Malignancies in UK children with HIV infection acquired from mother to child transmission

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Abstract
By April 1995, 302 cases of vertically acquired HIV infection had been reported through the British Paediatric Association Surveillance Unit. Over 50% of these children had developed an AIDS indicator disease, including nine malignancies (seven cases of non-Hodgkin’s lymphoma (NHL) and two of Kaposi’s sarcoma). There were two other malignancies that were not AIDS indicator diseases. In children less than 5 years of age the incidence of NHL was approximately 2500 times greater than expected in the UK child population. Three children presented with NHL as their AIDS indicator disease and four developed NHL at a median of 14 (range 10–19) months after the initial diagnosis of AIDS. Six of the seven children died at a median of 6.5 (range 2–14) months after the diagnosis of NHL. The seventh child responded to treatment and is alive nearly four years later. Histology was available in five cases, of which four were of B cell and one of T cell origin. Epstein-Barr virus was detected in all three patients with NHL where it was sought; all had B cell lymphomas. Although comparatively rare, malignancies occur in children infected with HIV and may be the presenting illness. Paediatricians now need to consider HIV infection as a predisposing cause of childhood cancer, especially NHL.

Keywords: HIV infection; malignancy; non-Hodgkin’s lymphoma

The risk of developing a malignancy, particularly a lymphoma, is higher in subjects with primary and secondary immunodeficiencies. Kaposi’s sarcoma and lymphoma are the most common malignancies associated with HIV infection and are classified as ‘AIDS indicator diseases’. Other cancers such as cervical carcinoma and soft tissue sarcomas are also associated with HIV. In children with HIV infection acquired from mother to child (vertical) transmission, the incidence of neoplastic disease is also increased, with the major malignancy being non-Hodgkin’s lymphoma (NHL). In Europe and the USA, NHL accounts for 0.9–1.4% of first AIDS indicator diseases in children vertically infected with HIV. This is an underestimate of the overall incidence, however, as children who develop NHL after their first diagnosis of AIDS are, by definition, excluded. In contrast, Kaposi’s sarcoma is rare in vertically acquired HIV infection outside areas of endemic Kaposi’s sarcoma in Africa. Other cancers have been sporadically reported in children infected with HIV, but these may be coincidental rather than a direct or indirect consequence of HIV disease.

The purpose of this paper is to describe the malignancies occurring in UK children vertically infected with HIV, with particular emphasis on NHL, and to estimate the risk of NHL in this group of children.

Patients and methods
In the British Isles, the surveillance of children with HIV infection is carried out through an active confidential reporting scheme. Paediatricians report cases of children seropositive for HIV through the monthly reporting scheme of the British Paediatric Association Surveillance Unit (BPASU), which has a response rate of over 90%. Details of the surveillance scheme, which has been operating since 1989, have been reported previously. Each report is followed up using a standard questionnaire.

The clinical data collected about infected children include the details and dates of AIDS indicator diseases, other HIV related symptoms and signs, prophylactic and antiretroviral treatment, and T cell subset results. The infected children are followed up annually to monitor their clinical progression, the age at onset of AIDS, and the age at death. Children reported to have a malignancy were identified through this source and further clinical and pathological data obtained from the reporting paediatricians.

The increased risk of NHL in children with vertically acquired HIV infection was estimated by calculating the ratio of observed cases of NHL in HIV infected children born in England, Wales, and Scotland with the expected number derived from age specific childhood NHL cancer rates for the same geographical area between 1978 and 1987. The annual number of births where the child was vertically infected with HIV can be estimated from reports of AIDS in vertically infected children born in the UK and from estimates of vertical transmission rates and AIDS incubation periods derived from prospective studies. The number of years at risk of NHL in HIV infected children were then derived using data on mortality from the European Collaborative Study of children born to HIV infected women. Analyses were confined to children
Table 1  Details of children with NHL and HIV infection acquired through mother to child transmission

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Ethnic origin</th>
<th>Age at HIV diagnosis (years)</th>
<th>Age at AIDS diagnosis (years)</th>
<th>Age at NHL diagnosis (years)</th>
<th>Age at death (years)</th>
<th>AIDS defining illness</th>
<th>CD4 count per mm³*</th>
<th>Site and histology of lymphoma</th>
<th>Treatment</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>White</td>
<td>†</td>
<td>0.7</td>
<td>2.1</td>
<td>3.4</td>
<td>FTT</td>
<td>40 (−1)</td>
<td>Left ear and cerebral Abdominal</td>
<td>Surgery/radiotherapy/COMP × 1, vincristine + prednisolone × 2</td>
<td>NHL</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Mixed</td>
<td>†</td>
<td>2.8</td>
<td>2.8</td>
<td>3.3</td>
<td>NHL</td>
<td>190 (0)</td>
<td>Abdominal Unknown</td>
<td></td>
<td>NHL</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>African</td>
<td>†</td>
<td>1.3</td>
<td>2.4</td>
<td>2.7</td>
<td>Enc</td>
<td>16 (0)</td>
<td>Cerebral (presumptive) Disseminated</td>
<td>Palliation</td>
<td>NHL</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>African</td>
<td>0.15</td>
<td>0.15</td>
<td>1.0</td>
<td>1.2</td>
<td>PCP</td>
<td>410 (−4)</td>
<td>Tonsil</td>
<td>Vincristine + prednisolone</td>
<td>NHL</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>White</td>
<td>1.0</td>
<td>1.0</td>
<td>2.2</td>
<td>3.3</td>
<td>FTT/ Enc</td>
<td>5 (−2)</td>
<td>Nasopharyngeal</td>
<td></td>
<td>NHL</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Hispanic</td>
<td>5.8</td>
<td>4.9</td>
<td>4.9</td>
<td>‡</td>
<td>NHL</td>
<td>390 (−13)</td>
<td>Nasopharyngeal NHL protocol 903</td>
<td>Vincristine + prednisolone</td>
<td>NHL</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>African</td>
<td>†</td>
<td>2.4</td>
<td>2.4</td>
<td>3.0</td>
<td>NHL</td>
<td>40 (0)</td>
<td>Soft palate</td>
<td>VP16 + prednisolone</td>
<td>NHL</td>
</tr>
</tbody>
</table>

* Figures in parentheses indicate timing of CD4 count measurements (in months) relative to NHL diagnosis.
† Mother known to have HIV infection during pregnancy.
‡ This is the only child still alive.

Results
By June 1995, 302 children with confirmed HIV infection as a result of vertical transmission had been reported from centres in England, Wales, and Scotland. Of these, 164 had AIDS and 95 had died. Eleven children had developed a malignancy. Two children, one of Ugandan and one of Zambian origin, had Kaposi’s sarcoma and have been reported elsewhere. Two children had developed malignancies which were not defining of AIDS. One boy developed a Ewing’s sarcoma of a fibula at 6 years of age and died six months later of HIV encephalopathy. The second child was a girl who developed a cerebral rhabdoid tumour at the age of 5.5 years, which was successfully treated with surgery and radiotherapy. She remains well at 11 years of age.

Non-Hodgkin’s lymphoma
Seven children were reported to have NHL and their details are shown in table 1. There was no significant association of NHL with ethnic group or maternal risk factors for acquiring HIV, such as intravenous drug use. Four mothers knew their HIV diagnosis before their child was born, but in three cases HIV was diagnosed only after the child presented with an AIDS indicator disease. The median age of the children at the diagnosis of AIDS was 14 months (range 3–33 months).

NHL was the initial AIDS indicator disease in three children, and in the remaining four it was diagnosed between 10 and 19 months (median 14 months) after the initial diagnosis of AIDS. All children had low CD4 counts for their age1 around the time of diagnosis of NHL, with the exception of one child whose HIV status was ascertained retrospectively after treatment for B cell lymphoma had been completed. This child is still alive nearly four years later, whereas the remaining children had all died at a mean of six (range 2–14) months after the diagnosis of NHL. Five of the six deaths were related to NHL. The two children with cerebral lymphoma were diagnosed on clinical and radiological grounds without histological confirmation, although one appeared to be a recurrence of a definitely diagnosed lymphoma (patient 1); the abnormalities seen with computed tomography were compatible with either lymphoma or toxoplasmosis, but both patients were unresponsive to treatment for toxoplasmosis.

TREATMENT
In two patients (patients 3 and 4), both of whom already had AIDS, no specific treatment was given for the lymphoma. The tonsillar lymphoma of patient 5 responded to a ‘palliative’ five week course of vincristine and high dose steroids; this patient continued to receive a small dose of steroids until her death 14 months later. Although no necropsy was performed there was no clinical evidence of a recurrence of the lymphoma. Patient 1 initially presented with a lymphoma affecting his left ear which responded to local radiotherapy; the recurrent presumed cerebral lymphoma was treated with one course of a modified COMP protocol (cyclophosphamide, vincristine, methotrexate, prednisolone), but had a limited response and major toxicity. Patients 6 and 7 also received specific chemotherapy; the treatment received by patient 2 is unknown (table 1). In patients 2 and 7 the lymphoma progressed rapidly and both children died within six months of presentation. Only the older boy with B cell NHL (patient 6) completed a nine month standard intensive chemotherapy regimen (NHL protocol 903); he remains free of lymphoma nearly four years later.

In the five patients where histology was available, four were of B cell origin and one was a T cell lymphoma. Three of the B cell lymphomas were high grade diffuse large cell malignancies, as shown in fig 1A (patient 5). The fourth (patient 6) is a classic ‘Burkitt’s lymphoma’ (fig 1B). Viral studies were undertaken in three children (patients 4, 5, and 6), all with B cell NHL; all three were positive for the Epstein-Barr virus latent membrane protein (fig 1C, patient 5).
INCIDENCE OF NHL

The incidence of NHL in children with vertically acquired HIV infection less than 5 years of age born in England, Wales, and Scotland was estimated to be 14.2/1000 each year. The observed number of cases (seven) in HIV infected children far exceeded the number expected in the general population (0.003), giving a rate ratio of 2288 (95% confidence interval 920 to 4715).

Discussion

The increased risk of malignant disease, particularly NHL and Kaposi’s sarcoma, was recognised early in the HIV epidemic. By December 1994, 6% of adult and 1.7% of paediatric AIDS indicator diseases in the USA were malignancies, approximately half of which were NHL. These figures almost certainly underestimate the overall incidence of malignant disease in infected subjects as up to one third of tumours may occur after the presentation of the first AIDS defining illness. Studies of children with HIV infection in Italy and the USA have shown an overall prevalence of malignancy of 1.8 and 5%, respectively, compared with a 3.6% prevalence of malignancy in our study. All 388 children in the Italian study acquired HIV infection from mother to child transmission. The US study of over 450 patients included children who had acquired HIV from transfusions of infected blood or blood products as well as those infected by mother to child transmission. The children were also possibly older and had more advanced disease than those in the Italian or UK studies, and the study was hospital rather than population based. All these factors may contribute to the higher overall prevalence of malignancy observed in the US study. NHL is the most common tumour type reported in all three studies.

Among children reported to AIDS surveillance programmes in the US and Europe up to 1993, Serraino and Franceschi reported that NHL occurred as a first AIDS indicator disease at almost twice the rate in black compared with white children, and twice as frequently in boys as in girls. No association between sex or ethnicity and NHL could be observed in either our study or the Italian study, but the overall number of children with NHL in the two studies was small.

In our study NHL developed before the age of 3 years in six of the seven children, a similar finding to the Italian study in which three of the five children with NHL were less than 2 years and all were less than 4 years of age at the diagnosis of NHL. This feature probably reflects the relatively young age of the HIV infected paediatric population in the two studies. Serraino and Franceschi reported a consistent increase in the frequency of NHL, as a first AIDS indicator disease, with age in both European and US surveillance data. The interpretation of these results is, however, complicated by the inclusion of children acquiring HIV infection via routes other than mother to child transmission.

Four of the seven children in this study already had an AIDS indicator disease, and two of the remaining three were very immunosuppressed at the time NHL was diagnosed. All six children subsequently died of NHL within 14 months. The young age and rapid course of NHL in the children in this study may reflect rapidly progressive HIV disease, as observed in 20–25% of HIV infected children born to infected mothers. The only surviving child presented at an older age, had the classical histology of a Burkitt’s lymphoma (high grade B cell lymphoma), and had a relatively higher CD4 count, a feature also reported in studies of HIV infected adults. The fact that this child survived intensive chemotherapy with no unusual infective complications and without the diagnosis of HIV infection being made is also evidence of a more intact immune system.

The immunological subtype of the tumours observed in this study is comparable with that reported in other HIV infected children and adults, and also in reports of NHL in children with other forms of congenital and acquired immune deficiencies. In all these situations the lymphomas are usually of B cell origin. The aetiology of NHL in the context of immunodeficiency is multifactorial, involving reduced

Figure 1 (A) High grade diffuse large B cell lymphoma of the tonsil (patient 5). (B) Diffuse B cell lymphoma of the nasopharynx (patient 6). (C) Positive immunostaining for Epstein-Barr virus latent membrane protein (patient 5).
Malignancies in children with HIV infection

The care of these children, including the multidisciplinary HIV team, infectious disease, and oncology subspecialists, so that decisions about treatment take account of the quality of life and are taken in the context of antiretroviral treatment and the treatment required for other HIV associated disorders. As cancer becomes more frequent in both adults and children living longer with HIV disease, there is a need for more trials of treatment for NHL. The small numbers of children are such that we will need to be guided by trials in adults, but we should not forget issues particular to children. We need to know when to treat and when to palliate, and, with treatment, how to minimise complications while achieving remission.

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References

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