Valsalva manoeuvre was effective were significantly younger.

The higher termination rate in patients with AVRT than among those with AVNRT has not previously been described. Tachycardias confined to the AV node might be expected to be sensitive to autonomic influences. The reason for this paradoxical effect is not clear and may indicate differences in anterograde intranodal pathways between AVRT and AVNRT. Termination of tachycardia with retrograde block in the accessory pathway in 1 patient suggests that the vagus may have some influence on the accessory pathways or their atrial insertion.

In our 35 patients no complications were encountered with any of the physical manoeuvres. Asystole, ventricular arrhythmias, and hemiplegias have been reported with carotid sinus stimulation[16,17] especially among older patients with atheromatous carotid disease. The diving reflex has been reported once to lead to ventricular tachycardia.[18] In younger patients, in the absence of sino-atrial or AV nodal disease the risk of complications with these physical manoeuvres is small, in contrast to the risks of chemical or electrical cardioversion.

In conclusion, of those physical manoeuvres that we evaluated, the Valsalva whilst supine was the most effective physical manoeuvre for terminating re-entrant SVT. The relative efficacy of various physical manoeuvres was directly related to their bradycardic response in sinus rhythm. Other factors associated with success included a younger age and AVRT rather than AVNRT. Right and left carotid sinus massage and the diving reflex were considerably less effective than the Valsalva manoeuvre. The Valsalva manoeuvre in the supine posture should thus be applied during spontaneous supraventricular tachycardias before other means of termination are tried.

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HLA HAPLOTYPE A1 B8 DR3 AS A RISK FACTOR FOR HIV-RELATED DISEASE

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Summary Of 32 patients exposed to a single batch of factor VIII contaminated with human immunodeficiency virus (HIV), 18 became antibody positive. Serial T cell subset analyses over the succeeding four years have shown a progressive decline in circulating T4 cells in those 18 but no change in the 14 who remain seronegative. 2 of the seroconverters have died and a further 7 have symptoms attributable to HIV infection. In the group as a whole, the HLA haplotype A1 B8 DR3 was weakly associated with an increased risk of seroconversion on exposure to the virus while, in those who seroconverted, it was strongly associated with a rapid decline in T4 cells and development of HIV-related symptoms within four years of infection.

Introduction

PATIENTS attending the Edinburgh haemophilia treatment centre have been assessed immunologically since 1983. The original purpose was to investigate the immunological effects of haemophilia and its treatment in the absence of the (then) putative AIDS virus. This was possible because most patients had received exclusively locally produced factor VIII or factor IX and at that time AIDS had not been reported in Scotland.[1] It was subsequently established that a single batch of locally produced factor VIII had been contaminated with human immunodeficiency virus (HIV).[2] That batch was used by 32 previously seronegative patients between March and May, 1984. Over the course of the next ten months, 18 of the 32 became HIV seropositive by a range of enzyme-linked immunosorbent assays (ELISAs) detecting antibodies to different components of the virus and confirmed on western blotting.[3] 31 have participated in follow-up studies that have included regular clinical examination, virological investigations, and analysis of circulating T cell subsets. The consequences of parenteral exposure to HIV have not been uniform within this cohort and we have identified a genetic factor that seems to contribute to the individual differences observed.

Methods

T Cell Subsets

The total lymphocyte content of whole blood is obtained by electronic counting (Coulter S-plus). Mononuclear cells are separated from heparinised blood by flotation over 'Ficoll-Hypaque' SG 1·078 and washed. The T4 and T8 lymphocytes are identified by two-stage immunofluorescence, mouse monoclonal antibodies (Dako) being used in the first stage and FITC-conjugated $F(ab')_2$ fractions of sheep anti-mouse Ig (Sigma) in the second; both incubations being for 30 min on crushed ice. After washing and final resuspension in saline with 1% formaldehyde, the cells are scored in a Becton-Dickinson FACS IV cytopherometer,

CLINICAL STATUS OF SEROPOSITIVE PATIENTS 1984–88

Patient no	HLA A1 B8 DR3 + or −	Yr of birth	Bottles of contaminated factor VIII used	AIDS status (CDC) category[6] by year				
				1984	1985	1986	1987	1988
1	−	1965	23	II	II	II	II	II
2	−	1959	9	II	III	III	IVc$_2$	IVc$_2$
3	−	1962	81	II	II	II	II	II
4	−	1946	20	II	II	II	II	II
5	−	1963	20	II	II	II	II	II
6	−	1947	10	II	II	IVc$_2$	IVc$_2$	IVc$_2$
7	−	1950	60	II	II	II	II	II
8	−	1944	20	III	III	III	III	III
9	−	1946	60	II	II	II	II	II
10	−	1941	10	II	II	II	II	II
11	+	1948	81	II	II	II	IVc$_2$	IVd
12	+	1962	43	II	III	IVa	IVa	IVa
13	+	1954	51	II	II	IVc*	IVc	IVc
14	+	1941	109	II	II	IVa	IVa	IVa
15	+	1969	30	III	III	III	III	III
16	+	1942	50	II	II	IVa	IVa	IVa
17	+	1970	54	I	IVa	IVb,c$_1$	IVd†	
18	+	1945	20	II	II	II	IVa†	

*Thrombocytopenia.
†Died.

right-angle light scatter being used to set gates round the lymphocyte population.

HLA Typing

Patients have been typed by a standard two-stage complement-dependent microlymphocytotoxicity technique[4] with panels of sera kindly provided by the UK National Transplant Service. For DR typing, T cells were first removed by rosetting with aminoethyl-isothiouronium-treated sheep erythrocytes[5] and sedimentation through Ficoll-Hypaque.

Virology

Sera collected from the clinic patients (including retrospective samples recovered from storage at −20°C for up to five years) are screened for antibody to total HIV antigens, to env gp 41, and to core p24 antigens by commercial ELISAs and for activity against the full range of HIV antigens by western blotting. Free p24 antigen is measured by antigen capture assay (Dupont) and by ELISA (Abbott). These studies are reported in detail elsewhere.[3]

Results

Clinical Course

Of the 14 patients who remain seronegative despite exposure to the contaminated batch of factor VIII, none has any signs or symptoms of HIV infection. Among the 18 who did seroconvert, 1 had an acute febrile illness (CDC class I)[6] with circulating atypical mononuclear cells.[7] He recovered from that episode, but one year later was showing symptoms of AIDS with weight loss, fever, malaise, and diarrhoea (CDC IVa). Later he had opportunistic infections (*Pneumocystis carinii* pneumonia, cryptococcal meningitis, CDC IVc) and AIDS encephalopathy (CDC IVb). He died in March, 1987, and Hodgkin's disease was discovered in abdominal lymph nodes at necropsy (CDC IVd). There has been one other death, indirectly attributable to HIV infection, in a patient who had experienced increasingly obvious symptoms of AIDS (CDC IVa) during the second part of 1987. 7 other patients have signs and symptoms that place them in CDC category IV. Of these, 1 is profoundly ill with lymphoma. Another is the only member of the cohort in whom continuous follow-up in Edinburgh has not been possible. He has moved abroad but, through the cooperation

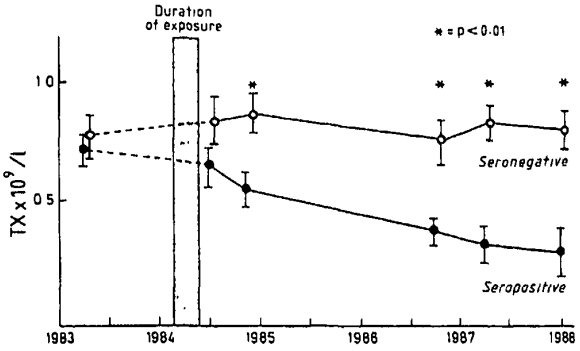

Fig 1—Mean (SE) absolute circulating T4 cell counts for haemophilia A patients exposed to HIV-contaminated batch of factor VIII March–May 1984.

Seronegative group, n = 14; seropositive group, n = 16. Data from 2 seropositive patients not included because they contributed too few blood samples.

of his current medical attendants, information on his progress has been obtained at intervals. Since 1986 he has had profound thrombocytopenia (platelets $< 20 \times 10^9$/l) judged to be due to HIV.[8] 2 patients have had generalised lymphadenopathy since 1984 (CDC III) without evidence of progression to more serious disease while 7 have remained symptom-free though HIV seropositive (CDC II). Details of the 18 patients and their clinical status in each of the years since 1984 are given in the table.

T Cell Subsets

Circulating T8 cell numbers have remained stable in the whole cohort. In the 14 who are seronegative, T4 cell numbers have also been stable since 1983. However those who seroconverted have shown a progressive fall in T4 (fig 1). The trend has been very consistent, only 2 of the 18 showing a different pattern. In both of them, T4 numbers were low ($< 0{\cdot}5 \times 10^9$/l) before exposure to the virus and have remained about the same level.

HLA Type and Correlations

The antigen combination A1 B8 DR3 was present in 11 of the 32 patients exposed to the contaminated batch of factor VIII (34%). From published data on the Scottish population this undoubtedly represents a haplotype (ie, the combination is inherited en bloc on the same chromosome) the expected frequency of which is about 25%. For the Edinburgh haemophilia clinic as a whole the frequency of A1 B8 DR3 is in fact 26% (19 out of 72 patients typed). No other haplotype would be expected to occur in this population with a frequency high enough to allow testing for statistically signficant associations.[9–11]

Of the 11 with the A1 B8 DR3 haplotype who used the infected batch, 8 seroconverted, compared with 10 of the remaining 21 patients. Thus the relative risk of seroconversion associated with A1 B8 DR3 was 2·9. Among the 18 who seroconverted, 11 have experienced symptoms attributable to HIV (CDC III or IV). 8 of these are A1 B8 DR3 while none of the 7 who remain symptom-free carry this haplotype. If persistent generalised lymphadenopathy (PGL) (CDC III) is discounted on the grounds that it does not predict progression to AIDS,[12,13] then only 9 of the group are symptomatic and 9 are well; but of these 7 and 1,

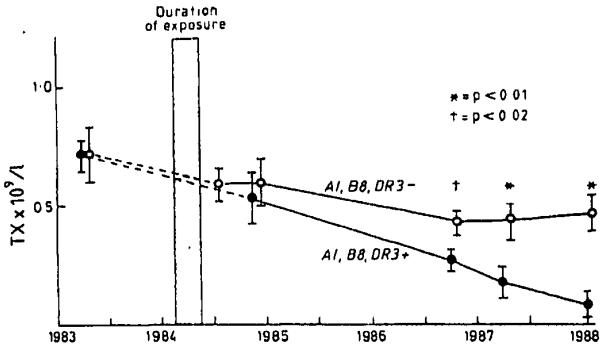

Fig 2—Mean (SE) absolute circulating T4 cell counts for 16 haemophilia A seroconverters with and without HLA haplotype A1 B8 DR3.

A1 B8 DR3 negative, n = 9; A1 B8 DR3 positive, n = 7.

respectively, have A1 B8 DR3 (relative risk = 28; $p < 0.05$, Fisher's exact test).

When sequential changes in T4 cells are compared in those with and without A1 B8 DR3 who seroconverted after use of the contaminated factor VIII (fig 2) it is evident that the haplotype is associated with a particularly rapid rate of decline. There is some indication that T4 levels have stabilised, since the second half of 1986, for the A1 B8 DR3-negative subgroup as a whole. The 2 patients, referred to earlier, who had low but stable T4 numbers both belong to this subgroup.

Discussion

While there have been several longitudinal studies of HIV infection extending over three years or more and including much larger numbers of subjects,[12-16] the Edinburgh cohort study is unique in at least three aspects. The patients had all been assessed before exposure to the virus; the period of exposure to infection has been defined with some precision; and, since no other risk factor has been identified in any of the members of the cohort, all are presumed to have been infected from the same source (probably representing a single virus strain[3]). Information on the subsequent clinical course of these patients is thus of special value.

The association between declining T4 cell numbers and progression to symptomatic AIDS found in this study is entirely consistent with findings in other cohorts,[12-16] but the overall progression rate to CDC IV disease of 50% four years after exposure to infection is much higher than has been reported either in haemophiliacs[15] or in other risk groups.[16] The Edinburgh cohort clearly divides into two categories—one showing a very high rate of disease progression, the other showing a pattern closely comparable with that recorded in most published studies. The less favourable clinical course is strongly associated with the HLA haplotype A1 B8 DR3.

In seeking an explanation for the link between A1 B8 DR3 and response to HIV, we have tried to exclude other compounding variables. The two seropositive subgroups (with and without the A1 B8 and DR3 haplotype) are indistinguishable in terms of age and severity of haemophilia. All patients in both groups are positive for antibody to hepatitis B core antigen. They are all negative for the hepatitis B antigen itself. We have already noted that the risk of seroconversion after exposure to the contaminated batch of factor VIII was related to the number of bottles of that batch actually used and to the number of units of factor VIII used per year.[2] By both criteria, the 11 exposed patients who were A1 B8 DR3 positive were at greater risk than the 21 who were negative for that haplotype (bottles of contaminated batch used, 42·8 SD 31·5 *vs* 23·0 SD 20·1; annual factor VIII use 76·7 SD 56·7 × 10^3 *vs* 54·9 SD 45·9 × 10^3 units). While neither of these differences is significant at the 5% level, they could account for—or contribute to—the increased seroconversion rate observed in the A1 B8 DR3 positive group. It is difficult to argue, however, that the course of HIV-related disease following seroconversion would be influenced to any great extent by small differences in mean infecting dose or in annual use of factor VIII, particularly since the groups overlap considerably in respect of both measurements.

Previous studies on HLA associations with HIV-related disease have suggested possible links between DR5 or DR2 and the risk of Kaposi's sarcoma,[17,18] between DR5 and PGL,[19] and between B35 and progression from PGL to full-blown AIDS.[20] Since none of our patients has Kaposi's sarcoma and none of the 4 who have (or had) PGL (CDC III) carried B35, DR2, or DR5, the present findings have little bearing on these published reports. One research group recorded that HLA B44 has a protective effect in HIV infection.[20] Our findings show only the weakest of trends in this direction. In the exposed cohort, 6 of the 18 who seroconverted were B44 positive compared with 6 of the 14 who remain seronegative. 4 of the 11 who became CDC stage III or IV have B44. Mann and his colleagues[21] have reported a link between DR1 and risk of AIDS in HIV seropositive white male homosexuals. In the present study, neither DR1 nor any other single HLA antigen, but only the complete A1 B8 DR3 haplotype, was associated with likelihood of seroconversion, with early onset of symptoms, or with rapidly falling T4 counts.

A1 B8 DR3 is by far the commonest haplotype in caucasians, with a particularly high frequency among those of northern European descent.[9-11] It is part of a "supratype" that includes a deletion of the genes encoding the C_4A complement component and 21-hydroxylase-A,[22] which is over-represented in several autoimmune diseases such as type I diabetes mellitus, systemic lupus erythematosus, and membranous glomerulonephritis.[23,24] This combination of histocompatibility gene products may have been much less common in some of the previously studied cohorts because of their different ethnic compositions. Furthermore, if it is associated with an accelerated progression to AIDS, that might not be readily apparent in groups where there is only a rough estimate of the time of seroconversion.

It is also possible that the association is peculiar to the single virus isolate responsible for infection in the Edinburgh cohort. Studies in well-documented groups of haemophilia patients from other centres are now in progress to examine this point. Meanwhile the general concept that individuals bearing the A1 B8 DR3 haplotype are immunologically hyperactive may have important implications for our understanding of the pathogenesis of AIDS. It has been proposed that "high responders", actively producing antibody to the HIV envelope glycoprotein, then generating an anti-idiotype that cross-reacts with the CD4 molecule on helper T cells, are effectively caught in an autoimmunosuppressive cycle.[25] Interestingly, we found no correlation between HLA type or disease status and levels of antibody to HIV envelope in

the Edinburgh cohort[3] and this remains the case when the published data are revised to take account of subsequent clinical developments. A simpler explanation might rest on the established fact that HIV replicates preferentially in *activated* T4 lymphocytes.[26] If such activation occurs more readily in A1 B8 DR3 positive patients then a logical explanation emerges for the increased rate of disease progression that we have observed. Our data certainly lend support to the view that HIV seropositive patients should be monitored for evidence of immunological hyperresponsiveness with a view to a trial of cautious immunosuppression in selected cases.[25]

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DIAGNOSIS OF ACUTE HERPES SIMPLEX ENCEPHALITIS BY BRAIN PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

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Summary Brain perfusion was studied in 14 patients with acute encephalitis by use of ^{123}I-iodoamphetamine or ^{99m}Tc-hexamethylpropyleneamine oxime and single photon emission computed tomography (SPECT), the first examination being made 4–11 days after onset of encephalitis symptoms. All 6 patients with herpes simplex virus encephalitis (HSVE) had strongly increased accumulation of radiotracer in the affected temporal lobe; in the remaining 8 results were normal. At the time of the first SPECT conventional CT images were normal in all patients. The SPECT abnormality in HSVE gradually converted over 4–10 weeks from increased tracer accumulation to greatly subnormal accumulation. Brain perfusion SPECT may be helpful in the early diagnosis of HSVE.

Introduction

CLINICAL symptoms and signs indicating temporal lobe dysfunction and viral infection are suggestive of herpes simplex virus encephalitis (HSVE).[1] However, the clinical picture alone may be misleading, and about 1 in 2 patients with suspected HSVE have some other disease.[1–4] Even brain biopsy, the most accurate method for demonstrating the presence of HSV,[1,2,5,6] may give a falsely negative result.[7] For reasonable diagnostic accuracy in the early stage of HSVE it has been necessary to use a combination of clinical, laboratory, electroencephalographic, computed tomographic, magnetic resonance, and brain scintigraphic data, as well as brain biopsy when available.[1,6,8,9] Because treatment of HSVE is most effective when started early, a sensitive and specific method for early diagnosis would be of great benefit. We have assessed the potential of brain perfusion scintigraphy using single photon emission computed tomography (SPECT).

Patients and Methods

We examined 14 patients with viral encephalitis, referred to the Department of Neurology, Helsinki University Central Hospital, using either ^{123}I-iodoamphetamine (IMP) or ^{99m}Tc-hexamethylpropyleneamine oxime (HM-PAO) and SPECT. The interval between first symptoms of encephalitis and the first SPECT varied from 4 to 11 days (mean 8·5 days in the HSVE group and 7·5 days in the non-HSVE group). Altogether 17 SPECTs were performed on 6 patients with HSVE and 10 SPECTs on 8 patients with non-HSVE. All patients received acyclovir (30 mg/kg per day).

Computed tomography (CT), electroencephalography (EEG), and tests on lumbar cerebrospinal fluid (CSF) were done on all patients during the first 2 days in hospital. Patients also had follow-up CT, SPECT, multiple EEGs, and CSF studies. CSF and serum were examined for HSV antibody; and microbial pathogens were sought by staining and culture of CSF. Blood tests were done for other infections and possible underlying systemic diseases.

Viral encephalitis was diagnosed if the patient had an abrupt or subacute onset of clinical signs and symptoms characteristic of