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PRION SURVEILLANCE IN PRIMARY IMMUNODEFICIENCY PATIENTS: Steering Group Annual Progress Report May 2018

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1. Background

Variant Creutzfeldt - Jakob disease (vCJD) is a very rare disease, associated with an abnormal form of a naturally occurring protein (the prion protein), the presence of which can be detected in certain body tissues. Most cases of vCJD have been attributed to eating bovine spongiform encephalopathy (BSE) contaminated meat. However infection may be spread through blood transfusion or treatment with certain plasma products. Two intravenous immunoglobulin products, BPL Vigam and SNBTS Human Immunoglobulin, were available for treatment between December 1996 and December 2000. The products were made from plasma from UK donors and had a variety of uses, including as a treatment for patients with primary immunodeficiency (PID).

For PID patients treated with these products there is a low risk of their being infected with vCJD in addition to the background risk through eating meat. By following-up these patients over several years, and testing any available tissue (for example, the tissue left over from routine biopsies) and blood (when a suitable blood test becomes available) for the abnormal prion protein that causes prion disease, this study can look for evidence of vCJD in patients with PID, assess if the infection was acquired through the use of these products and consider the wider implications to patients' and public health.

At the time of writing, a total of 178 cases of vCJD have been reported in the UK, including three blood transfusion-associated cases. A further 53 cases have been reported in other countries.

2. Aims & Objectives

A. To identify whether there is evidence of abnormal prion protein/vCJD in the blood and/or body tissues of primary immunodeficiency patients exposed to UK sourced immunoglobulin between 1996 and 2000.

B. To describe the type of infection, the timing of infection relative to exposure, cumulative dose of immunoglobulin and codon 129 genotype, and the clinical, pathological and epidemiological characteristics of the patients involved (and how these may differ from other patients)

C. To assess the risk of infection with vCJD through dietary exposure to infected meat, exposure to blood/blood products and other iatrogenic routes and the likelihood that vCJD infection was acquired through the use of UK sourced immunoglobulin.

D. To determine how blood tests results (when such a test becomes available) correlate with the results from examining tissues.

3. Summary of progress

The study began in 2006 under sponsorship of Central Manchester University Hospitals NHS Foundation Trust and transferred to the University of Edinburgh in April 2015. Changes were subsequently made to the protocol and associated study instruments with the aim of simplifying the research process, with participating centres and patients informed.

A total of 79 patients have been recruited since the study started in 2006, contributing 1414 person-years of observation following their first exposure to UK-sourced immunoglobulin. Of these, 55 patients are alive and currently participating in the study.

To date there has been no evidence of vCJD/abnormal prion protein in this patient group, however we remain vigilant to this possibility.

4. Recruitment

Patients with PID who received UK sourced immunoglobulin products (BPL Vigam and/ or SNBTS Human Immunoglobulin) between December 1996 and December 2000 are eligible for inclusion in the study, with informed consent. Based on UK PID registry figures (personal communication, Cathy Bangs, 31/03/2015), approximately 175 patients are thought to have been exposed to UK sourced immunoglobulin between 1996 and 2000. A total of 79 patients, registered in 16 immunology centres have participated in the study to date. Of these 16 have died, with a further 8 lost to follow-up (including 2 withdrawals), leaving 55 participants currently registered with the study over 12 sites.

Participation in the study is voluntary and not all centres or patients have agreed to be involved. We continue to make regular contact with study participants and their immunology teams as part of the routine follow-up of this patient group. Of the 55 patients currently registered with the study, 53 have been visited by the Edinburgh study team and all agreed to their continued participation in the study. The remaining 2 patients have meetings with the research nurse being scheduled over the next few months.

Working closely with the UK Primary Immunodeficiency Network (UK PIN) of clinicians and the patient and family support group PID UK, the wider patient community have been informed about the study and asked to contact their care team or the study researchers if they would like to consider joining the study or find out more.

5. Participant characteristics.

All participants had been exposed to UK sourced immunoglobulin, with 8 known to have been treated with implicated batches. These have now been followed up for approximately 1414 person-years following first exposure to UK sourced immunoglobulin. In this time, no patients have shown any clinical features of vCJD. Participant characteristics are provided in Table 1.

6. Tissue investigations

At the time of writing, a total of 44 participants have donated 213 tissue specimens for examination for evidence of abnormal prion protein following their first exposure to UK sourced immunoglobulin. Of these 34 specimens from 19 patients were considered of sufficient quality, based on standard haematoxylin and eosin-staining, to inform the analyses (five or more lymphoid follicles or brain tissue available, see Table 2). These included 17 specimens from 5 post-mortem examinations. Based on the histopathology, as well as immunohistochemistry and PET blot analysis, no patients showed any pathological features of vCJD or evidence of abnormal prion protein.

All participants have agreed to donate blood for storage for future testing when such a test becomes available.

7. Publications & reports

1. Helbert MR, Bangs C, Bishop M, Molesworth A, Ironside J.(2015). No evidence of asymptomatic variant CJD infection in immunodeficiency patients treated with UK-sourced immunoglobulin. Vox Sang. 2015 Nov 3. doi: 10.1111/vox.12358. [Epub ahead of print]

2. Hughes E, Molesworth A. Prion infection in antibody deficient patients. UK Primary Immunodeficiency Network Conference 2015, 19-20th November 2015. Belfast (Northern Ireland). [Poster presentation]

3. PID UK (2016). New home for the prion infection surveillance project. PID UK e-bulletins 2016 August update, available at http://www.piduk.org/static/media/up/PIDUKupdateAugust.pdf

4. PID UK (2017). Celebrating Rare Disease Day 2017: Prion surveillance in primary immunodeficiency patients. PID UK Rare Disease Bulletin, 2016 March, available at: http://e-news.ipopi.org/wp-content/uploads/2017/03/PIDUK_Rare-Disease-Bulletin.pdf

5. Karekwaivanane K, C.Bangs, D.Ritchie, S.Lowrie, K.Ladhani, J.Cooper, M.Helbert and A.Molesworth. Prion Surveillance in Primary Immunodeficiency Patients Exposed to UK-Sourced Immunoglobulin. European Society for Immunodeficiencies 2017 Meeting, September 11-14th 2017. Edinburgh (UK). [Poster]

6. K.Karekwaivanane, C.Bangs, D.Ritchie, S.Lowrie, K.Ladhani, J.Cooper, M.Helbert and A.Molesworth. Karekwaivanane K. Prion Surveillance in Primary Immunodeficiency Patients Exposed to UK-Sourced Immunoglobulin PRION 2017, May 23rd-26th 2017. Edinburgh (UK). [Poster]

Table 1. Participant characteristics (n=78, data to 15th May 2018)

Characteristic	All participants (n=78) Number	(%)
Sex		
Male	46	(59%)
Female	32	(41%)
Year of birth		
before 1940	6	(8%)
1940-59	26	(33%)
1960-79	28	(36%)
1980+	18	(23%)
Diagnosis		
CVID	56	(72%)
XLA	14	(18%)
Other	8	(10%)
Codon-129**		
MM	35	(45%)
MV	30	(39%)
VV	12	(16%)
Not available	1	
Country of current / last known treatment		
England	43	(55%)
Scotland	30	(38%)
Wales	5	(6%)
Total person-years of observation (time from first exposure to last follow-up/death)***	1413.9 (mean=18.1, sd 2.8, range 8.9-21.3)	

* total excludes information relating to 1 patient who requested samples and data be withdrawn from the study.

** codon-129: MM (methionine homozygous), VV (valine homozygous), MV (heterozygous); genotype is not available for one participant

*** Pyrs of observation: first exposure estimated as the mid-point of the potential exposure period where missing

Table 2: Tissue investigations (n=78 participants, data to 15th May 2018)[a]

	Total number of participants	Total number of specimens	Number of specimens by time from first exposure to tissue specimen collection/death (yrs)			
			0-4	5-9	10-14	15+
Total participants	78					
With specimens available	44	213				
Of suitable quality[b]	19	34				
Total specimens suitable for analysis[b]	19	34	10	6	6	12
a) By source						
biopsy/relevant surgery	15	17				
autopsy	5	17				
b) By tissue type						
Brain, pituitary, spinal cord	6	12	0	3	1	8
Tonsil	0	0	0	0	0	0
Lymph nodes	6	6	1	2	2	1
Spleen	9	9	5	1	0	3
Appendix	1	1	1	0	0	0
Other gut	5	6	3	0	3	0
Bone marrow trephine	0	0	0	0	0	0
Other (pre 1st April 2015)[c]	0	0	0	0	0	0

Footnotes

[a] Specimens collected following the participant's first exposure to UK sourced immunoglobulin.

[b] Specimens suitable for analysis are those meeting laboratory quality control criteria. Negative results are based on specimens with 5 or more lymphoid follicles or analysis of brain tissue. Average time from first exposure to specimen collection= 10.5 yrs (n=34 specimens, sd 5.8 yrs, range 0-20 yrs)

[c] Other specimens analysed before 1st April 2015 include: skin, lung, liver, nasal mucosa, csf and bone marrow aspirate. These specimens were of insufficient quality and their collection was subsequently dropped.