

SPECIAL REPORT

HIV infection in haemophilia – a European cohort

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Abstract

Ten haemophilia centres in northern Europe have pooled data on 202 haemophilic children who were infected with HIV between 1979 and 1986. All cases were under 16 years of age on 1 July 1985. The age at infection ranged from 1–15 years.

Thirty seven cases (18%) had progressed to AIDS by 1 July 1991 and 15 of these have died. Persistent generalised lymphadenopathy has been noted in 102 patients of whom 18 (17%) have developed AIDS. Twenty three of the remaining patients (23%) have not.

CD4+ T cell counts have fallen steadily. Of 36 patients who have had shingles since seroconversion, 19 (53%) had counts below $0.2 \times 10^9/l$. Thirty five out of 145 patients without shingles (24%) had similar values. The mean IgA concentration in patients with CD4+ T cell counts above $0.5 \times 10^9/l$ was 2.38 g/l, between 0.2 and 0.5 was 3.07 g/l, and in those with CD4+ T cell counts below $0.2 \times 10^9/l$ the mean IgA concentration was 4.58 g/l.

Treatment patterns have altered between 1989 and 1991, with increased use of zidovudine in patients without AIDS and a marked increase in primary prophylaxis against pneumocystis pneumonia. This has been associated with a decline in the incidence of pneumocystis as an indicator disease in new AIDS cases from 56% in 1989 to 20% in 1991.

These observations indicate that persistent generalised lymphadenopathy does not worsen the outlook, but shingles does. Rising IgA concentrations are markers for disease progression. Modern prophylactic regimens are delaying the onset of indicator disease, but CD4 values continue to fall steadily.

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The first cases of AIDS in haemophiliacs were reported in 1982¹ but retrospective analysis of frozen plasma samples has shown seropositivity as early as October 1979.² Many of the children with haemophilia who were infected with HIV as a result of contaminated clotting factor concentrates are now in their teens and early twenties. They provide a unique worldwide cohort, not only because of their age, but because their HIV status was established in the asymptomatic phase in the majority of cases. The advent of virally inactivated therapeutic materials has successfully prevented further transmission of HIV

infection and so this cohort is finite in numbers, with no new cases reported since 1986.³

Several reports have documented the clinical course of HIV infection in children with haemophilia,^{4,6} but the disease is rare and it has not been possible for a single centre to document enough cases to be significant. We have therefore pooled information from 10 haemophilia centres in northern Europe and report a cohort of 202 children with haemophilia who were infected between six and 11 years ago.

Patients, methods, and definitions

Information has been provided on an annual basis by the 10 participating centres since July 1989. HIV positive patients included were, or would have been, aged less than 20 years on that date. Basic information on each patient was obtained at that time and clinical and laboratory information is being updated annually. This paper is based on information available at 1 July 1991 and excludes cases who died before July 1989. However, in analysing the patients who have progressed to AIDS, details of the three deaths before 1 July 1989 are included because of the importance of that information.

AGE

Age was taken at 1 July 1991. In the case of those who had died the age was taken as if they had lived to 1 July 1991.

PERSISTENT GENERALISED LYMPHADENOPATHY

Persistent generalised lymphadenopathy was diagnosed in the presence of palpable lymphadenopathy (lymph node enlargement of 1 cm or greater) at two or more extrainguinal sites persisting for more than three months in the absence of a concurrent illness or condition other than HIV infection to explain the findings.

AIDS

AIDS was diagnosed using the revised criteria defined by the Centers For Disease Control in Atlanta, Georgia, USA.⁷

DATE OF INFECTION

Several centres were able to carry out retrospective testing on stored sera for HIV antibody. The date of infection was taken to be the midpoint

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between the dates of the last negative and the first positive sample. If the earliest sample available was HIV antibody positive, no estimation of seroconversion date was made, unless the sample was taken before the end of 1982. In these cases the timing of infection was determined as the midpoint between the date of the first positive sample and 1 October 1979.

We then subdivided the patients into four groups: (1) 39 patients (19%) infected in 1980/81; (2) 107 patients (53%) infected in 1982/83; (3) 26 patients (13%) infected from 1984 to 1986; and (4) 30 patients (15%) with a first positive result too late for seroconversion dates to be estimated without a possible error of more than two years.

LABORATORY INVESTIGATIONS

Immunoglobulin concentrations were measured by immunonephelometry. CD4+ T cell counts were measured by flow cytometry using commercial monoclonal antibody reagents obtained from different manufacturers.

STATISTICAL METHODS

The differences between means were assessed using Student's *t* test. The significance of differences between percentages was assessed on the actual numbers of observations by calculating χ^2 using a 2×2 table.

PATIENTS

Altogether 202 cases have been followed up since 1 July 1989. Of these 182 had haemophilia A, 18 haemophilia B, and two von Willebrand's disease. One hundred and ninety five cases were classified as severe, six as moderate, and one as mild.

Results

YEAR OF INFECTION

The number of cases of AIDS and the mean CD4+ T cell counts in each of the groups 1980/1, 1982/3, 1984-6, and those on whom no estimate could reasonably be made, are shown in table 1. There are no significant differences between the number of AIDS cases or the mean CD4 counts in any of the four groups.

CLINICAL FEATURES

AIDS

Thirty seven cases (18% of all patients) had had AIDS diagnosed by 1 July 1991. Of these, 16 were known before entry into the study, six had AIDS diagnosed during the first year of the study and 15 in the second year. Nine of the first 16 cases (56%) presented with *Pneumocystis carinii*

Table 2 Number (%) of patients with CD4+ T cell counts falling into each band over two years

CD4+ T cell counts ($\times 10^9/l$)	1 July 1989	1 July 1990	1 July 1991
<0.2	38 (19)	40 (20)	57 (31)
0.2-0.5	84 (43)	87 (44)	80 (43)
>0.5	75 (38)	71 (36)	47 (26)

pneumonia, three of the next six (50%), and three of the latest 15 (20%). Other indicator diseases were: disseminated toxoplasmosis (n=6), wasting syndrome (n=3), HIV encephalopathy (n=3), multiple recurrent bacterial infections (n=5), *Mycobacterium avium intracellulare* (n=2), and one each of disseminated cytomegalovirus infection, lymphocytic interstitial pneumonia, and non-Hodgkin's lymphoma.

The mean (SD) age of the patients with AIDS at 1 July 1991 was 17.1 (2.8) years and that of the remaining patients was 16.0 (3.4) years. The difference was not significant ($p < 0.1$). Persistent generalised lymphadenopathy was present in five of the 16 cases (31%) known at the start of the study. Ten cases had been described in the 22 cases known by 1 July 1990 (45%). This figure rose to 18 cases out of 37 known a year later (49%).

Fifteen cases (41%) have died, three before 1 July 1989, four during the next year, and eight in the year ending 1 July 1991.

Persistent generalised lymphadenopathy

Forty nine cases of persistent generalised lymphadenopathy were known on 1 July 1989, 61 a year later, and 102 a year after that. Fifty per cent of all cases were therefore known to have had persistent generalised lymphadenopathy by 1 July 1991.

Eighteen (17%) of the cases of persistent generalised lymphadenopathy have developed AIDS, as have 23 of the 99 cases without persistent generalised lymphadenopathy (23%). There is no significant difference between these two groups.

Herpes zoster (shingles)

Thirty nine patients have had an episode of shingles since seroconverting. Ten of these individuals (25%) and 27 out of 163 patients (17%) without shingles have gone on to develop AIDS. The difference between these two groups was not significant.

Thirty six surviving patients with shingles had CD4+ T cell counts measured during 1990-1. Nineteen (53%) had values below $0.2 \times 10^9/l$. Thirty five out of 145 patients (24%) without shingles had CD4+ T cell values below that figure. The difference is highly significant ($\chi^2 = 9.97$, $p < 0.005$). The mean (SD) IgA concentration in patients who have had shingles was 3.27 (2.54) g/l and those who have not had a mean concentration of 3.44 (2.85) g/l. The difference was not significant.

LABORATORY RESULTS

CD4+ T cell counts

A total of 197 patients had these estimated within

Table 1 Incidence of AIDS and mean CD4+ T cell counts according to presumed year of infection

	1980/1 (n=39)	1982/3 (n=107)	1984-6 (n=26)	Not known (n=30)
No (%) with AIDS	7 (18)	21 (20)	3 (12)	6 (20)
Mean (SD) CD4+ T cell count ($\times 10^9/l$)	0.33 (0.25)	0.39 (0.32)	0.39 (0.20)	0.30 (0.21)

Table 3 Mean (SD) immunoglobulin concentrations (g/l) at 1 July 1991 in each band of CD4+ T cell counts

CD4+ T cell counts ($\times 10^9/l$)	IgG	IgA	IgM
<0.2	18.79 (5.77)	4.58 (3.70)	1.90 (0.96)
0.2–0.5	20.80 (7.55)	3.07 (2.09)	2.11 (0.94)
>0.5	19.60 (4.95)	2.38 (1.32)	2.15 (1.09)

the six months before 1 July 1989, 198 within six months of 1 July 1990, and 184 within six months of 1 July 1991. These have been banded by counts and the results are shown in table 2. The mean (SD) age of patients in 1991 with CD4 counts over $0.5 \times 10^9/l$ was 15.4 (3.6) years and those with CD4 counts below $0.2 \times 10^9/l$ was 16.7 (2.8) years. The difference was significant ($p < 0.05$).

Immunoglobulins

IgG, IgM, and IgA concentrations were estimated in patients within the same time scales as their CD4+ T cell estimations. The immunoglobulin concentrations were banded according to the CD4+ T cell counts, and the mean values are shown in table 3. IgG concentrations fell significantly in the lowest CD4+ T cell band ($p < 0.05$). There was no discernible pattern to the IgM concentrations, but IgA concentrations rose steadily and significantly with falling CD4+ T cell counts ($p < 0.01$ between mean values in those with CD4+ counts below $0.2 \times 10^9/l$ and the other two groups).

Fifty five patients had IgA concentrations above 4.0 g/l. Of these, 10 (18%) had AIDS and 32 (58%) had persistent generalised lymphadenopathy. Twenty three of these patients (42%) were clinically well, and 11 of these (20% of the 55) had CD4+ T cell counts of over $0.2 \times 10^9/l$.

TREATMENT

The numbers of patients on zidovudine, *Pneumocystis carinii* pneumonia prophylaxis, and intravenous gammaglobulin at the midpoints of 1989, 1990, and 1991 are shown in table 4. There has been a steady increase in numbers of patients on zidovudine and *Pneumocystis carinii* pneumonia prophylaxis (which was usually given by nebulised pentamidine, but occasionally with cotrimoxazole or dapsone). Use of intravenous gammaglobulin rose sharply in 1989–90 and fell back equally sharply in 1990–91. This was due to a controlled study evaluating the efficacy of this product in HIV infection carried out in one of the centres participating in our study.⁸

Discussion

No significant differences were found between AIDS incidence or mean CD4+ T cell values in the groups divided into the presumed year

infected and those in whom presumptions could not be made, suggesting that this cohort can be analysed as a single entity.

The incidence of progression to AIDS in this HIV infected cohort, six to 11 years after seroconversion is 18%. This is less than in other recently reported cohorts of haemophiliacs.^{9,10} Our group were all under 15 years at the time of infection, and these results confirm the now well established pattern of worsening outlook related to increasing age.¹¹ Further, our results show that this age advantage extends to individuals infected before the age of 15 and is in accord with a recent study reported on behalf of the Transfusion Safety Study Group in the USA.¹²

The death rate in our cohort doubled during the last year reported, while the incidence of AIDS rose by 1.5 times.

The decline of *Pneumocystis carinii* pneumonia as an indicator disease, presumably related to the increased use of prophylaxis, suggests a need to review the definition of AIDS. Our study has shown a continued depletion of CD4+ T cell counts in HIV disease in spite of increased use of zidovudine and this implies that these values are becoming relevant in defining the syndrome.

Persistent generalised lymphadenopathy is an increasingly frequent feature of our HIV positive patients, but does not appear to worsen the outlook. Indeed, the most recent estimations of CD4 counts shows the highest proportion of cases of persistent generalised lymphadenopathy in those patients with CD4+ T cell counts over $0.5 \times 10^9/l$.

IgA concentrations rise progressively and significantly with falling CD4+ T cell counts, confirming the observations of Cuthbert *et al* in 1990.¹⁰ They concluded that high plasma IgA concentrations correlated well with the presence of clinically evident disease but were of little predictive value. We have shown that 42% of patients with IgA concentrations over 4.0 g/l were clinically well, and nearly half of these had CD4+ T cell counts of over $0.2 \times 10^9/l$. High IgA concentrations in HIV positive individuals are thus likely to have some prognostic significance.

Patients who have had shingles since seroconversion have significantly lower CD4+ T cell counts than those who have not, and it is thus possible that herpes viruses might play a part in accelerating the progression of immunological deterioration in HIV disease. Progression to AIDS has been shown to be faster in patients with previous cytomegalovirus infection.⁹ There is thus accumulating evidence of viral triggers causing enhanced HIV activity.

It is possible that raised IgA concentrations may be a response, but we have not shown any significant difference between IgA in those patients who have and those who have not had shingles. Herpes viruses are therefore unlikely culprits and HIV itself should be considered a possible cause.

The CD4+ T cell counts over the past two years of this study provide a grim commentary on the outlook for these patients. The steady erosion of patients with values over $0.5 \times 10^9/l$ from 38% to 26% contrasts with the increase in patients with values of less than $0.2 \times 10^9/l$ from 19% to 31%.

Table 4 Treatment regimens over two years (numbers of patients)

	1 July 1989	1 July 1990	1 July 1991
Zidovudine	33	63	76
<i>Pneumocystis carinii</i> pneumonia	29	46	70
Intravenous gammaglobulin	35	50	32

Our study shows the clinical progression of HIV disease in a group of haemophilic children infected for between six and 11 years. The data is taken from the standard clinical practices of 10 established northern European haemophilia centres. Further follow up will continue to provide insight into the progression of HIV infection in this age group.

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Epstein-Barr virus and cystic fibrosis

Non-bacterial causes of respiratory exacerbations in cystic fibrosis include respiratory syncytial virus, adenovirus, influenza virus, and rhinovirus. A recent study in Albany, New York state (Glenna Winnie and Robert Cowan, *The Pediatric Infectious Disease Journal* 1992; 11: 722-6) points for the first time to Epstein-Barr virus (EBV) as an important pathogen in this disease.

Thirty five patients with cystic fibrosis and chronic respiratory tract colonisation with *Pseudomonas aeruginosa* were studied retrospectively. All had been seen regularly at the Albany Cystic Fibrosis Center and their ages ranged from 6 to 18 years. Sixteen of them had serological evidence of previous EBV infection but, of the 19 EBV susceptible patients, 12 were admitted to hospital with an exacerbation of chest infection during an 18 month period beginning on 1st July 1987. Five of these 12 had serological evidence of EBV infection acquired shortly before the exacerbation and their clinical features were compared with those of the seven control patients who had an acute exacerbation without EBV infection.

The patients with recent EBV infection were older (mean age 16.8 v 12.5 years) but their preadmission clinical (Shwachmann-Kulczicki) and chest x ray (Brasfield) scores were similar to those of the controls. Infection with EBV was associated with worse scores during the hospital admission and on follow up for six months afterwards. Spirometric tests confirmed a greater deterioration in the EBV infected group. Average percentage falls from preadmission values at the time of hospital admission for EBV infected (control) patients were: clinical score 24.7 (3.9), chest x ray score 20.2 (6.5), forced vital capacity (FVC) % predicted 21.0 (8.2), forced expiratory volume in one second (FEV₁ %) 28.7 (9.4). At six months' follow up the figures were: clinical score 21.9 (-1.7), chest x ray score 17.9 (4.6), FVC 9.0 (0.9), FEV₁ % 18.4 (4.9). During the follow up period readmission to hospital was more than 10 times more frequent in the EBV group. Clinical evidence of infectious mononucleosis was not found in the patients with recent EBV infection and only one developed the characteristic atypical lymphocytosis. Anorexia and weight loss were the best clinical clues to EBV infection.

If these figures can be replicated then clearly the implications are considerable both for understanding deterioration in cystic fibrosis and possibly for preventing it. It is not clear whether the deterioration in lung function with EBV infection was caused by viral infection of the lungs or was a result of abnormal immune mechanisms induced by the virus. Such altered mechanisms might either lead directly to lung damage or cause increased pathogenicity from pseudomonas.