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Surveillance for asymptomatic carriage of abnormal prion protein in primary immunodeficiency patients
(Greater Manchester South N REC 05/Q1403/98);
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Prion Surveillance in Primary Immunodeficiency Patients

INFORMATION FOR PATIENTS

VERSION 7.0, 25/02/2016

We understand that you have been diagnosed with a primary immunodeficiency. We would like to invite you to take part in our research study on prion infection in antibody deficient patients, or to continue in the study if you have already joined.

Before you decide, we want you to understand why this research is being done and what participation involves. Please take time to read the following information carefully. If you are then interested and would like to find out more, ask your immunology care team who can then arrange a meeting with our study research nurse. **Your Immunology Team will contact you after a week, or you can do this by phone or in person, or by returning the attached slip to your Immunology Team.** The meeting will normally last about an hour.

The Prion Study Team

We are doctors, scientists and nurses from the National Creutzfeldt-Jakob Disease Research & Surveillance Unit (NCJDRSU), which is part of the University of Edinburgh, who have a special interest in prion disease. Prion diseases are a very rare group of diseases that affect nerve cells in the brain and spinal cord. Around 100 people are diagnosed with prion disease in the UK every year. Prion disease can exist in different forms, but the most common is Creutzfeldt-Jakob Disease (CJD). We provide doctors with information about prion disease, and advice on how to look after their patients. We also do research into the causes of prion disease. In this research project we are finding out more about the risks that may be associated with past treatment with blood products.

What is the purpose of this study?

Prion diseases are caused by a normal body protein (the prion protein) that has changed into an abnormal form. This usually happens “sporadically” by chance or for genetic reasons. However one type of prion disease, called variant Creutzfeldt-Jakob Disease (vCJD), has been linked to eating beef infected with a prion disease of cattle called bovine-spongiform encephalopathy (BSE). Very rarely, variant CJD has also been passed from person-to-person by blood transfusion. It may also be spread by treatment with certain blood products that were made from mixing plasma from several thousand donors.

We do not know how long it may take for disease symptoms to develop, but it may take several years. A total of 177 vCJD cases have been reported in the UK to date, the last occurring in 2012, although as many as 1 in 2000 people in the UK may be infected without signs of disease. Three of the vCJD patients are thought to have been infected by blood transfusion. Another two people are known to have been infected although they died of other causes. One person had received blood from a donor who later developed vCJD. The other, identified by the UK Haemophilia Centre Doctors Organisation, may have been infected as a consequence of past exposure to multiple batches of Factor VIII.

At the time of writing, there is also no blood test for prions that can reliably tell us if someone is infected with CJD before they develop symptoms of disease. Instead, prion infection can be confirmed by doing tests on small pieces of tissue that have previously been removed from the body, for example during biopsy procedures. If prion infection is found we also look at something called the codon-129 genotype, which can help us understand more about the infection as well as the diagnosis, for example if it is typical of vCJD or not.

The purpose of this study is to see if we can find any evidence of vCJD infection in people who were treated with certain blood products in the past. We will do this by following patients up over several years, and testing any available tissue (for example, the tissue left over from routine biopsies) and blood samples (when a test becomes available). This in turn will help health professionals in the future in protecting patient and public health.

How does this affect me?

Donated plasma is used to make a range of blood products, including immunoglobulin. Immunoglobulin has a variety of uses, including as a life-long treatment in patients with primary immunodeficiency. To date, there is no evidence that anyone has been infected with prions or developed vCJD through immunoglobulin treatment. The risk of this is thought to be very low because:

- Most intravenous immunoglobulins are manufactured from plasma donated in countries where BSE and vCJD are rare. Subcutaneous immunoglobulins are not affected.
- Only two intravenous immunoglobulin products (Vigam from the Bioproducts Laboratories and Human Immunoglobulin from the Scottish National Blood Transfusion Service) were made from plasma from UK donors. They were available for treatment between 1996 and 2000. None are still available for use.
- Unlike blood transfusions, each batch of immunoglobulin was manufactured from several thousand blood donations from people who have not developed vCJD. Even if a proportion of these were infected, this is thought to be very small, so any prion infection present would be very diluted and would be further reduced by the manufacturing process.
- Up to now, 11 batches of Vigam have included plasma from blood donors who later developed vCJD. In September 2004, risk assessments were conducted on primary immunodeficiency patients who had received these products; the results showed they had less than a one -in-a-hundred chance of being infected.

Although this is reassuring, the risk assessments were based on theoretical calculations and did not actually use tests to determine whether anyone was infected. So, since 2006 patients who received UK sourced immunoglobulin products between 1996 and 2000, have been invited to join this study so we can look for evidence of vCJD infection and confirm whether or not the risk of prion infection is greater than that in the general population.

Why have I been invited to take part?

You are being invited to take part in this study as you have previously been diagnosed with primary immunodeficiency and received UK sourced immunoglobulin products between December 1996 and December 2000.

Do I have to take part?

No. It is up to you to decide whether you wish to take part in the research or not. If you do wish to participate you will be asked to sign a consent form. You are still free to withdraw at any time and this will not affect your care, or your legal rights.

If you lose your capacity to make an informed decision about participation after you have joined the study, then your previous wishes will be respected and the study will continue under existing consent arrangements. In these situations we will check with your representative that they are happy with these arrangements. We will then ask you to renew your consent when capacity is regained.

What will happen if I take part?

If you agree to meet with the study research nurse, we will arrange a meeting with you at the time of your next routine appointment to discuss the study and what it means for you to take part. There are several parts to the research and you can contribute to any of them.

1. Exposure assessment & review

We would like to ask you some questions about your medical history and for your permission to review your medical records. This is so we can record your past immunoglobulin treatment, any transfusions of blood or other blood products you have received and surgery you have undergone, including operations and biopsies. In addition, we will ask you some questions about where you have lived and your occupation and whether you have any family history of neurodegenerative disease.

This information will help us assess the most likely source of your infection, should we find evidence of prion disease, as well as to identify any spare tissue samples that might be available for research.

2. Prion protein genotyping

If you agree, we will also ask whether you wish to donate some of your blood, so we can study what is called your prion protein “codon-129 genotype”. Your genes can affect your health in different ways. We all have a prion protein codon-129 genotype. It does not cause prion disease, and is a normal genetic variation. The test involves only one 2ml blood sample. Some of your genetic material (DNA) will be extracted from the blood sample and tested in our laboratory. Any remaining blood and DNA will be disposed of

after the end of the study, once investigations have been completed and they are no longer needed for the research.

3. Donation of blood for future testing

In addition, when we first meet you and every two years afterwards we will invite you to donate another 15ml of blood. The blood will be taken at your immunology clinic and then the samples sent in an anonymous form to the CJD Resource Centre at the UK National Institute for Biological Standards and Control (NIBSC), where they will be frozen and stored in a secure laboratory for future testing for evidence of prion infection, when an appropriate blood test becomes available. The samples will then be used, still in an anonymised form, for the future research and disposed of lawfully when they have served this purpose. An oversight committee will determine the specific conditions of the use of the samples before approving their use.

When tests do become available, the results will be reported to the Research team at NCJDRSU. We will not inform you if they have been tested or the results.

4. Tissue analysis

Tissue testing over a long period will allow us to identify whether there is evidence of prion infection and when this arose. We would like to collect samples from different parts of your body, if these become available. This includes samples from lymph node, tonsil, spleen, gut (includes the appendix), bone marrow trephine and brain. We hope to obtain these samples in two different ways:

A. Tissues from past operations or biopsies.

First of all, we would like to test samples of tissue that have been removed in the past. You may have had biopsies done previously to diagnose complications of your immune deficiency. Some of these tissues may still be available in the laboratory that did the testing at the time. If you agree, every year we will ask you if you have previously undergone surgery and search the hospital notes for past operations or biopsies to see if samples were taken. We will then ask the hospital if they can provide these and we will arrange for them to be tested. Any remaining tissue will be sent back to the laboratory at which it was originally stored.

B. Post-mortem examination

Secondly, if you were to die during the study, we invite you to consider donating post-mortem tissue samples for use in research. For any form of prion disease, post-mortem examination is the only way by which we can confirm the diagnosis. Post-mortem investigations can also help us find out if someone has an underlying vCJD infection even when they had no signs of disease. They can also detect infection that might not have shown up in the tissues from past operations.

What do the post-mortem investigations involve?

If you agree, then after death your body will be taken to the nearest hospital mortuary that can undertake the post-mortem examination. Here a pathologist, who is a doctor trained in tissue examination, assisted by highly skilled technicians, will examine the head and body. The brain, as well as the appendix, spleen, tonsil and lymph glands will be carefully removed and examined, and a wide range of samples will be taken before being returned to the body.

Because the distribution of prion infection in the body may vary a lot from person to person, and because parts of the body outside the brain can be affected by prion disease, a full post-mortem is preferable, but you can limit the samples to a certain region of the body or to certain organs if you prefer. The body will then be returned to the funeral director who will be responsible for the funeral.

After the examination the samples will be sent to us in Edinburgh, where they will be investigated by the study team for evidence of prion disease. These investigations involve a number of different tests and can take several weeks. Tissue used in the research would normally be lawfully disposed of after the end of the study, once investigations have been completed and they are no longer needed for the research. Samples from any patients that are suspected to be CJD or any other prionopathy will routinely be retained at NCJDRSU.

How is the post-mortem examination arranged?

In the event of your death we ask that your family and local team contact us so we can make arrangements for the post-mortem examination. For a research post-mortem, normally this will be conducted between one and four days after death and whilst we are unable to pay for funeral costs there should be no costs passed on to your family for transport arrangements to and from the mortuary.

Your representative will be asked to complete the hospital post-mortem authorisation form, which confirms your representative's support of your wishes to donate tissue for research. Throughout the process your family will be treated with great respect.

We appreciate that deciding whether or not you wish to have a post-mortem examination takes time. We are able to provide you with further information about what is involved and can discuss this with you whenever you would like. However you do not need to decide until you have also had the opportunity to discuss this with your relatives and you are ready. You should also make your decision known to your family and your GP, so they can understand what will happen in the event of your death.

5. Annual follow-up

We would like to follow your progress over the duration of the study. After our initial meeting you will be offered a 30 minute appointment with the study Research Nurse once every two years, with an annual telephone call inbetween to provide you with any new study related information, and the opportunity to discuss your continued participation. You may also contact us any time you would like.

What if you think I have prion infection?

This study is run on the basis that you would not be told the results of the research investigations. This is because if we find a positive result, we don't know what this may mean to the patient in terms of their chances of developing prion disease and no treatment is available. There is therefore a risk that this information would cause the patient more psychological harm than any possible benefit of knowing.

This means that if blood or tissue samples from the study give positive results, we will not tell the patient concerned and we will also not tell the doctors and nurses looking after the patient. However, we will make sure that the findings are fed back to the primary immunodeficiency community as a whole, and take advice from public health experts,

immunologists and patient support groups on how best to manage and reduce any ongoing risk. In doing so we will discuss the results, but your personal details will not be disclosed.

What if I have prion disease?

If a patient develops symptoms of dementia they would normally be referred by their doctor, or GP, to a local specialist. It is very unlikely that you will develop prion disease, however, if CJD or another form of prion disease is suspected then, with your clinician's approval, you would be referred to the dedicated surveillance team at NCJDRSU for further assessment, in line with standard referral procedures for new and suspect cases of CJD.

Will my taking part in the study be kept confidential?

Yes. The study is run by a team from the NCJDRSU, supported by medical statistics, computing and administrative staff. All staff are trained in data protection and have a professional duty of confidentiality. All the information we collect about you is held securely by the NCJDRSU, with access restricted to authorised personnel on a need-to-know basis.

To ensure that the study is being run correctly, we will ask for your consent for responsible representatives from the sponsors (University of Edinburgh and NHS Lothian) to access your medical records and data collected during the study, where it is relevant to your taking part in this research.

Will my doctors be informed about my participation?

Yes. With your consent, after our initial meeting we will send a letter to your GP and the consultant in charge of your care providing an outline of the study, letting them know that you are taking part and to request to see your medical notes.

What are the possible benefits of taking part?

By participating in this research you will be helping us better understand the risk of CJD associated with medical treatment. No one who has received immunoglobulin needs to be treated any differently from other patients, but finding that patients have been infected with prions from immunoglobulin may mean that public health precautions need to be taken in order to prevent infecting others.

What are the possible disadvantages and risks of taking part?

Our initial visit will take about one hour, during which time you will be able to discuss any aspects of the study and raise further questions. The blood samples will only be taken when other samples are required as part of your routine care, so there is no need to have extra needles. We will do our best to deal with any issues that worry you. You will also be given our contact details so that you can speak to us if you have research-related concerns.

Can I agree now and change my mind later?

Yes. It is possible to withdraw from any part of the study if you change your mind later on. You can also withdraw permission for any samples to be tested up until the time they are tested and your sample will be destroyed.

What happens when the study is finished?

This study involves the long-term follow-up of participants, and will end when testing the tissue samples in the final participant is completed. Blood and tissue samples that are held by NCJDRSU as part of the investigation record will be retained for up to 5 years after completion of the study and then disposed of lawfully if of no further value to this research. However tissue samples that show evidence of CJD or any other prionopathy will routinely be retained indefinitely by NCJDRSU. Information about you will be retained for a minimum of 5 years past the end of the study, and then it's retention will be reviewed with a view to permanent disposal or long-term archiving for future research, audit or as part of your medical record.

What will happen to the results of the study?

The results of the study will be written up for publication as journal articles and presented at national conferences and worldwide. We will be able to give you an overview of the results and explain how to gain access to the full report. We will also report our findings to the funding bodies, relevant expert panels and other stakeholders. You will also be told about new developments during your routine visits to your Immunology team or annual research clinic appointment. You will not be identifiable in any reports or published results.

Who is overseeing the research?

The study is lead by the NCJDRSU under the co-sponsorship of the University of Edinburgh and NHS Lothian and with the technical and scientific oversight of an external steering committee. All research in the NHS is considered by an independent group of people, called a Research Ethics Committee (REC). A favourable ethical opinion has been obtained from Greater Manchester South N REC. NHS management approval has been given by participating NHS Trusts.

What if there is a problem?

If you have a concern about any aspect of this study, please contact the NCJDRSU study team who will do their best to answer your questions. If you wish to make a formal complaint then this can be done through the normal National Health Service complaints mechanism, details of which can be obtained at your hospital. Alternatively you may contact NHS Lothian:

NHS Lothian Complaints Team
2nd Floor, Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Tel: 0131 536 3370
Email: craft@nhslothian.scot.nhs.uk

What if I have already joined the study?

This study began in 2006 under the sponsorship of Central Manchester and Manchester Children's University Hospitals NHS Trust. In April 2015 management of the study was transferred to NCJDRSU (Edinburgh); now the study has transferred we would like to invite you to continue.

Please read this information sheet before deciding, and if you would like to consider continuing, our study research nurse will meet up with you at a routine appointment to explain the changes to the study arrangements that may affect you and answer questions. If you decide to go ahead, you will need to sign the updated version of the consent form. If you decide not to continue then simply tell your local immunology team at your next appointment.

Thank you for taking the time to read this information leaflet.

If you would like further information please contact one of the study team:

Mrs Kudzai Karekwaivanane (Research Nurse)
Professor Richard Knight (Consultant Neurologist)
Dr Anna Molesworth (PhD, Study Chief Investigator)

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Independent advice about the study is available from:

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This study is funded by the Department of Health Policy Research Programme.





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REPLY SLIP

Prion Surveillance in Primary Immunodeficiency Patients

After you have read the information in this leaflet, please take time to consider whether you want further information on the study "Prion surveillance in primary immunodeficiency patients". Please use this sheet to let us know whether you want to go ahead and have an appointment with the research nurse. Having an appointment with the research nurse does not commit you to taking part in the study.

I would like to have an appointment with the research nurse to receive further information about the study and consider taking part.

I do not want an appointment with the research nurse or any further information on the study.

Name:

Address :.....

Signed :..... Date:.....

Please return this sheet to your local Immunology Team:
Contact details: