV dysfunction in HIV-infected children accords with previous reports. Al-Atta et al. reported that encephalopathy, wasting, a decreased CD4 count and a history of a serious cardiac event were all predictors of cardiac complications associated with HIV infection in children. Lipshultz et al. found a clinical relationship between development of encephalopathy and deterioration of left ventricular function, but no relationship between CD4 cell count and LV dysfunction. In this study, cardiac dysfunction did not relate to age, CDC classification, nutritional status or encephalopathy. The number of subjects, however, was small and most patients died early from infection. Severity of LV dysfunction might be an important indicator of future survival.

In the P2C2 (Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus Infection) study, a prospective multi-centre study of 197 HIV-infected children, multivariate analysis showed that fractional shortening was a significant clinical predictor of mortality (RR = 1.91, p < 0.001). With optimal treatment of HIV infection, including highly active antiretroviral therapy (HAART) and attention to the treatment of congestive heart failure, it might be possible to lower the high mortality rates from cardiac dysfunction.

Pericardial effusion was detected in 12 cases (44%). It was more common in HIV-infected children in Zimbabwe (60%) and a previous Thai study (42%) than in the USA (16–26%). The advanced stage of HIV disease is commonly associated with the development of pericardial effusion. HAART, which is now regular therapy in industrialised countries, might decrease the prevalence of pericardial effusion in HIV-infected children. Although pericardial effusion in HIV-infected patients is generally small and asymptomatic, large or symptomatic effusions in all age groups are often associated with tuberculosis, other opportunistic infections and malignancy.

Pulmonary hypertension accounted for 8–17% of HIV-infected children in the USA before 1991 (and HAART). However, it is now less prevalent and there was no single case of pulmonary hypertension in the prospective P2C2 multi-centre study. The prevalence of pulmonary hypertension was relatively high in this study compared with cases in Zimbabwe and the previous study from Thailand. The possible causes of pulmonary hypertension were LIP, left ventricular dysfunction, recurrent bronchopulmonary disease and primary pulmonary hypertension. Most of the pulmonary hypertension cases were associated with acute pneumonia. Only two cases were associated with LV dysfunction, which can also contribute to pulmonary...
hypertension. In Zimbabwe, besides chronic hypoxia from lower respiratory disease, the high altitude was also considered to contribute to the high frequency of cor pulmonale. Common echocardiographic abnormalities in HIV-infected children in Thailand are pericardial effusion, right ventricular dilatation, pulmonary hypertension, diminished left ventricular fractional shortening, left ventricular dilation and combined ventricular dilatation. Optimal care, including HAART, might reduce the frequency and morbidity of HIV-related cardiac disorders.

References


