UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

Department of Clinical & Laboratory Haematology
The Birmingham Children's Hospital
Steelhouse Lane
Birmingham
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February 2003

Dear Colleague

Re: Surveillance of vCJD-DOH funded UKHCDO study

As you are aware, Professor Christine Lee, on behalf of the TTI Working Party, has obtained Department of Health funding for a UKHCDO vCJD surveillance study of haemophilia (and other bleeding disorder) patients.
We know that some of our patients have been exposed to products that contained donations from individuals who subsequently developed vCJD. All UK residents, including people with haemophilia, may have also been exposed to this risk in the 1980s and 1990s through the food chain. For this reason, it is important that the study contains those exposed to implicated batches (see attached). Those who have not been exposed to implicated UK factor concentrates will also be included in the study and will constitute an important control group.

The study will have the following components (for details refer to attached information):
1. Collection of data on those exposed to implicated batches throughout the UK.
2. Notification of any confirmed clinical cases.
3. Prospective study of tissues taken at operation.
4. Prospective study of postmortem material.
5. Retrospective study of postmortem and biopsy material.

It is proposed that the data will be collected and collated through the UKHCDO and the data stored in the National Haemophilia Database. All patients should be provided with a copy of the green patient information leaflet about the database. The Haemophilia Society, Haemophilia Nurses Association and UKHCDO informed the CJD Incident panel that it was preferable for these data to be collected on the National Haemophilia Database than on the proposed separate national database recording vCJD exposures/incidents.

This is obviously a very important study for the UK haemophilia population and I hope you will participate. If you wish to discuss any aspect more fully then please contact myself or Professor Christine Lee.

Yours sincerely

Professor Frank Hill
Chairman, UKHCDO

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Surveillance of vCJD-UKHCDO/DOH

In response to the concern that vCJD may be transmitted by blood and/or blood products, the Department of Health has commissioned and funded a 5 year surveillance study of patients with haemophilia. All UK haemophilic patients who have been treated with clotting factor concentrate, in particular of British donor pool origin, should be considered to be at risk of vCJD infection and we, as their clinicians, have a shared responsibility to ensure that appropriate measures are taken to enable effective retrospective and prospective surveillance. It is anticipated that this study will assist in elucidating the size of the risk, if any, posed by blood products in the transmission of vCJD.

It is proposed that all data will be collated through the UK Haemophilia Doctors Organisation (UKHCDO) database and it is important that patients are provided with a UKHCDO patient information leaflet about the nature of the database. (Appendix I)

This study has full MREC approval (see notes, page 4)

The components of the study are as follows:

1. Identification of Patients exposed to implicated batches

Details of haemophilia centre patients who have received concentrates prepared from the plasma of donors who subsequently developed vCJD will be collected. This will be achieved using the existing confidential database of the UKHCDO. It is the responsibility of the doctor providing the haemophilia care of the patient to provide the relevant information. Copies of the Notification Form are enclosed (Appendix II) and a copy of this should be filed in the patient notes.

To date, there have been three **BPL** Recalls of the following products. The details of batch(es) issued to your centre have been highlighted together with all other known implicated batches below:

Year of Recall	Product Name	Batch Number	Date of Issue
1997	Factor VIII 8Y	FHB 4419	9/08/95-14/09/95
	Factor VIII 8Y	FHB 4547	6/12/96-20/01/97
	Replenate	FHE 4548	28/10/96-22/11/96
2000	Factor VIII 8Y	FHB 4596	13/05/97-13/08/97
	Replenate	FHD 4579	8/03/97-15/07/98
	Replenate	FHE 4536	11/09/96-8/10/96
	Replenate	FHE 4579	25/02/97-8/01/98
	Replenate	FHF 4577	10/02/97-20/03/97
	Replenine-VF	FJM 4596	30/04/97-19/05/97

There has been one **SNBTS** recall for products which were issued between **1987** and **1989**:

Factor VIII Z8	0301-70320
	0304-70510
Factor IX DEFIX	3502-70210
	3506-70250

Many patients who received affected batches were notified at the time of the recalls. However, it should be stressed that in situations where the affected patients did not wish to be informed, surveillance should go ahead regardless. This also applies to patients who received these batches but have since died.
Should there be future notifications resulting from the finding that newly diagnosed vCJD patients have contributed to plasma pools then the database should be notified and it will be the responsibility of the clinician to do this.

Assistance in providing this information can be given by the Study Co-ordinator:

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Clinical Research Fellow
Haemophilia Centre and Haemostasis Unit
Royal Free Hospital
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London NW3 2QG
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A general information sheet is enclosed (Appendix III) which may be helpful for patient information.
In addition to enabling appropriate monitoring and follow-up, the identification of 'at risk' patients will provide valuable epidemiological data. This may assist in confirming or refuting whether blood products transmit vCJD; information that is currently unknown. Furthermore, there is potential to expand further and look for any possible correlation between the various methods of fractionation and the emergence of new cases of vCJD.

2. Notification of clinical cases of vCJD
The investigation and management of suspected cases should be carried out in conjunction with a local neurologist and the CJD Surveillance Unit in Edinburgh. (see Appendix IV). It should be noted that although the median age of diagnosis of vCJD is 26, it is quite possible that vCJD is being underdiagnosed in older patients with symptoms of dementia. Therefore all haemophilic patients with dementia or unexplained neurological symptoms, irrespective of age, should be clinically assessed and investigated as appropriate.

If a patient with haemophilia develops vCJD, the study co-ordinator and database should be notified. Details of previous clotting factor treatment and other risk factors for developing vCJD should be provided where possible.
In instances where a patient has been investigated for suspected vCJD but the results are negative (e.g. MRI, EEG, LP), the database should be informed (Appendix V)

3. Prospective study of tissues taken at operation
In vCJD, prion protein accumulates within the central nervous system, in peripheral sensory ganglia and in lymphoid tissues from all areas of the body including tonsil, lymph nodes, spleen and gut associated lymphoid tissue. Surveillance by biopsy is needed to obtain more evidence for any possible vCJD infectivity from plasma products and all haemophilic patients undergoing such biopsies should be encouraged to participate in this study. *(Of note, an anonymous retrospective study of tonsillar and appendix tissues removed from normal individuals over the period 1996-99 is currently underway in an attempt to provide an estimate of the proportion of the population who may be incubating vCJD. The first 3000 samples from an estimated total of 15,000 appendices and 1,000 tonsils examined using immunocytochemistry methods have not revealed any positive cases.)*
A specifically designed, MREC approved form (Appendix VI) should be used to obtain consent from the patient and to ascertain whether he/she wish to know the results of the findings. This study applies only to tissues that were destined to be taken-i.e. not opportunistic. The study co-ordinator should be informed. Histology should be performed locally and appropriate samples should also be anonymously referred to the CJD Unit for specialist examination. The patient's general practitioner should be informed. (Appendix VII)
If a patient declines consent at the time of surgery, form (Appendix VIII) should be completed. This will provide useful epidemiological information.

4. Prospective study of postmortem material

Following the adverse media coverage of events such as Alder Hey, the numbers of post mortems being performed in hospitals has fallen dramatically. Historically, many haemophilic patients underwent autopsies in the AIDS era, however, since the introduction of highly active antiretroviral therapy (HAART) and consequent improved survival in these patients, the need for histopathological investigation and diagnosis has subsided.

Wherever possible, request for autopsy on all patients with haemophilia should be made.

Consent should be obtained from relatives using the normal post mortem consent form (in conjunction with the Royal College of Pathologists 'Information about postmortems for relatives', March 2000). Extra consent from the patient's next-of-kin (Appendix IX) regarding whether they wish to know the results should also be sought. The study co-ordinator should be informed and lymphoid and brain tissues sent to the CJD Unit in Edinburgh with the patient's UKHCDO database number as a means of identification.

5. Retrospective study of postmortem and biopsy material

In the period 1985-1998, at least 88 postmortems were performed out of a total 1300 haemophilic deaths (as reported to the UKHCDO database). Wherever possible, centres should establish the extent of their postmortem material and refer relevant sections to the CJD Unit following liason with the study co-ordinator. Help with the tracking and retrieval of specimens may be available.

No additional consent is required for this

In the case of biopsy material available in deceased patients, similar action should be taken.

Where the patient is still alive, consent would be required for such an examination using the retrospective analysis consent form (X).

NOTES

The database is confidential:- the patient's National Haemophilia Database Number and date of birth only are sent to the UKHCDO database now held in Manchester (previously held in Oxford). In this way, only the clinician responsible for an individual patient's care will be aware of the names of his/her affected patients.

- The study will be co-ordinated through the Transfusion Transmitted Infection (TTI) Working Party of UKHCDO and regular updates will be reported to the UKHCDO advisory committee and the Department of Health.

- Normal routine histology will be performed in local hospitals. Analysis for vCJD will be performed by Professor James Ironside at the National CJD Surveillance Unit in Edinburgh.

- The Haemophilia Society is fully aware of this study.

- **Ethics**

  The study has received full MREC approval and enclosed is a copy of the London Multicentre Research Ethics Committee approval letter. (Appendix XI)

  Your attention is drawn to the 3rd page of the MREC approval letter under the heading 'LREC involvement' paragraphs 3 and 4 which state:

  > 'When such tasks are performed by centrally based researchers it should be assumed that the MREC has reviewed their competence to undertake the tasks and it is not necessary to inform the LREC of the contact details but only that the research will take place.
  > You are not required to wait for confirmation from the LREC before starting your research.'

  The study was approved according to the new guidelines issued by Professor Terry Stacey in November 2000 for research where there is no local researcher. These guidelines were distributed to all the LRECs within the UK and are available on the website www.corec.org.uk.

  You are required to inform your LREC of your participation in this study as a matter of courtesy only. You are not required to complete an Annexe D form.

A sample letter is enclosed (Appendix XII), which may be of assistance in doing so.

CONTACT DETAILS

- **The Clinical Co-ordinator of the study is:**

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- **UKHCDO Database in Manchester:**

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- **CJD Unit, Edinburgh:**

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