Public Health Laboratory Service

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PROTEIN FRACTIONATION CENTRE
Received: 21 NOV 1984

23rd October 1984

Our ref JC/PH File No: Your ref

[illegible] S.E. SCOTLAND DR. R. J. PERRY

Dear

Factor VIII batch HL 3186: Possible risk of infection with Human T-cell lymphotropic virus type 3 (HTLV-3) with subsequent development of the acquired immune deficiency syndrome (AIDS)

You will have already heard that one of the donors who contributed to the plasma pool used in the manufacture of the batch of factor VIII is a practicing homosexual, and was recently admitted to hospital with clinical features consistent with the diagnosis of AIDS. I am afraid that this has now been confirmed. The patient has developed Pneumocystis carinii pneumonia and two specimens of serum collected in September and October 1984 have been found to be positive for antibody to HTLV-3 by competitive radioimmunoassay (RIA).

I have responsibility for the epidemiological follow-up of recipients of this batch to confirm whether any hazard exists, and to assist in the investigation of patients where required. I hope that we can obtain the maximum information from this unfortunate incident, and devise methods for the prevention of the disease. We also need to confirm the association of HTLV-3 infection and transfusion of factor VIII concentrate.

From studies already underway on recipients of batches of factor VIII transfused to the two haemophilia A patients who contracted AIDS in 1983, we have already provisionally identified one batch of factor VIII which was transfused to one of the AIDS patients and was associated with seroconvertion to HTLV-3 antibody positive in seven out of thirteen recipients . One of the patients who acquired HTLV-3 infection subsequently developed AIDS, a second developed thrombocytopenia, and the other five have remained symptomless. There was no correlation between the number of bottles of factor VIII each patient received and the chance of contracting HTLV-3 infection. The most likely explanation for this is that only a small proportion of the total bottles of the batch were contaminated with HTLV-3.

contd/...

Risk to the patient

From the forgoing discussion you will see that it is difficult to be certain of the precise risk of any recipient contracting AIDS, but the following facts may help you to appreciate the position.

1) Only a proportion of the patients transfused with an infected batch are likely to contract HTLV-3 infection.

2) Some patients who have received commercial factor VIII since 1.1.80 will already have contracted HTLV-3 infection from other infected batches.

3) The proportion of patients who are infected with HTLV-3 who eventually contract AIDS is unknown, but as serum from 34% of symptomless haemophiliacs are positive for HTLV-3 antibody, it is likely that a significant proportion of patients will remain in good health. So far 21 patients are known to me who have clinical features of AIDS (4) or the AIDS related complex. It is likely that the proportion of patients who contract HTLV-3 infection who contract AIDS will be of the order of 1/100 - 1/500.

4) The long term prognosis for patients with HTLV-3 infection is unknown. The incubation period of AIDS based on projection of the epidemic curve at C.D.C. Atlanta is from 9 months to 6 years, with a mean of 4 years.

5) There is evidence that HTLV-3 infection can be transmitted by sexual contact. Therefore some sexual partners of recipients of factor VIII contaminated with HTLV-3 may be at risk.

6) We cannot yet distinguish those patients who are likely to transmit infection, or who are likely to contract AIDS by means of laboratory tests.

Methods of Investigation

With the above facts in mind, I propose the following strategy.

a) Identify all patients who have received factor VIII batch HL3186
If a serum specimen taken before the date of transfusion of factor VIII HL 3186 is available, then this should be tested for HTLV-3 antibody. This will identify persons already exposed to infection. If no specimen is available then a specimen of serum (2.0ml) should be collected as soon as possible to exclude the possibility of prior HTLV-3 infection.

b) Follow up of patients
Patients identified should be followed up at least at four monthly intervals for 6 years. Further review should be undertaken if a patient becomes ill to exclude the possibility of an AIDS related illness. A control patient who has not received batch number HL3186 should be selected for each index patient. These should be matched as far as possible for age, severity of disease and transfusion history.

Returns for each patient can be made after each clinic visit by filling in a case record form (a specimen copy enclosed) and returning it to me at Manchester PHL together with a specimen of serum (2.0ml) for HTLV-3 antibodies.

contd/...

Follow up should be carried out even if a patient is found to be positive for HTLV-3 antibody in the first specimen tested. This will assess whether exposure to more than one batch of factor VIII contaminated with HTLV-3 have any effect on the chance of contracting AIDS.

c) Four monthly review Forms (A/1) should be completed and sent to Miss Spooner at Oxford. This history and medical examination should be designed to exclude AIDS related disease. Laboratory investigations should include haemoglobulin, E.S.R., white count, absolute lymphocytic count and differential, platelet count, and total serum IgG, IgA and IgM estimations. Blood should be taken for hepatitis B, and other viral antibodies as appropriate. Two mls of serum should be retained for HTLV-3 antibody tests and sent to Dr. Craske at Manchester PHL.

The follow-up may be carried out using the alternative of two different strategies:-

i) If the patient has been informed of the risk associated with this contaminated batch of factor VIII, testing could be carried out on each specimen as it is obtained at each four monthly review. In addition, it would be wise to warn the index patient that his spouse may be at risk from contracting HTLV-3 infection as a result of any sexual contact. An antibody test for HTLV-3 antibodies can be offered at the time of follow-up of the index case for the contact. Alternatively they can be referred to their own doctor and follow up can be arranged through him as thought necessary by the Haemophilia Centre Director.

ii) An alternative strategy would be not to tell the patient of the risks involved but to observe him at regular clinical review four monthly, to collect serum specimens for HTLV-3 antibody examination and send them to me at Manchester. These would not be examined until two years after the initial exposure, or until the patient develops clinical features suggestive of AIDS, or testing is requested by the Haemophilia Centre Director.

The ethical problems involved in these two alternative methods of follow up are discussed in an appendix at the end of this letter.

Further investigations can be carried out as local facilities and these could include virus isolation specimens of faeces, urine and a throat swab for virus isolation. Assessment of immune response by examination of T-cell subsets, the response of T-cells in vitro to transformation using mitogens and the response to intradermal injection of skin test antigens as an assessment of cell mediated immunity.

d) Investigation of spouses This will be at the discretion of the Haemophilia Centre Director, and will depend upon whether it is decided to inform the index patient of the possibility that the batch of factor VIII was contaminated with HTLV-3 virus. (see page 4 "other preventative measures")

Should the patient be told?

Ideally I think he should, but this will depend on many factors, including the amount of anxiety concerning AIDS there is already present at the Centre, and the degree to which the patient is capable of understanding the situation. An alternative might be to inform the patient's spouse or other close relative, as is done when patients develop malignant diseases. This will be at the discretion of the local Haemophilia Centre Director.

Other preventative measures

1) When a patient is told of the risk of exposure to HTLV-3 infection he should also be warned that his sexual partner might also be exposed to infectio The use of 'barrier' forms of contraception, e.g., a sheath should be recommended. It would be advisable to offer the sexual partner and any other members of the family tests for HTLV-3 antibody where appropriate. Regular follow up either by the Haemophilia Centre Director or by the relatives G.P. should be encouraged. The G.P. should be informed of the situation subject to the patient's consent.

2) Preliminary information suggests that HTLV-3 is readily inactivated by heat at 60°C. It is possible that a heat treated factor VIII will be available before long.

J. Craske
23.10.84.

Appendix

ETHICAL PROBLEMS ASSOCIATED WITH HTLV-3 INFECTION IN HAEMOPHILIACS

The accompanying letter details a protocol with 2 alternative strategies for the follow up of patients who have received a batch of factor VIII contaminated with plasma collected from a donor who subsequently is shown to have AIDS or to have acquired HYLV-3 infection.

1) Informing the patient and his family of the risks This allows information of the development of HTLV-3 infection to be available to the caring physician as soon as possible, and thereby to identify and treat all complications as they arise where treatment is available.

   It also allows the patients spouse to be informed of the risk of contracting infection through sexual intercourse, for advise to be given as early as possible after the patient has been exposed to HTLV-3 infection. Such measures as using 'barrier' types of contraception, e.g., a sheath may lessen the chances of transmission.

   It also maintains a trusting relationship between the physician and his patient which is essential if difficult problems arising from HTLV-3 infection are to be surmounted.

2) Restricted follow-up In this strategy the identification of patients who contract HTLV-3 infection will not be made for 2 years or at the request of the Centre Director. It will be impossible to warn spouses and advise preventative measures to limit the risk of transmission of infection, since it will not be known when the index patient first contracts HTLV-3 infection. If a patient develops AIDS related illness it will be too late, as the period of maximum infectivity will already have passed.

   Any benefit or peace of mind for the patient will be temporary if any other persons exposed develops AIDS. If the patient finds out that he has had this batch, then the trust of the patient will be lost, and the Haemophilia Centre Director placed in a delicate situation.

   It is quite likely that any patient who has received commercial factor VIII since 1980, and thus had already possibly been exposed to HTLV-3 infection will not have a greatly increased chance of contracting AIDS, compared with a patient who has received only NHS concentrate until now.

   In my view option (1) is the only one tenable on moral and ethical grounds.

J. Craske
29.10.84.

UK HAEMOPHILIA DIRECTORS A.I.D.S. INVESTIGATION

[Record Form No:1 to be filled in for each patient at first follow up, and at subsequent follow ups.]

1:GENERAL INFORMATION

NAME....._____

DATE OF BIRTH.....__/__/__

NAT.FILE NO:....._/____

HAEM. CENTRE....._____

2(a).CLINICAL FEATURES

Month/Year.....__/__

Onset Symptoms.....__/__/__

Date AIDS Suspected.....__/__/__

Date of Death.....__/__/__

Was P.M. carried out?.....___

2(b).MAIN SYMPTOMS/SIGNS/RELATED ILLNESS

Has patient any abnormal features indicated below?....._____

If no then proceed to section 2(c).

CLINICAL FEATURES

Malaise....._	Nephrotic Syndrome....._
Weight Loss....._	Candida Infection....._
Fever....._	Amoebiasis....._
Enlarged L.N....._	Non-Hodg. Lymphoma....._
Diarrhoea....._	Diabetes....._
Dyspnoea....._	Encephalitis....._
Cough....._	Other tumours....._
Night Sweats....._	Opportunistic Inf....._
Pupura....._	If yes, specify...._____
Kaposi's Sarcoma....._	_____
Haemolytic Anaemia....._	_____

Any Other Clinical Features? If Yes Please Specify..._____

_____

2(c).EPIDEMOLOGICAL DATA: HISTORY OF PAST 5 YEARS

Sexual Contact:

No....._
Yes...._

If Yes:

Heterosexual....._
Homosexual....._
Bisexual....._

Heroin Addiction:

No....._
Yes...._

If Yes:

Parenteral....._
Non-Parenteral....._
How Long....._____

Contact With A.I.D.S. or High Risk Group?

No....._
Yes...._

Was Contact In Same Household?

No...._
Yes..._

Has The Patient Received Immunosuppresive Drugs?

No...._
Yes..._

If Yes:

Specify Type.._____
_____
_____

Has The Patient Received Deep X-Ray Therapy? No...._
Yes..._

Does The Patient Suffer From Congenital or Acquired Immune Defiency? No...._
Yes..._

If Yes:

Specify.._____
_____
_____

Has The Patient Visited Any Countries Where A.I.D.S. Is Endemic? No...._
Yes..._

If Yes:

Specify.._____
_____
_____

DIAGNOSIS OF PRESENT CONDITION:-

DATE OF REPORT:-

REPORTING PHYSICIAN:-

U.K. HAEMOPHILIA A.I.D.S. INVESTIGATION

Record Form No:2 Laboratory Investigations:

HAEMATOLOGY
IMMUNOLOGY

NAME....._____

NAT.FILE NO....._/____

DATE of TESTS.....__/__/__

If patient has developed relevant symptoms and clinical features, please complete Form No:1
If Asymptomatic and no disease then tick here....._

Bilirubin....._

ALT.....__

Haemoglobin.....___

Total White Cell Count.....____

Total Lymphocyte Count.....____

Total B Cells.....____

Total T Cells.....____

Total 'Helper' T Cells.....____

Total 'Suppressor' T Cells.____

Helper:Suppressor Ratio....____

Total IgG.....____

Total IgM.....____

Total IgA.....____

Platelet Count.....___

Response Lymphocytes To Mitogens In Vitro:

Diminished....._

Normal....._

Increased....._

Mitogens used..._____

Presence Of Immune Complexes:

Result...._____

Method Used..._____

Response To Intradermal Skin Test Antigens:

Result...._____

Antigens Used..._____

DIAGNOSIS OF PRESENT CONDITION:-

DATE OF REPORT:-

REPORTING PHYSICIAN:-

UK HAEMOPHILIA AIDS INVESTIGATION

RECORD FORM NO.3 LABORATORY INVESTIGATIONS

VIROLOGY

NAME:....._____

NAT.REG.NO:....._/____

DATE OF TESTS:.....__/__/__

Hepatitis B Surface Antigen:

Pos/Neg Titre.....___

Method Used..._____

Hepatitis B E Antigen/Anti-E:

Antigen Pos/Neg

Antibody Pos/Neg

Method Used..._____

Anti HBc:

Pos/Neg

% Reduction.....___

Method Used..._____

Anti HBs:

Pos/Neg

Ratio (+/-).....__

Method Used..._____

Hepatitis A Antibody:

Pos/Neg

Method Used..._____

Human T-Cell Leukaemia Virus Type 3 Antibody:

Pos/Neg Titre.....___

Method Used..._____

Cytomegalovirus Antibody:

Pos/Neg Titre.....___

Method Used..._____

Epstein Barr Virus Capsid Antibody:

Pos/Neg Titre.....___

Paul Burnell:

Pos/Neg Titre.....___

Toxoplasma Antibody:

Pos/Neg Titre.....___

Method Used...._____

Herpes Simplex (CFT):

Pos/Neg Titre.....___

Varicella Zoster:

Pos/Neg Titre.....___

Method...._____

Other Tests:.....

DIAGNOSIS OF PRESENT CONDITION:-

DATE OF REPORT:-

REPORTING PHYSICIAN:-