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Appendix I

UPDATE ON HIV RELATED ILLNESS - SEPTEMBER 1986

For the past 6 months there has been a lot of natural concern regarding the confidentiality of data reported to the National Survey at Oxford. Arising from this there was a noticeable drop in the rate of case reporting early this year. This has increased again in recent months, but I think it is still important to emphasise that reporting is necessary to enable us to obtain information on the size of the problem; to establish the efficiency of preventative measures e.g. safety of heat treated factor VIIII, and to identify new patterns of the disease associated in the HIV infection.

Second HIV antibody survey

The response to requests for this information has been very encouraging. We hope that this will provide effective evidence regarding the safety of heat treated factor VIII. The returns will be evaluated shortly.

Study of HIV infection association with NHS unheated factor VIII

The returns made last year on batches of NHS factor VIII identified either with an anti-HIV positive donor, or a donor who developed HIV related illness have now been analysed.

Eight batches of NHS factor VIII and 2 of factor IX have been studied. Evidence of transmission of the virus was identified in 5 batches of factor VIII and one of factor IX. A further 2 batches of factor VIII were considered as possibly being associated with infection. No information is yet available on one batch of factor VIII and one batch of factor IX.

We are sending a detailed report of the results to the Directors who sent returns in this Survey together with suggestions for follow up of patients. Using the results of this Survey we have drawn up a set of criteria by which transmission of infection associated with heat treated factor VIII can be identified. These will be published in due course and will be used in the analysis of the second anti-HIV antibody survey.

Surveillance of AIDS related illness

The total number of patients reported to Oxford with HIV related illness by 22.4.86 was 109. This was 12.9% of the total antibody positive patients identified in the Survey in August 1985 (896). The data will be reanalysed when the results of the second anti-HIV survey are known. The number of AIDS cases reported of which 15 have died is 23. Eighteen cases are known to the Communicable Disease Surveillance Centre, Central Public Health Laboratory, Colindale. Two of these had not been notified to Oxford so that the total may come to 25.

There is still a marked preponderance of patients aged over 40 years. At least 5 have died with P.C.P. within a few weeks of the diagnosis of AIDS being confirmed. Three patients with A.R.C. have also died. There is information suggestive of an excess incidence of haemorrhage attributable

to HIV infection. Proposals to investigate this possibility will be made at the Clinical Meeting in October.

The minimum time between seroconversion to HIV antibody positive, and the onset of AIDS is between 6 and 9 months. For cases associated with blood transfusion in USA, it is 4 months.[1] A recent model derived for the reported cases of blood transfusion associated AIDS in the USA[2] gave a maximum likelihood estimate of the mean incubation period of 54 months (4.5 years) with upper and lower 95% confidence limits of 2.6 and 14.2 years.

The implications of this estimate for haemophilia A and B patients are that a significant number of HIV infected persons will continue to develop AIDS related illness over a number of years, despite the efficiency of heat treated factor VIII and IX in preventing further patients being infected.

A more detailed analysis of the other categories of HIV related illness is given in the tables accompanying this bulletin. The thirty cases of P.G.L. are well below the number expected. One patient with non-Hodgkin's lymphoma fulfills the criteria for AIDS.

Further action

1) We will send each reporting Centre a list of patients already notified to Oxford so that any patients who have been overlooked can be included in the survey. Please could you report any cases of P.G.L. especially, we need to know if the pattern of disease in this group is the same as other high risk groups. 2) I think it is important to obtain information about the date of seroconversion to anti-HIV positive where this is available so that patients can be linked in a long term follow up to look at the course of HIV infection over time. 3) The problem of HIV infection in pregnancy will be reviewed in discussions at the Annual meeting.

References

[1] Transfusion associated Acquired Immune deficiency Syndrome in the United States. JAMA (1985) 254, 2913-2917. Peterman, T.A. et al.

[2] A model-based approach for estimating the mean incubation period of transfusion associated Acquired Immunodeficiency Syndrome. Proc. Nat. Acad. Sci. USA (1986) 83, 3051-3055. Kung-Jong, L. et al.

J. Craske
10.9.86

HTLV–3 RELATED DISEASE IN HAEMOPHILIA
CUMULATIVE CASES TILL 22–4–86

		No.	INCIDENCE	DIED	CONSORT
AIDS	PCP	15	23 2.5%†	12	1
	OI*	8		3	
	KS	0		0	
ARC		20	2.2%	3	1 suicide 1 septacaemia 1 pneumonia

UNCLASSIFIED

Abdominal lymphoma 1 1

2 further cases under investigation

* Includes 1 with cerebral toxoplasmosis

† Denominator = 89% anti-HTLV–3 positive patients in survey

OTHER SYNDROMES

	No.	INCIDENCE	DIED	
Thrombocytopenia	28	3.1%	1	Haemorrhage post splenectomy
+ Purpura	5		0	Subdural haematoma - recovered
PGL	30	3.3%	0	
Acute 'glandular' fever	10	1.1%	1	Died - AIDS 2 years later
+ Encephalopathy	2	0.22%		

5 Thrombocytopenia patients also had PGL

Total 109 (12.9%) total 'at risk' 896; total died 19 (2.1%)

ANTI-HTLV–3 IN HOUSEHOLD CONTACTS OF HAEMOPHILIA A PATIENTS

INDEX PATIENTS	CONTACTS				
	Wife or girlfriend	Parents (of haemophilic children)	Sibs	Children	Other
ANTI-HTLV–3 NEGATIVE	0/42	0/46	0/18	0/19	—
ANTI-HTLV–3 POSITIVE	*5/153	0/47	0/7	0/21	0/2

*Includes 1 drug addict : Index patient also addict
1 sexual contact has AIDS : Index patient ARC
Others symptomless

PREVALENCE OF HTLV–3 INFECTION IN HAEMOPHILIA B PATIENTS

				No. Died	
AIDS	PCP	0		0	
	OI	1	5.0%	1	
ARC		0			
Thrombocytopenia		1	5.0%	0	
PGL		1	5.0%	0	
	TOTAL	3		1	Total at risk 20

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Appendix II

RETROSPECTIVE STUDY OF HIV INFECTION ASSOCIATED WITH UNHEATED NHS FACTOR VIII AND IX

We have now completed the analysis of the returns from Haemophilia Centres for 7 batches of NHS factor VIII and one batch of NHS factor IX. Returns for one batch of factor VIII and IX are still awaited.

Results

Tables I and II summarise the results obtained. These batches were investigated because a donor whose plasma contributed to the pool from which the concentrate was derived either developed HIV related illness or was subsequently found to be anti-HIV positive. In one instance a recipient of a batch of factor VIII developed a glandular fever like illness and subsequently an anti-HIV positive donor was also traced who had contributed to the implicated batch of concentrate.

The batches were used between 1981 and 1985. Since HIV testing was started in the Autumn of 1984, this means that the pre-exposure anti-HIV status is not known for many patients and the number of seroconversions identified unequivocably was small.

The demonstration of one or more seroconversions associated with a batch was taken as evidence of HIV infection being caused by a batch of concentrate. Additionally the post-exposure anti-HIV prevalence should be at least 40% for NHS factor VIII concentrate. For instance, in the first batch investigated (E table 2) only two seroconversions were identified amongst the 38 patients at risk. A post-exposure anti-HIV prevalence of 76% was however found among 22 patients at risk where the results of pre-exposure anti-HIV tests were available. For factor IX there was only one batch for which adequate data was available. Of 24 patients at risk, 3 were anti-HIV positive before exposure and 1 out of 20 anti-HIV negative seroconverted to anti-HIV positive. The remaining patient was found to be anti-HIV positive to post-exposure but no pre-exposure antibody tests were done. This gives a seroconversion rate of 5%. The small proportion of haemophilia B patients so far infected with HIV (20) is therefore partly accounted for by a lower contamination rate of factor IX concentrate compared with factor VIII. This is confirmed by independent observations at the Edinburgh Haemophilia Centre where 16 out of 32 patients seroconverted after transfusion with one batch of contamined factor VIII.

It should also be noted that out of 8 plasma pools which were contaminated with an HIV-positive donor, factor IX was prepared from only 2 whereas factor VIII was prepared from all the plasma pools. Hence the number of contaminated batches of factor IX used in British haemophilia B patients was less than contaminated Haemophilia A patients. Information is not yet available as to whether this represents a difference in proportion of the total number of batches used for each group of patients.

Further Follow-up

So far two patients who received these batches of factor VIII who are anti-HIV positive have developed AIDS and one has ARC. Fourteen patients are known to have seroconverted and therefore the time at which they were first infected is known. No other AIDS related illness has so far been

reported in this group.

The next step will be to identify the patients who are HIV-positive post-exposure to increase cohort to at least 30 or 40 patients. These patients should therefore be followed six monthly in their usual review clinic. The only additional investigations necessary will be -

1. Full blood count and differential, platelet count

2. Total immunoglobulins determination

3. Collection of 10 ml of clotted blood for HIV serology.

Additional investigations will be at the discretion of each Haemophilia Centre Director.

Report Form

I enclose a Report Form JC4 for reporting follow-ups which has been discussed at the Haemophilia AIDS Group. This is a simplified version and is meant as a substitute for the forms JC 1, 2, 3 which have proved too complicated to use. Please return these to Miss R.J.D. Spooner at the Oxford Haemophilia Centre when completed.

Controls

It is desirable in these investigations for control patients to be included. Please include one antibody negative patient treated with the same implicated batch of concentrate for every antibody positive patient followed as part of this study. If you have any queries or suggestions do please let me know.

Conclusions

This Survey has provided alot of information regarding transmission of HIV infection by factor VIII and IX concentrate. More information will be presented at the Annual Meeting in October. One useful result of this survey has been to provide firm criteria by which the transmission of HIV infection by a batch of concentrate can be judged. These will be used in the analysis of the second anti-HIV antibody survey.

J. Craske
10.9.86

Table I

BATCHES OF NHS FACTOR VIII AND IX SUSPECTED OF TRANSMITTING HTLV-3

BATCH	REASON FOR SUSPECTING BATCH	TOTAL PATIENTS EXPOSED	ANTI-HTLV-3 POSITIVE PRE	ANTI-HTLV-3 POSITIVE POST	ANTI-HTLV-3 NEGATIVE PRE	ANTI-HTLV-3 NEGATIVE POST	SEROCONVERSIONS	INSUFFICIENT INFORMATION	DATE BATCH USED	TRANSMISSION
FVIII E	Donor contracted AIDS ANTI-HTLV-3 POSITIVE	38	8	16	8	6	2	16	8-12/84	YES
F VIII F	Donor developed HTLV-3 RELATED DISEASE: ANTI-HTLV-3 POSITIVE	50	NK	17	NK	20	?	11+	6-7/83	?
FVIII G	Patient contracted GF-LIKE SYNDROME: IMPLICATED DONOR NOT TRACED	31	19	26	12	5	7*		10-12/84	YES
FIX H	ANTI-HTLV-3 POSITIVE DONOR	24	3	5	20	19	1	1PT ab+ve Post only	3-6/85	YES
FVIII H	NO INFORMATION YET AVAILABLE									

*ONE PATIENT CONTRACTED A GF LIKE SYNDROME PRIOR TO SEROCONVERSION

+11 PATIENTS NOT YET TESTED FOR ANTI-HTLV-3: 2 PATIENTS HAVE DIED SINCE RECEIVING THIS BATCH
1 PATIENT WHO IS ANTI-HTLV-3 POSITIVE HAS ARC.

J. CRASKE
JUNE 1986

Table II

BATCHES OF NHS FACTOR VIII AND IX SUSPECTED OF TRANSMITTING HTLV-3

BATCH	REASON FOR SUSPECTING BATCH	TOTAL PATIENTS EXPOSED	ANTI-HTLV-3 POSITIVE PRE	ANTI-HTLV-3 POSITIVE POST	ANTI-HTLV-3 NEGATIVE PRE	ANTI-HTLV-3 NEGATIVE POST	SEROCONVERSIONS	INSUFFICIENT INFORMATION	DATE BATCH USED	TRANS-MISSION
FVIII A	ANTI-HTLV-3 POSITIVE DONOR	8	6	8	2	0	2	0	1/84	YES
FVIII B	"	21*	NK	11	1	8	1	1 NOT TESTED	7/83	YES
FIX B	"	INFORMATION AWAITED							1/83	?
FVIII C	"	24	NK	3	NK	6	0	15	6-9/83	?
FVIII D	"	7	NK	6	1	0	1		1/81	YES

NB SAME DONOR IMPLICATED IN ALL BATCHES

*1 PATIENT DIED POST EXPOSURE

J. CRASKE
JUNE 1986

U.K. HAEMOPHILIA CENTRE DIRECTORS' AIDS GROUP Form JC4

Please complete and return to Miss R.J.D. Spooner, Oxford Haemophilia Centre, Churchill Hospital, Headington, Oxford. OX3 7LJ

CONFIDENTIAL

Follow-up of NHS Factor VIII Batch No. _____

Name of Patient: _____ d. of b.: _____

Haemophilia Centre: _____

National file Diag/Reg. No.: _____

Follow-up Number: _____ Time since transfused with above batch (months): _____

Date: _____

Clinical Features:-

		Date of onset
None (well)	( )	_____
*Lymphadenopathy	( )	_____
**Persistent generalised lymphadenopathy	( )	_____
Thrombocytopenia (<100 x 10^9/L)	( )	_____
Lymphopenia (<1.5 x 10^9/L)	( )	_____
ARC	( )	_____
AIDS	( )	_____
Other specify _____		_____
Glandular Fever Syndrome	( )	_____

Investigations:-

	Date	Results
Hb.		
WBC		
Total Lymphocyte count		
Platelets		

Serum taken for HTLVIII Antibodies? Yes/No

If yes:-	Date	Type of Test	Result

Definitions:-

*Lymphadenopathy: Enlargement of lymph nodes in 1 or more fields lasting 1 month or more.

**PGL: Enlargement of 2 or more fields lasting 3 months or more.

Anterior and posterior cervical Right and Left
Axilla " "
Inguinal " "

Number:

Signed: _____

Date: _____