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30th November, 1984

Our ref JC/PH Your ref

Dr. C. Ludlam,
Department of Haematology,
Edinburgh Royal Infirmary.

Haemophilia Directors.
AIDS Working Party

Dear Dr. Ludlam,

"Suspect" batches of Edinburgh Factor VIII and Factor IX: Possible risk of infection with Human T-cell lymphotropic virus type 3 (HTLV-3) with subsequent development of the acquired immune deficiency syndrome (AIDS)

Further to our telephone conversations, I enclose a set of forms (JC1, JC2 and JC3) which I would be pleased if you could arrange to have completed for the patients who received the batches we discussed.

As you know, I have responsibility for the epidemiological follow-up of recipients of "suspect" batches of concentrates 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 study 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.

You will remember that we conducted a survey of the blood products transfused to AIDS cases A1 (Cardiff) and A4 (Bristol) earlier this year. Investigation of the relationship of sero-conversion to HTLV-3 antibody and transfusion of specific batches of factor VIII has shown that it is not possible to identify specific batches of factor VIII in retrospective studies. The reasons for this are set out in a letter accompanying the latest AIDS Update (Update 5).

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.

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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% (1) 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 have been reported to me as having the clinical features of AIDS (4 patients) or the AIDS-related complex (17 patients). It is likely that the proportion of patients who contract HTLV-3 infection who develop 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 "suspect" batches
If a serum specimen taken before the date of transfusion of the "suspect" batch 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 (2.0 ml) 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 the "suspect" batch should be selected for each index patient. These should be matched as far as possible for age, severity of disease and transfusion history.

Reference:
(1) CHANGSONG-POPOV, R. et al. Lancet (1984) ii, 47-80

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A set of simplified record forms have been devised (JC1, JC2 and JC3) for this study. They should be completed and returned to me as follows:-

Form JC1: Patient Data and Clinical Features.

Please complete on initial visit and at each follow-up and return it to me at Manchester PHL together with a specimen of serum (2.0 ml) for HTLV-3 antibodies.

Form JC2: Laboratory Investigations: Haematology
Immunology

Please fill in relevant results after each clinic visit and return to me.

Form JC3: Laboratory Investigations: Virology

To be filled in after each clinic visit and returned to me when the relevant investigations have been performed at your local laboratory.

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 concentrate contaminated with HTLV-3 has any effect on the chance of contracting AIDS.

c) Four monthly review

Forms JC1, JC2 and JC3 should be completed and sent to Dr. Craske at Manchester PHL. The history and medical examination should be designed to exclude AIDS related disease. Laboratory investigations should include haemoglobin, E.S.R., white count, absolute lymphocyte count and differential, white 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 an alternative of two different strategies:-

i) If the patient has been informed of the risk associated with a "suspect" batch of concentrate, 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. A test for HTLV-3 antibodies can be offered to Directors at the time of follow-up of the index case. Follow-up can be arranged by the Director or in collaboration with the G.P. as thought necessary.

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ii) An alternative strategy would be not to tell the patient of the risk 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 permit. These could include 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 was contaminated with HTLV-3 virus (see "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. Every effort should be made to encourage the patient to discuss the problem with his spouse and help them to face the problem together. The General Practitioner should also be informed by letter.

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 infection. 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.

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.

Yours sincerely,

GRO-C

J. Craske
Consultant Virologist

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.

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