National CJD Research & Surveillance Unit
Western General Hospital,
Edinburgh, EH4 2XU

PRION SURVEILLANCE IN PRIMARY IMMUNODEFICIENCY PATIENTS:
Steering Group Annual Progress Report
November 2023

Author: Professor Richard Knight (CI), on behalf of the Study Management Team
Date of report: 13 November 2023

Management Team
Professor Richard Knight, Lead Neurologist, NCJDRSU (Chief Investigator)
Mrs Kudzai Karekwaivanane, Clinical Research Nurse, NCJDRSU
Dr Lovney Kanguru, Senior Epidemiologist, NCJDRSU
Dr Kaetan Ladhani, Scientist, NIBSC
Ms Suzanne Lowrie, Laboratory manager, NCJDSRU
Professor Colin Smith, Lead Neuropathologist, NCJDRSU

Steering Committee
Professor Marc Turner, SNBTS (Chair)
Mrs Rae McNairney, PIDUK
Dr Matthew Buckland, UKPIN
Dr Jillian Cooper, NIBSC

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 this report, 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. A total of 80 patients have been recruited since the study started in 2006, contributing 1699.4 person-years of observation following their first exposure to UK-sourced immunoglobulin. Of these, 46 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 80 patients, registered in 17 immunology centres have participated in the study to date. Of these 24 have died, with a further 10 lost to follow-up (including 3 withdrawals), leaving 46 participants currently registered with the study over 12 sites. Currently, recruitment of new sites and patients is ongoing. We continue to make regular contact with study participants and their immunology teams (face-to face and via telephone) as part of the routine follow-up of this patient group.

Participation in the study is voluntary. Working closely with the network of clinicians, the British Society of Immunology –Clinical Immunology Professional Network (BSI-CIPN) and the primary immunodeficiency patient and family support group (Immunodeficiency 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 information.

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 1699.4 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 this report, a total of 47 participants had donated 248 tissue specimens for examination for evidence of abnormal prion protein following their first exposure to UK sourced immunoglobulin. Of these, 53 specimens from 23 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 33 specimens from 8 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. K Karekwaivanane, L. Kanguru, S Lowrie, K Ladhani, J Cooper, R. Knight. Prion surveillance in primary immunodeficiency patients exposed to UK-sourced immunoglobulin. British Society for Immunology- Clinical Immunology professional network (BSI-CIPN) Conference, 4th-5th December, Belfast, UK

2. L Kanguru, K Karekwaivanane, S Lowrie, K Ladhani, J Cooper, C Smith, R Knight. UK-Sourced Immunoglobulin: Surveillance for Asymptomatic Carriage of Abnormal Prion Protein in Primary Immunodeficiency Patients Exposed between 1996 and 2000. BBTS conference, 10th -12th October 2023, Harrogate, UK [Poster]

3. L Kanguru, K Karekwaivanane, S Lowrie, K Ladhani, J Cooper, C Smith, R Knight. Surveillance for Asymptomatic Carriage of Abnormal Prion Protein: Primary Immunodeficiency Patients Exposed to UK-Sourced Immunoglobulin. Prion conference, 16th -19th October 2023, Faro, Portugal [Poster]

4. Immunodeficiency UK (2023) Report from the Prion Surveillance study August 2023, available at: http://www.immunodeficiencyuk.org/static/media/up/Prionsurveillance%20study_Aug%202023.pdf

5. L. Kanguru, K. Karekwaivanane, S. Lowrie, K. Ladhani, J. Cooper, C. Smith, R. Knight. Primary Immunodeficiency Patients Exposed to UK-Sourced Immunoglobulin: Surveillance for Asymptomatic Carriage of Abnormal Prion Protein. ISBT congress, 17-21st June 2023, Gothenburg, Sweden. [Poster]

6. K Karekwaivanane, L. Kanguru, S Lowrie, K Ladhani, J Cooper, D. Ritchie, C. Smith and R. Knight. Prion Surveillance in Primary Immunodeficiency patients Exposed to UK-sourced Immunoglobulin Immunology & Allergy Nurses' conference (IANG), May 15th-16th 2023, Cardiff (UK). [Oral presentation]

7. K Karekwaivanane, L. Kanguru, S Lowrie, K Ladhani, J Cooper, D. Ritchie, C. Smith and R. Knight. Prion Surveillance in Primary Immunodeficiency patients Exposed to UK-sourced Immunoglobulin UK PIN 2021, November 2-3rd Sheffield (UK). [Poster]

8. K Karekwaivanane, L. Kanguru, S Lowrie, K Ladhani, J Cooper, R. Knight, C. Smith and A.Molesworth. Prion Surveillance in Primary Immunodeficiency patients Exposed to UK-sourced Immunoglobulin. UK PIN 2019, December 5-6th Liverpool (UK). [Poster]

9. PID UK (2019) Report from the Prion Surveillance Study May 2019, available at: http://www.piduk.org/whatarepids/treatment/immunoglobulinreplacementtherapy/prionsurveillancestudyreport2019

10. K Karekwaivanane, S Lowrie, K Ladhani, J Cooper, D Ritchie, C Smith and A.Molesworth. Prion Surveillance in Primary Immunodeficiency Patients Exposed to UK-Sourced Immunoglobulin UK PIN 2017, December 7-8th Brighton (UK). [Poster]

11. 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]

12. 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]

13. 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

14. 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

15. 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]

16. 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]

Table 1. Participant characteristics (n=79, data to 31st October 2023) *

Characteristic	All participants (n=79) Number	(%)
Sex		
Male	46	(58%)
Female	33	(42%)
Year of birth		
before 1940	6	(7%)
1940-59	26	(33%)
1960-79	29	(37%)
1980+	18	(23%)
Diagnosis		
CVID	56	(71%)
XLA	14	(18%)
Other	9	(11%)
Codon-129**		
MM	36	(46%)
MV	30	(39%)
VV	12	(15%)
Not available	1	
Country of current / last known treatment		
England	43	(54%)
Scotland	30	(38%)
Wales	6	(8%)
Total person-years of observation (time from first exposure to last follow-up/death)***	1699.4 (mean=21.5, sd 4.8, range 8.9-26.7)	

* total excludes information relating to 1 patient who requested all their 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 who was lost to follow-up before bloods were taken)

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

Table 2: Tissue investigations (n=79 participants, data to 31st October 2023)[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	79					
With specimens available	47	248				
Of suitable quality[b]	23	53				
Total specimens suitable for analysis[b]	23	53	10	7	6	30
a) By source						
biopsy/relevant surgery	17	20				
autopsy	8	33				
b) By tissue type						
Brain, pituitary, spinal cord	8	20	0	3	1	16
Tonsil	1	1	0	0	0	1
Lymph nodes	8	11	1	2	2	6
Spleen	10	12	5	1	0	6
Appendix	2	2	1	1	0	0
Other gut	6	7	3	0	3	1
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. Some participants provided more than 1 specimen. 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= 14.2 yrs (n=53 specimens, sd 7.2 yrs, range 0-25.5 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.