23rd ANNUAL REPORT 2014

CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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

www.cjd.ed.ac.uk

Table of Contents

Section

1

SUMMARY

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Research & Surveillance Unit (NCJDRSU) became a WHO Collaborative Centre for Reference and Research on the surveillance and epidemiology of human transmissible spongiform encephalopathies (TSEs). In September 2001, the National Care Team was formed in response to concerns regarding the care of CJD patients. The team currently comprises two care coordinators (who are senior nurses) with secretarial and clinical neurological support from within the NCJDRSU where it is based.

The information provided in this 23rd Annual Report continues to indicate that the annual mortality rates for sporadic CJD (sCJD) has remained around 1.4/million since 2008 (the data for 2014 may still be incomplete). Detailed clinical and epidemiological information has been obtained for the great majority of patients. Although the general autopsy rate in the UK is low, it remains relatively high in suspected cases of CJD (being around 60% of all referred cases to the NCJDRSU). The number of brain specimens examined for sCJD in the neuropathology laboratory in 2014 was 30 (compared with 32 in 2013).

In 1990-2014 average annual mortality rates from sCJD in England, Wales, Scotland and Northern Ireland were, respectively, 1.07, 1.33, 1.11 and 0.83/million/year. The differences between these rates are not statistically significant ($p=0.5$). The mortality rates from sCJD in the UK are comparable to those observed in most other European countries and elsewhere in the world, including countries that are free of BSE.

Up to 31st December 2014, 177 cases of definite or probable variant CJD (vCJD) had been identified in the UK (122 definite and 55 probable who did not undergo post mortem). All 177 cases have died. The clinical, neuropathological and epidemiological features of the cases of vCJD are remarkably uniform and consistent with previous descriptions. Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - all 160 clinically affected definite and probable cases of vCJD with available genetic analysis have been methionine homozygotes. Analysis of vCJD diagnoses and deaths from January 1994 to December 2011 indicates that a peak has passed. While this is an encouraging finding, the incidence of vCJD may increase again, particularly if different genetic subgroups with longer incubation periods exist. The identification of an individual of the *PRNP*-129 MV genotype as a possible case of vCJD (reported in the NCJDRSU 17th Annual Report, 2008) and, in a separate case, disease-related prion protein in the spleen of a clinically unaffected blood recipient (reported in 2004) is consistent with such a hypothesis. These cases, along with the report of the prevalence of abnormal prion protein in the large study of appendix and tonsil tissues (two of the positive specimens from VV individuals) suggests the possibility of a greater number of asymptomatic infections (either preclinical or subclinical) in the population than might be indicated by the present numbers of confirmed clinical cases.

To help prevent any possible spread of CJD between people, we continue to ask clinicians to refer all new suspect CJD cases to their local infection control and health protection teams. This is important as a local response may be required with respect to limiting potential secondary transmission, infection control and other issues that may arise over time concerning the protection of the wider community. The NCJDRSU continues to assist local health protection teams in local audit and investigations of cases in response to local concerns.

The NCJDRSU continues to collaborate with health departments and public health teams throughout the UK in relation to a range of activities, for example, in relation to the follow up of those identified as at increased risk of CJD. The activities of the NCJDRSU are strengthened by collaboration with other surveillance projects, including the Transfusion Medicine Epidemiology Review and the study of Progressive Intellectual and Neurological Deterioration in Children. The collaboration of our colleagues in these projects is greatly appreciated; the effectiveness of this collaboration allowed the identification in 2003 of a case of vCJD associated with blood transfusion and the identification in 2004 of disease-related PrP in the spleen of a recipient of blood donated by someone incubating vCJD. A patient was also identified in 2010 who had evidence of vCJD infection in the spleen (but no evidence of clinical vCJD), considered probably due to blood products (treatment for haemophilia).

The relatively recently described form of prion disease originally termed Protease Sensitive Prionopathy and renamed Variably Protease Sensitive Prionopathy, is of uncertain nosological significance but is presently considered a form of sporadic prion disease, alongside sCJD. The NCJDRSU has so far identified at total of 9 such cases in the UK and is continuing to monitor this form of disease.

The data concerning CSF RT-QuIC are given in Section 3.5; the sensitivity of CSF RT-QuIC for a diagnosis of sCJD is comparable with that of CSF 14-3-3. The specificity is superior to that of CSF 14-3-3 with no positives in cases with a confirmed alternate diagnosis.

The success of the National CJD Research & Surveillance Unit continues to depend on the extraordinary level of co-operation from the neurology and neuropathology communities and other medical and paramedical staff throughout the UK. Ongoing support is provided by the Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine. We are also particularly grateful to the relatives of patients for their collaboration.

Section

2

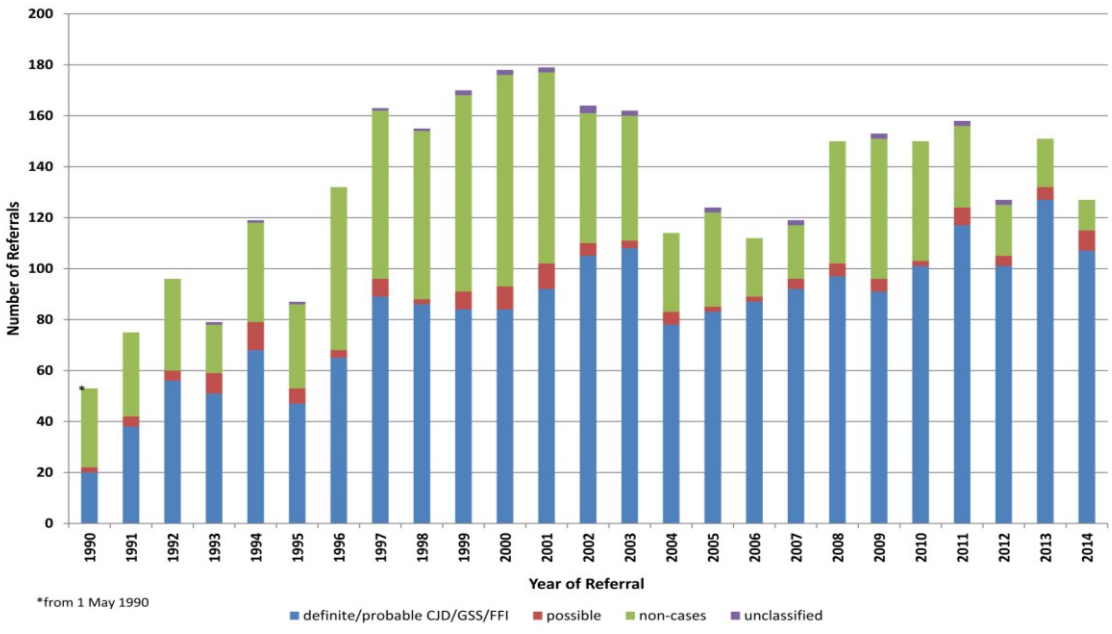
CLINICAL SURVEILLANCE

The national surveillance of CJD in the UK was initiated in May 1990. Surveillance is funded by the Department of Health, UK and by the Scottish Government Health Department. The NCJDRSU aims to monitor characteristics of CJD, specifically sCJD and vCJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings in relation to UK cases of sCJD and vCJD as well as genetic and iatrogenic forms of disease referred up to 31st December 2014 (with data ascertained up to 31st May 2015). Mortality data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective mortality data are available from 1985. Case definitions for the various types of CJD can be found at www.cjd.ed.ac.uk/documents/criteria.pdf. Cases classified as definite or probable are included in all analyses.

2.1 Referrals to NCJDRSU

The NCJDRSU receives referrals of suspect cases of CJD and a proportion of these will turn out not to have CJD. Referrals of suspect cases increased after the present surveillance system began in 1990, particularly following the description of vCJD in 1996. Numbers of referrals fluctuate over time, and may be attributed to variation in case ascertainment and reporting practice, including changes in the number of non-CJD cases referred to the NCJDRSU (see Figure 1)

Figure 1 Referrals to NCJDRSU: 1 May 1990 – 31st December 2014



2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2014, 2012 cases of sCJD were identified in the UK, of which 24 cases were alive on 31st December 2014 and one case moved abroad after diagnosis and is therefore lost to follow-up. Of these UK cases, 1425 (71%) were classified as definite cases with the remainder classed as probable. Seven further cases have been identified: 3 in Jersey, 2 in the Isle of Man and 2 cases who were repatriated to the UK when they became ill but had been living abroad. These 7 cases are not included in the following UK analyses.

Figure 2 shows the annual mortality rates from sCJD for the UK between 1985 and 2014. The number of deaths identified each year has increased over time. A similar phenomenon has been observed in other European countries, and may reflect improved case ascertainment, particularly in those aged over 70 years.

Figure 2 Mortality Rates from sCJD, UK, 1985-2014

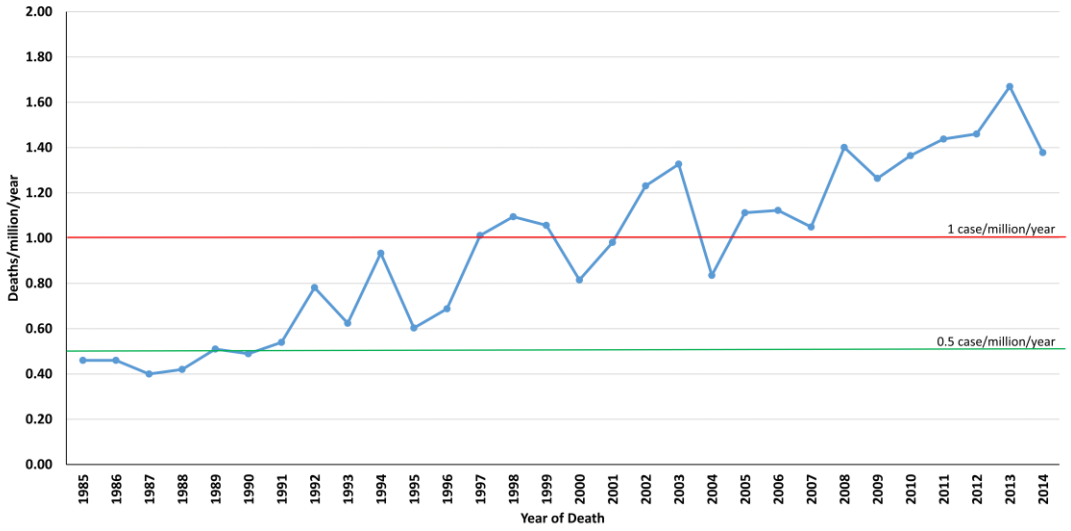
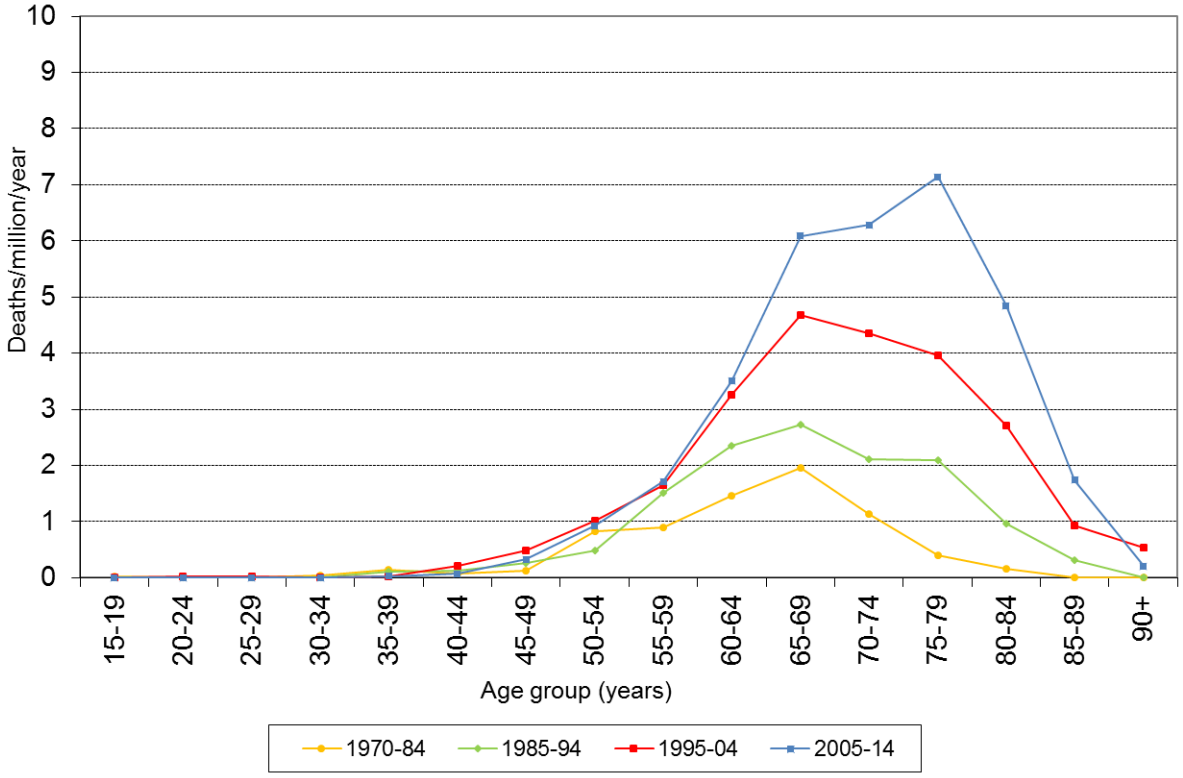


Figure 3 shows average annual age-specific mortality rates over the time periods 1970-1984, 1985-1994, 1995-2004 and 2005-2014. These data also emphasise the very small numbers of cases of sCJD occurring in individuals aged <50 years. The median ages of cases at death during these four time periods were 63, 66, 67 and 69 years, respectively. In all four time periods, the mortality rates below 40 years of age were extremely low (< 0.02/million/year). Thereafter, in all four periods, the mortality rates increased up to ages 65-79 years and then declined. This decline might be explained by an under-ascertainment in the most elderly. Comparison between the different time periods, indicate an increase in age-specific recorded mortality over time in all age groups over 50. These observations are consistent with improved case ascertainment in all ages over 50 years, but with the greatest increase occurring in the elderly.

Figure 3 **Age-specific mortality rates from sporadic CJD in the UK 1970-2014 (note: from 1970-1984 only England and Wales, thereafter UK)**



1970-1984 Mortality rates calculated using mid-1981 England & Wales population estimates based on the 1981 Census
1985-1994 Mortality rates calculated using mid-1991 UK population estimates based on the 1991 Census
1995-2004 Mortality rates calculated using mid-2001 UK population estimates based on the 2001 Census
2005-2014 Mortality rates calculated using mid- 2011 UK population estimates based on the 2011 Census

Geographical distribution of sCJD

Over the period 1990-2014 the average crude annual mortality rates from sCJD per million population were 1.07 in England, 1.33 in Wales, 1.11 in Scotland and 0.83 in Northern Ireland (Tables 1a and 1b). When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant (p=0.5).

Age- and sex- standardised mortality ratios (SMRs) for the 12 government office regions of the UK for the period 1st January 1990 to 31st December 2014 were calculated (Figure 4). An SMR of 100 equates to the national average mortality rate; an SMR above or below this value reflects relative high or low mortality, respectively. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant (p=0.6).

Figure 4 Standardised sporadic CJD mortality ratios (SMRs)
1 January 1990 - 31 December 2014, by region of residence at death

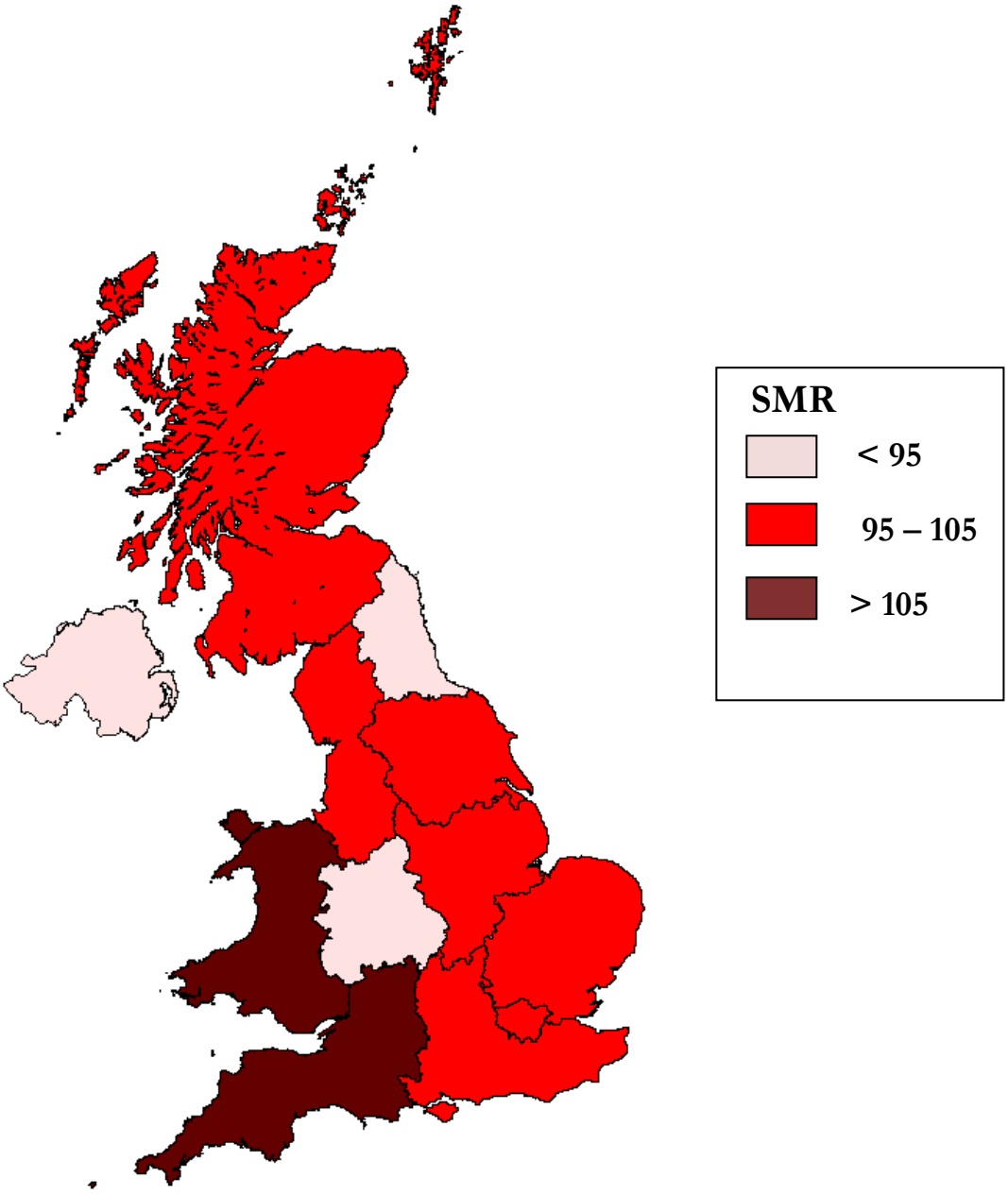


Table 1a Deaths from definite and probable sporadic CJD shown by region and local authority of residence at death: 1st January 1990 to 31st December 2014

ENGLAND	No. of cases	Mortality Rate*	ENGLAND	No. of cases	Mortality Rate*
North East	**57**	**0.90**	**East**	**154**	**1.14**
Darlington UA	2		Luton UA	3	
Hartlepool UA	2		Peterborough UA	2	
Middlesbrough UA	1		Southend-on-Sea UA	5	
Redcar & Cleveland UA	3		Thurrock UA	4	
Stockton-on-Tees UA	2		Bedfordshire	12	
Durham	8		Cambridgeshire	9	
Northumberland	8		Essex	48	
Tyne & Wear	31		Hertfordshire	20	
			Norfolk	28	
North West	**189**	**1.12**	Suffolk	23	
Blackburn with Darwen UA	6				
Blackpool UA	3		**London**	**153**	**0.84**
Halton UA	3		Inner London	43	
Warrington UA	8		Outer London	110	
Cheshire	17				
Cumbria	18		**South East**	**228**	**1.14**
Greater Manchester	61		Bracknell Forest UA	3	
Lancashire	31		Brighton and Hove UA	1	
Merseyside	42		Isle of Wight UA	3	
			Medway UA	3	
Yorkshire and the Humber	**130**	**1.04**	Milton Keynes UA	3	
East Riding of Yorkshire UA	8		Portsmouth UA	3	
Kingston Upon Hull, City of UA	4		Reading UA	3	
North East Lincolnshire UA	5		Slough UA	1	
North Lincolnshire UA	4		Southampton UA	3	
York UA	6		West Berkshire UA	6	
North Yorkshire	21		Windsor and Maidenhead UA	4	
South Yorkshire	35		Wokingham UA	3	
West Yorkshire	47		Buckinghamshire	11	
			East Sussex	18	
East Midlands	**110**	**1.05**	Hampshire	38	
Derby UA	7		Kent	45	
Leicester UA	9		Oxfordshire	21	
Nottingham UA	6		Surrey	28	
Rutland UA	1		West Sussex	31	
Derbyshire	22				
Leicestershire	19		**South West**	**166**	**1.34**
Lincolnshire	17		Bath & North East Somerset UA	5	
Northamptonshire	8		Bournemouth UA	7	
Nottinghamshire	21		Bristol, City of UA	10	
			North Somerset UA	9	
West Midlands	**130**	**0.98**	Plymouth UA	10	
Herefordshire, County of UA	4		Poole UA	3	
Stoke-on-Trent UA	2		South Gloucestershire UA	11	
Telford and Wrekin UA	2		Swindon UA	2	
Shropshire	8		Torbay UA	3	
Staffordshire	33		Cornwall and Isles of Scilly	21	
Warwickshire	7		Devon	20	
West Midlands (Met County)	56		Dorset	16	
Worcestershire	18		Gloucestershire	16	
			Somerset	21	
			Wiltshire	12	
TOTAL FOR ENGLAND	**1318****	**1.07**			

* number of deaths/million/annum based on mid-2001 population estimates in England (source: ONS) over the 25 -year period of the study. Postcode of residence obtained from AFD Postcode Plus.

**address for one case not known

Table 1b Deaths from definite and probable sporadic CJD: Wales, Scotland and NI 1st January 1990 to 31st December 2014

WALES†	No. of cases	WALES†	No. of cases
Isle of Anglesey	4	Neath Port Talbot	1
Gwynedd	6	The Vale of Glamorgan	3
Conwy	6	Cardiff	7
Denbighshire	1	Bridgend	2
Flintshire	2	Rhondda, Cynon, Taff	7
Wrexham	5	Merthyr Tydfil	3
Powys	13	Caerphilly	8
Ceredigion	3	Blaenau Gwent	0
Pembrokeshire	2	Torfaen	4
Carmarthenshire	4	Monmouthshire	3
Swansea	9	Newport	4
TOTAL FOR WALES (MORTALITY RATE*)	**97 (1.33)**	†unitary authorities	

SCOTLAND†	No. of cases	SCOTLAND†	No. of cases
Aberdeen City	6	Highland	2
Aberdeenshire	10	Inverclyde	3
Angus	1	Midlothian	1
Argyll & Bute	3	Moray	4
Clackmannanshire	2	North Ayrshire	4
Dumfries & Galloway	3	North Lanarkshire	6
Dundee City	6	Orkney Islands	0
East Ayrshire	2	Perth & Kinross	1
East Dunbartonshire	3	Renfrewshire	6
East Lothian	3	Scottish Borders	3
East Renfrewshire	1	Shetland Islands	3
Edinburgh, City of	20	South Ayrshire	4
Eilean Siar	0	South Lanarkshire	7
Falkirk	5	Stirling	3
Fife	9	West Dunbartonshire	2
Glasgow City	13	West Lothian	4
TOTAL FOR SCOTLAND (MORTALITY RATE*)	**140 (1.11)**	†council areas	

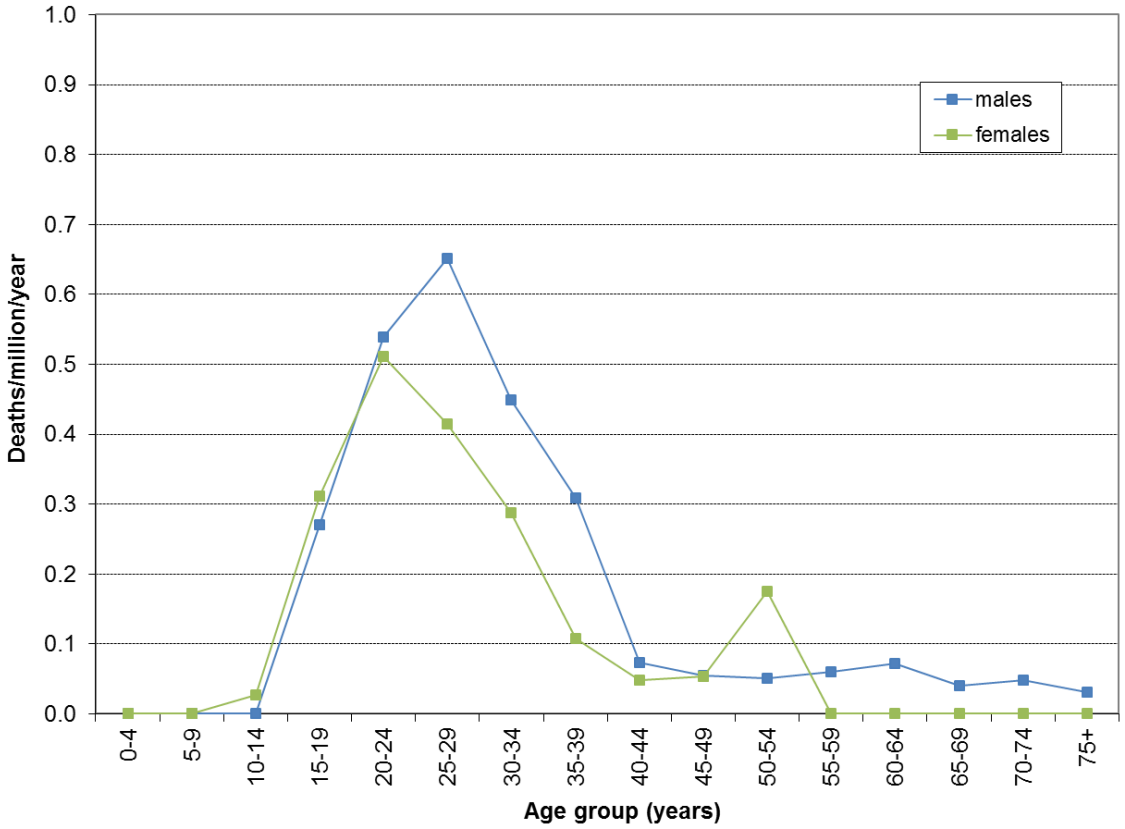
NORTHERN IRELAND†	No. of cases	NORTHERN IRELAND†	No. of cases
Antrim	3	Down	3
Ards	1	Dungannon	0
Armagh	1	Fermanagh	0
Ballymena	0	Larne	1
Ballymoney	1	Limavady	0
Banbridge	1	Lisburn	5
Belfast	8	Magherafelt	0
Carrickfergus	0	Moyle	0
Castlereagh	0	Newry & Mourne	1
Coleraine	2	Newtownabbey	0
Cookstown	1	North Down	0
Craigavon	4	Omagh	1
Derry	1	Strabane	1
TOTAL FOR N IRELAND (MORTALITY RATE*	**35 (0.83)**	†district council areas	

* based on mid-2001 population estimates for unitary authorities in Wales, council areas within Scotland and district council areas in Northern Ireland (ONS) over the 25-year period of the study. Postcode of residence obtained from AFD Postcode Plus.

2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2014, 177 cases of definite or probable vCJD had been identified in the UK (122 definite and 55 probable cases who did not undergo post mortem; no cases still alive). Seventy-five (43%) of the 176 cases were female and 102 (58%) were male. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 67 years for the median age at onset and 68 years for the median age at death for sCJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2014 are shown in Figure 5. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-114) compared with a median duration of illness for cases of sCJD of 4 months (range 1 to 74) during the period 1990-2014.

Figure 5 Age- and sex-specific mortality rates from variant CJD in the UK 1 May 1995 - 31st December 2014



Mortality rates calculated using ONS mid-2001 population estimates

All definite and probable cases of vCJD with genetic analysis have been *PRNP*-129 MM individuals (a single case of possible vCJD with an MV genotype was described in the Seventeenth Annual Report 2008 (www.cjd.ed.ac.uk/documents/report17.pdf). To date, no case of vCJD has been identified in the UK in individuals born after 1989.

Deaths from variant CJD

Results from modelling the incidence of vCJD deaths indicate the epidemic peaked in about the year 2000 when there were 28 deaths and has since declined[1]. The last case of vCJD in the UK was

[1] Analysis undertaken by N J Andrews, Senior Statistician, Statistics Unit, Centre for Infections, Health Protection Agency. Further detail is available at http://www.cjd.ed.ac.uk/cjdq72b.pdf

diagnosed in 2013 and died the same year; no cases have been reported subsequently. Data were last reviewed in 2012 and further details are given in the full report which is available at www.cjd.ed.ac.uk/documents/cjdq72.pdf

It is important to note that although a peak has been passed, it is possible that there will be future peaks, possibly in other genetic subgroups. To date, however, there is no evidence of a second wave. There is also the possibility of ongoing person to person spread as seen with 4 cases of transfusion association vCJD infection to date, who received blood in 1999 or earlier from donors who were later diagnosed with clinical vCJD.

Geographical distribution of variant CJD

Tables 2a and 2b present data on the geographical distribution by residence at onset (for all 177 vCJD cases) and residence at death (for 174 vCJD cases who had died by 31st December 2014 and were resident in the UK at death), along with the crude mortality rate per million population per annum of each standard region.

Table 2a Cases of definite and probable variant CJD shown by residence at onset (n=142) and residence at death (n=143†) in England (region & local authority)

	No. resident at onset	No. resident at death	Mortality rate*		No. resident at onset	No. resident at death	Mortality rate*
North East	**11**	**11**	**0.22**	**East**	**13**	**13**	**0.12**
Darlington UA	0	0		Luton UA	0	0	
Hartlepool UA	0	0		Peterborough UA	0	0	
Middlesbrough UA	1	1		Southend-on-Sea UA	1	1	
Redcar & Cleveland UA	1	1		Thurrock UA	0	0	
Stockton-on-Tees UA	1	1		Bedfordshire	0	0	
Durham	0	1		Cambridgeshire	1	1	
Northumberland	3	4		Essex	2	2	
Tyne & Wear	5	3		Hertfordshire	3	3	
				Norfolk	3	3	
North West	**27**	**27**	**0.20**	Suffolk	3	3	
Blackburn with Darwen UA	0	0					
Blackpool UA	1	1		**London**	**20**	**18**	**0.13**
Halton UA	0	0		Inner London	7	7	
Warrington UA	2	2		Outer London	13	11	
Cheshire	5	6					
Cumbria	1	1		**South East**	**23**	**20**	**0.13**
Greater Manchester	10	9		Bracknell Forest UA	1	1	
Lancashire	4	4		Brighton and Hove UA	0	0	
Merseyside	4	4		Isle of Wight UA	0	1	
				Medway UA	0	1	
Yorkshire and the Humber	**17**	**18**	**0.18**	Milton Keynes UA	0	0	
East Riding of Yorkshire UA	1	1		Portsmouth UA	1	2	
Kingston Upon Hull, UA	0	0		Reading UA	0	0	
North East Lincolnshire UA	1	1		Slough UA	0	0	
North Lincolnshire UA	0	0		Southampton UA	1	0	
York UA	0	0		West Berkshire UA	0	0	
North Yorkshire	4	4		Windsor & Maidenhead UA	0	0	
South Yorkshire	5	5		Wokingham UA	0	0	
West Yorkshire	6	7		Buckinghamshire	0	1	
				East Sussex	2	2	
East Midlands	**8**	**10**	**0.12**	Hampshire	5	2	
Derby UA	0	0		Kent	5	4	
Leicester UA	0	0		Oxfordshire	1	1	
Nottingham UA	0	0		Surrey	6	4	
Rutland UA	0	0		West Sussex	1	1	
Derbyshire	0	1					
Leicestershire	4	5		**South West**	**17**	**16**	**0.16**
Lincolnshire	2	2		Bath & NE Somerset UA	0	0	
Northamptonshire	1	1		Bournemouth UA	1	1	
Nottinghamshire	1	1		Bristol, City of UA	1	1	
				North Somerset UA	0	0	
West Midlands	**6**	**10**	**0.10**	Plymouth UA	0	0	
Herefordshire, County of UA	0	0		Poole UA	0	0	
Stoke-on-Trent UA	0	0		South Gloucestershire UA	1	0	
Telford and Wrekin UA	0	0		Swindon UA	0	0	
Shropshire	1	1		Torbay UA	0	1	
Staffordshire	0	0		Cornwall and Isles of Scilly	2	1	
Warwickshire	2	3		Devon	3	3	
West Midlands (Met County)	3	5		Dorset	0	0	
Worcestershire	0	1		Gloucestershire	1	1	
				Somerset	4	5	
				Wiltshire	4	3	
TOTAL FOR ENGLAND	**142**	**143**	**0.15**				

* number of deaths/million/annum based on mid 2001 population estimates (source: ONS): 1 May 1995 to 31 Dec 2014. Postcode of residence obtained from AFD Postcode Plus.

† excludes 3 cases who died abroad.

Table 2b Cases of definite and probable variant CJD shown by residence at onset (n=35) and residence at death (n=31): Wales, Scotland and NI

WALES†	No. resident at onset	No. resident at death	WALES†	No. resident at onset	No. resident at death
Isle of Anglesey	0	0	Neath Port Talbot	0	0
Gwynedd	1	1	The Vale of Glamorgan	1	1
Conwy	0	0	Cardiff	0	0
Denbighshire	1	0	Bridgend	0	0
Flintshire	0	0	Rhondda, Cynon, Taff	0	0
Wrexham	0	0	Merthyr Tydfil	0	0
Powys	1	1	Caerphilly	0	0
Ceredigion	0	0	Blaenau Gwent	0	0
Pembrokeshire	2	2	Torfaen	0	0
Carmarthenshire	1	1	Monmouthshire	0	0
Swansea	1	0	Newport	0	0
TOTAL (MORTALITY RATE*)	**8**	**6 (0.10)**	†unitary authorities		

SCOTLAND†	No. resident at onset	No. resident at death	SCOTLAND†	No. resident at onset	No. resident at death
Aberdeen City	1	1	Highland	3	2
Aberdeenshire	0	0	Inverclyde	0	0
Angus	0	0	Midlothian	0	0
Argyll & Bute	0	0	Moray	0	0
Clackmannanshire	0	0	North Ayrshire	0	0
Dumfries & Galloway	0	0	North Lanarkshire	3	3
Dundee City	0	0	Orkney Islands	1	0
East Ayrshire	1	1	Perth & Kinross	0	0
East Dunbartonshire	1	1	Renfrewshire	1	1
East Lothian	0	0	Scottish Borders	0	0
East Renfrewshire	1	1	Shetland Islands	0	0
Edinburgh, City of	2	2	South Ayrshire	1	1
Eilean Siar	0	0	South Lanarkshire	1	1
Falkirk	1	1	Stirling	0	0
Fife	2	2	West Dunbartonshire	0	0
Glasgow, City of	3	3	West Lothian	2	2
TOTAL (MORTALITY RATE*)	**24**	**22 (0.22)**	†council areas		

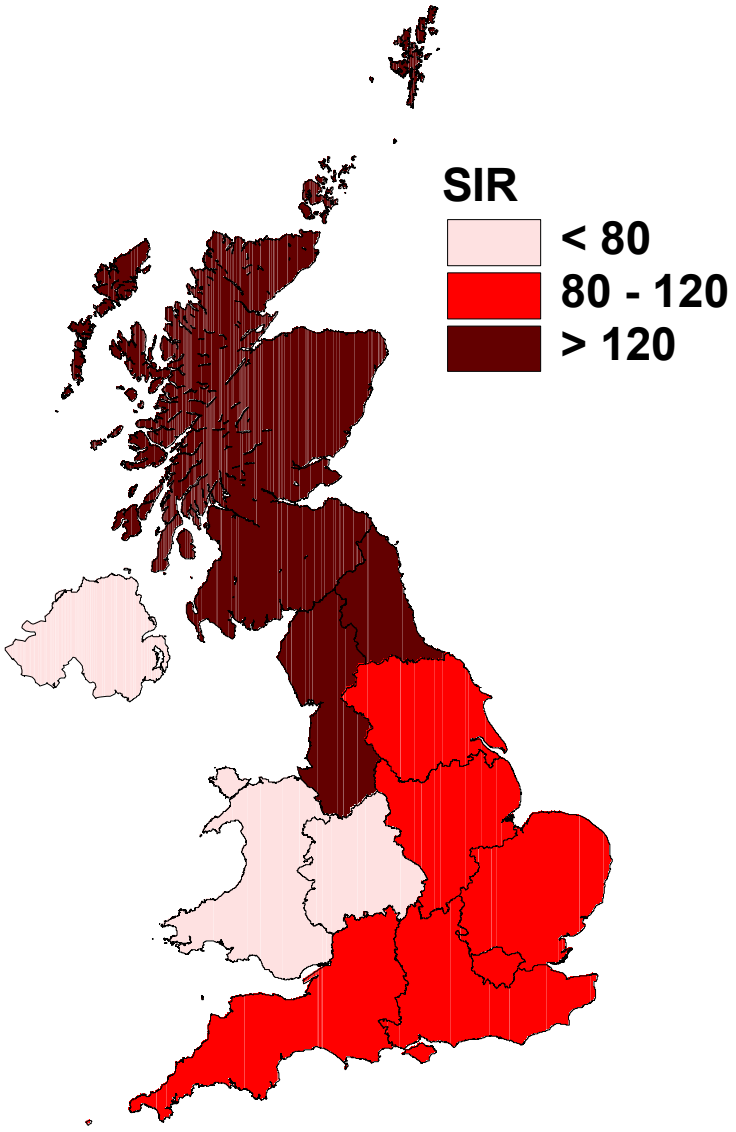
N IRELAND†	No. resident at onset	No. resident at death	N IRELAND†	No. resident at onset	No. resident at death
Antrim	0	0	Down	0	0
Ards	0	0	Dungannon	0	0
Armagh	0	0	Fermanagh	0	0
Ballymena	0	0	Larne	0	0
Ballymoney	0	0	Limavady	0	0
Banbridge	0	0	Lisburn	1	1
Belfast	1	1	Magherafelt	0	0
Carrickfergus	0	0	Moyle	0	0
Castlereagh	0	0	Newry & Mourne	0	0
Coleraine	0	0	Newtownabbey	1	1
Cookstown	0	0	North Down	0	0
Craigavon	0	0	Omagh	0	0
Derry	0	0	Strabane	0	0
TOTAL (MORTALITY RATE*)	**3**	**3 (0.09)**	†district council areas		

* number of deaths/million/annum based on mid-2001 population estimates (source: ONS): 1 May 1995-31 Dec 2014. Postcode of residence obtained from AFD Postcode Plus.

Cases have been widely spread throughout the UK. Age- and sex- standardised incidence ratios (SIRs) based on cases' place of residence in 1991 (shortly after the time when exposure to the BSE agent is assumed to have peaked) are shown in Figure 6. There remains a relatively high incidence amongst those who lived in the north (Scotland, North East, North West, Yorkshire & Humberside; 16.9 million people, 74 vCJD cases) compared to the south (Wales, East Midlands, West Midlands, South West, South East, London, East of England; 31.7 million people, 99 vCJD cases) of Great Britain in 1991.[2] The rate ratio controlling for age and sex is 1.41 (95% CI 1.04-1.90), ie individuals living in the "North" in 1991 are about one and a half times more likely to have developed vCJD than individuals who were living in the "South" in 1991.

Investigations into geographically associated cases of vCJD (either through proximity of residence or through an occupational, educational or social/recreational link with the same location) have found no convincing evidence of factors that may have augmented local risks for vCJD[3].

Figure 6 Standardised variant CJD incidence ratios (SIRs) up to 31st December 2014, by region of residence on 1st January 1991



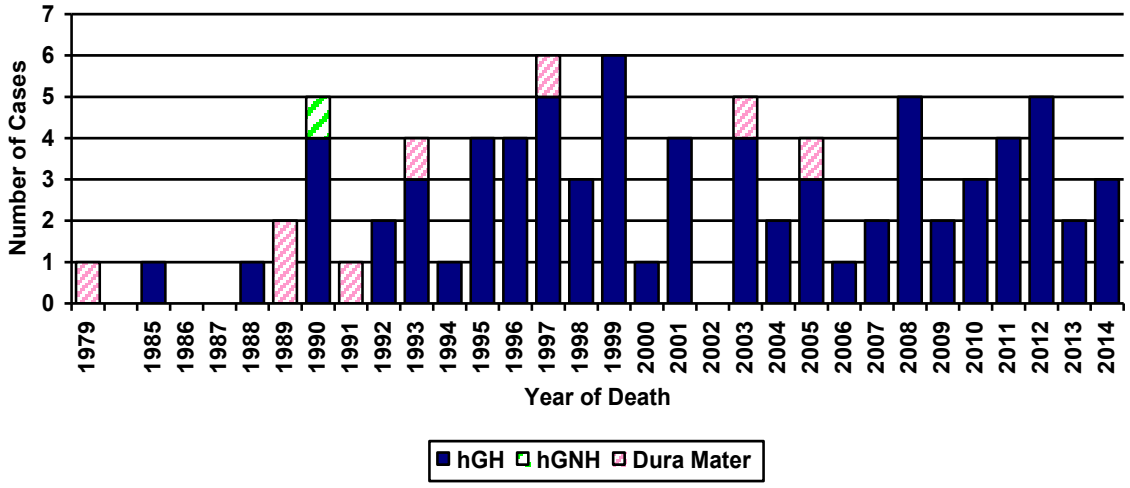
[2] Cousens S, Smith PG, Ward H, Everington D, Knight RSG, Zeidler M, Stewart G, Smith-Bathgate EAB, Macleod MA, Mackenzie J, Will RG. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. Lancet 2001; 357: 1002-1007.

[3] Molesworth AM, Cousens SN, Gill ON, Ward HJT on behalf of the local investigation teams. Variant Creutzfeldt-Jakob disease in the United Kingdom: a countrywide or local risk? J Epid Comm Health 2010; 64: 616-621.

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2014, 84 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 75 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN) who was treated in Australia. All these individuals have died (Figure 7). The mean age at death of the hGH/hGN group was 35 years (with a range of 20-51 years) and for the dura mater cases 46½ years (range 27-78 years).

Figure 7 Deaths from iatrogenic CJD, 1979-2014



The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Since 1985 in the UK, human pituitary-derived hormones have been replaced by synthetic preparations. Details of the UK human pituitary-derived hormone cases, with a discussion of the incubation periods, were published in 2003.[4] A study of the accumulated UK experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.[5]

Iatrogenic transmission of CJD/vCJD is also studied by the Unit through the identification and investigation of surgical or other links between cases. The Unit continues to collect risk factor information for all suspect cases of human prion diseases referred to the Unit as part of its core work.

2.5 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDRSU and UK Blood Services (UKBS). The main purpose is to investigate whether there is any evidence that CJD or vCJD may have been transmitted via the blood supply. Cases (definite and probable) are notified to the UKBS by NCJDRSU; a search establishes whether any have acted as donors or received blood transfusions. Donation/transfusion records are checked and all components traced through hospital records. Details of all identified recipients/donors are forwarded to NCJDRSU for subsequent checking to ensure none appear on the NCJDRSU database as a case of CJD. Further details are given in the 19th Annual Report (www.cjd.ed.ac.uk/documents/report19.pdf)

[4] Swerdlow AJ, Higgins CD, Adlard P, Jones ME, Preece MA. Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. Neurology 2003; 61: 783-91.

[5] Heath CA, Barker RA, Esmonde TFG, Harvey P, Trend P, Head MW, Smith C, Bell JE, Ironside JW, Will RG, Knight RSG. Dura mater-associated Creutzfeldt-Jakob disease: experience from surveillance in the UK. JNNP 2006; 77: 880-2.

Four instances of probable transfusion transmitted infection have been identified. The first recipient (Case 1) developed symptoms of vCJD 6½ years after receiving a transfusion of red cells donated 3½ years before the donor (Donor 1) developed symptoms of vCJD[6]. The second recipient (Case 2) died from a non-neurological disorder 5 years after receiving blood from a donor (Donor 2) who subsequently developed vCJD[7]; at post mortem protease-resistant prion protein (PrP^{res}) was detected in the spleen but not in the brain. This was the first recorded case in the UK of autopsy detection of presumed pre- or sub-clinical vCJD infection. The third recipient (Case 3) developed symptoms of vCJD 7 years, 10 months after receiving a transfusion of red cells donated about 21 months before the donor (Donor 3) developed symptoms of vCJD[8]. The fourth recipient (Case 4), who received a transfusion from the same donor as Case 3, developed symptoms of vCJD 8 years, 4 months after receiving a transfusion of red cells donated about 17 months before the donor (Donor 3) developed symptoms of vCJD[9].

The identification of 3 cases of vCJD in the small cohort of known recipients of blood from persons incubating vCJD, together with the fact that 2 of the cases were associated with a common blood donor, establishes beyond reasonable doubt that blood transfusion is a transmission route for vCJD.

(Collaborators on this project: Dr PE Hewitt, Dr CA Llewelyn).

2.6 Study of Progressive Intellectual & Neurological Deterioration (PIND)

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an Expert Neurological Advisory Group comprising nine paediatric neurologists, one geneticist and a representative from the National CJD Research & Surveillance Unit, which allocates the cases to a diagnostic category[10-11].

As of 31st December 2014, after nearly 18 years of surveillance, 3785 patients with suspected PIND had been reported and the Expert Group had discussed 2491 of these. 1580 cases had a confirmed underlying cause other than vCJD, being categorised into over 190 known neurodegenerative diseases[3]. There have been six cases of vCJD; four definite and two probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest UK case of vCJD identified to date.

(Collaborators on this project: Dr C Verity, Prof A Nicoll, Ms L Stellitano, Ms AM Winstone)

---

6 Llewelyn CA, Hewitt PA, Knight RSG, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004; 363: 417-421.

7 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004 364: 527-529.

8 Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. Lancet 2006; 368: 2061-2067.

9 Health Protection Agency. Fourth case of transfusion-associated variant-CJD. Health Protection Report 2007;1(3):

10 Verity CM, Nicoll A, Will RG, Devereux G, Stellitano L. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. Lancet 2000; 356: 1224-1227.

11 Devereux G, Stellitano L, Verity CM, Nicoll A, Will RG, Rogers P. Variations in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). Arch Dis Child 2004; 89: 8-12.

2.7 Surveillance of potential occupational exposure to CJD

Public Health England in collaboration with NCJDRSU have set up an occupational surveillance study with two parts: 1) a registry for the prospective long term monitoring of healthcare and laboratory workers who have incurred occupational exposures to prion diseases and 2) the retrospective review of possible occupational exposures of CJD cases who have been healthcare or laboratory workers.

By the end of 2014, 2 healthcare workers and one laboratory worker had reported prion-disease exposures as a result of needle stick/sharps injuries. None have subsequently developed prion disease. Retrospective investigations of possible occupational exposures of CJD cases continues to be undertaken to determine if any exposure to prion disease occurred.[12]

(Collaborators on this project: K Sinka, J Thorpe)

2.8 Enhanced surveillance of individuals identified as at increased risk of CJD

The potential for secondary transmission of CJD has led to collaborative studies with the UK Haemophilia Centre Doctors Organisation, Institute of Child Health (London), NHS Blood and Transplant, National Prion Clinic, Public Health England, Health Protection Scotland aimed at identifying whether there is evidence of clinical or sub-clinical infection in those judged to be at increased risk of CJD, such evidence is investigated through review of clinical records and medical histories, and through post-mortem investigations.

As at 31st December 2014, three cases of vCJD and one asymptomatic infection had been identified in recipients of blood from donors who later developed vCJD (see section 2.5 TMER) and one asymptomatic infection in a bleeding-disorder patient who received UK sourced plasma products.[13]

(Collaborators on this project: P Adlard, O Blatchford, H Ward, C Creasey, L Dewhurst, N Gill, C Hay, P Hewitt, M Makris, S Mead, P Minor, B Palmer, A Rankin, K Sinka)

[12] Thorpe J, Mackenzie J, Molesworth A, Sinka K, Will R. Occupational exposures to prion diseases in healthcare and laboratory workers. Poster presentation at Prion 2012, 9-12 May, Amsterdam.

[13] Peden A, McCardle L, Head MW, Love S, Ward HJT, Cousens SN, Keeling DM, Millar CM, Hill FGH, Ironside JW. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia 2010; 16: 296-304.

Section

3

LABORATORY ACTIVITIES

Laboratory investigations are part of the internationally-agreed diagnostic criteria for CJD, both during life (CSF protein analysis, PrP genetic studies, brain biopsy neuropathology and prion protein studies) and post-mortem (autopsy neuropathology and prion protein studies). The NCJDRSU has facilities to perform all of these investigations, which aid the timely and accurate diagnosis of all forms of CJD and are essential for surveillance purposes.

3.1 Neuropathology – Statement of Progress and Surveillance Activities

The neuropathology laboratory in the NCJDRSU continues to maintain its diagnostic and research activities, with most of the cases investigated referred from other centres across the UK (see Table 3). The laboratory maintains close links with other neuropathology centres across the UK and overseas with scientific, medical, technical and student visitors over the past year for specialist training purposes. The laboratory has continued to maintain an active research programme both in-house and by collaboration with other research centres in UK, Europe and across the world and provides tissues to researchers through the CJD Brain and Tissue Bank, which is part of the MRC-funded Edinburgh Brain Bank.

In the contemporary referrals for 2014, the numbers of cases diagnosed as prion diseases was similar to those in the previous year; the numbers of cases in which there was no evidence of CJD or an alternative diagnosis was made is also very similar. No cases of vCJD were identified in the UK and none were referred from outside the UK. No cases of variably protease-sensitive prionopathy were identified prospectively in 2014.

In addition to the UK CJD surveillance work, the neuropathology laboratory is involved in CJD screening studies in patients identified as being at increased risk of CJD, including through exposure to vCJD through blood products or plasma products (Table 3). The laboratory is also involved as a reference centre for a PHE study on the prevalence of vCJD infection in appendix tissue samples from the UK, and in a series of international collaborative studies in relation to neuropathological diagnosis of CJD and other human prion diseases.

The laboratory and its staff continue to participate in a range of EQA activities related to both technical and diagnostic neuropathology. As before, the laboratory continues to act as a source of information to a wide range of professionals involved in health and safety issues relating to CJD. We are most grateful to all neuropathologists, general pathologists and their technical, secretarial and autopsy room staff for their continuing support of the NCJDRSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

Table 3 Breakdown of Laboratory Activities: Period 1st January 2014– 31st December 2014

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	30	32
Familial CJD	2 *	0
Variant CJD	0	0
Iatrogenic CJD (GHT)	0	1
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	1	0
Fatal Familial Insomnia	1	0
Variably protease sensitive prionopathy	0	2
No evidence of CJD	13	20
Alzheimer's disease	3	2
Dementia with Lewy Bodies	1	2
Lewy Body disease	1	0
Other forms of brain disease†	8	6
REFERRED CASES (EU)		
CJD, probable sporadic	1	2
Sporadic CJD	0	3
Familial CJD	0	1
Variant CJD	0	0
Variably protease sensitive prionopathy	0	1
GSS	0	0
No evidence of CJD	1	1
Other forms of brain disease	0	1
REFERRED CASES (ROW)		
CJD, probable sporadic	1	1
Other forms of brain disease	0	0
UK PRION SCREENING STUDIES		
Haemophilia Cases-UKHCDO	0	0
Primary Immune deficiency patients-PIDSUK	20	5
TOTAL NUMBER OF CASES	**83**	**80**

NOTES

† Other**:** Encephalopathy - 1
Frontotemporal dementia (FTD) - 2
Cerebrovascular disease - 1
Tumour - 2
Progressive multifocal leukoencephalopathy -1
Corticobasal degeneration (CBD) - 1

*Biopsy and autopsy samples received for 1 case

Abbreviations:

GHT	Growth Hormone Therapy	UKHCDO	UK Haemophilia Centre Doctors' Organisation
ROW	Rest of World	PIDSUK	UK Primary Immunodeficiency Screening Project
EU	European Union		

3.2 Prion Protein Laboratory

Prion protein detection and typing

Prion protein typing is carried out as a routine diagnostic test on all suspected cases of CJD from which frozen brain tissue is received by the NCJDRSU. Small quantities of cerebral cortex or cerebellum are homogenised, treated with protease and the size and relative abundance of the protease resistant prion protein (PrP^{res}) fragments determined by Western blot analysis. The recognised PrP^{res} types, their nomenclature and their association with different human prion diseases are shown in Figure 8 and described in the accompanying legend. In cases from which only peripheral tissues are available (such as those in which diagnostic tonsil biopsy is performed), or in cases in which the patient is thought to have been at risk of developing CJD due to potential iatrogenic exposure and is enrolled in a UK prion screening study, a modified Western blot procedure is used which employs centrifugal concentration or sodium phosphotungstic acid precipitation to enrich for PrP^{res} and increase the sensitivity of the test.

Figure 8

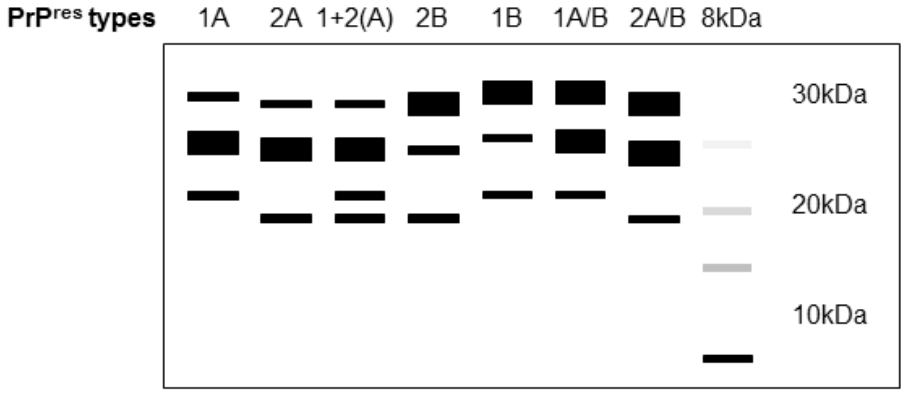


Figure 8 shows the diagrammatic representation of the main protease resistant prion protein (PrP^{res}) types found in the human prion disease brain as determined by proteinase K digestion and Western blot analysis. The classification of the banding pattern has two components, one numerical depending on the migration of the bands and the other alphabetical depending on their relative abundance. The pattern is termed type 1 if the non-glycosylated (bottom) band is ~21kDa, type 2 if the non-glycosylated band is ~19kDa or type 1+2 if both bands are found. In cases and samples in which both types are present but one type predominates the less abundant type is placed in parentheses [ie type 1(+2) or type 2(+1)]. The pattern is given the suffix A if the middle or bottom (mono-, or non-glycosylated) bands predominate, B if the top (di-glycosylated) band predominates or A/B if the glycosylated bands (middle and top) predominate at the expense of the non-glycosylated (bottom) band. A pattern dominated by a low molecular mass unglycosylated band is here termed 8kDa. The faint ladder of bands that sometimes accompanies the 8kDa band is shown in grey. Types 1A, 2A, 1+2(A) are characteristic of sporadic and iatrogenic CJD. Type 2B is associated with variant CJD. Types 1B, 1A/B and 2A/B are often found in genetic CJD, GSS and FFI. The 8kDa pattern is characteristic of some cases of GSS and of VPSPr.

UK Referrals

A total of 40 UK cases with frozen tissue were received and analysed in 2014, which is similar to the number analysed in the previous year. The results of the analysis were as follows:

Table 4 Breakdown of cases analysed in 2014

Diagnosis	Type	PrP^{res} +ve CNS
CJD	Sporadic	26/26
	Familial	2/2
FFI		1/1
GSS		1/1
Alternative final diagnosis or not determined		0/10[1,2]

[1]Includes an enhanced surveillance patient
[2]Includes a brain biopsy

Further sub-classification by PrP^{res} type and *PRNP* genotype yields the following results:

Table 5 PrP^{res} type / *PRNP* genotype breakdown of CJD cases analysed in 2014

Diagnosis	*PRNP* genotype	Type 1A	Type 2A	Type 1+2(A)	Type 1A/B	Type 2A/B	Type 8kDa
Sporadic CJD	MM	16	1	2			
	MV		2				
	VV	1	3	1			
Familial CJD(E200K)	MM				1		
	MV					1	
FFI (D178N)	MM					1	
GSS (Q212P)	MM						1[2]

[1]Faint PrP^{res} bands seen only in the cerebellum after sodium phosphotungstic acid precipitation

Historical UK referrals

Western blot analysis was performed on frozen brain tissue from an additional 21 historical UK cases from the Institute of Neurology in London.

Non-UK referrals

Western blot analysis was performed on frozen tissue from one non-UK case from Sweden with a negative result.

3.3 Brain banking activities

The bank of fixed and frozen tissues in the Research and Surveillance Unit was used extensively in 2014 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. Funding from MRC was renewed in 2013 to support the activities of the CJD bank as part of the Edinburgh Brain Bank (Director – Professor Colin Smith) for a further 5 years. The Edinburgh Brain Bank is a member of the MRC Network of UK Brain Banks, which works to strengthen banking activities and ensure uniform high standards of operation. The Bank has a website, on which further details are available including instructions on how to request tissue samples for research (https://www.wiki.ed.ac.uk/display/edinburghbrainbanks/CJD+BRAIN+AND+TISSUE+BANK) The activities of the Bank comply with current guidelines from the Royal College of Pathologists, the Human Tissue (Scotland) Act 2006 and the Human Tissue Act 2004.

3.4 Molecular Genetics

Genetic CJD

One hundred and forty-five cases of genetic CJD (excluding cases of GSS) have been identified since 1970 by the NCJDRSU (these data are incomplete as formal investigation of genetic CJD in the UK is undertaken by the National Prion Clinic in London). Of the 145 cases, 128 were resident in England, 9 were resident in Wales, 3 were resident in Northern Ireland and 5 were resident in Scotland. Twenty-two cases were still alive as at 31st December 2014. Sixty-five of the cases had insertions in the coding region of the PrP gene, 44 carried the mutation at codon E200K, 15 at codon D178N, 4 at codon V210I, one at codon D167G, 2 at codon V163STOP, one at codon G54S, one at codon E211Q and one at codon E196K. The remaining 11 were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55½ years (range 29-95 years).

PRNP Codon 129 distribution in sporadic CJD

The distribution of *PRNP* codon 129 genotypes in sCJD has been analysed since the inception of the Unit in 1990. The overall distribution of *PRNP* codon 129 genotypes in sCJD is 62% MM, 19% MV, 19% VV (see Table 6). There appears to be evidence (p=0.003) of a change in the *PRNP* codon 129 distribution in sCJD between the periods 1990-1995 and 1996-2014. The explanation for this remains unclear. It should be noted that not all cases are genotyped (data available on 62%) and, therefore, changes in *PRNP* codon 129 distribution may reflect changes in the way in which cases are selected for analysis.

Table 6 *PRNP* codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2014

Deaths from sCJD	**MM(%)**	**MV(%)**	**VV(%)**
Deaths from 1 January 1990 – 31 December 1995	101 (75)	16 (12)	17 (13)
Deaths from 1 January 1996 – 31 December 2014	514 (60)	170 (20)	172 (20)
Total	615 (62)	186 (19)	189 (19)
Genotype distribution for the normal population[14]	(44)	(45)	(11)

PRNP codon 129 distribution in variant CJD

All clinical cases for whom genetic data are available (n=160, 90%) were methionine homozygotes at *PRNP* codon 129 of the PrP gene.

The genetic laboratory undertakes genetic analysis on a national and international basis.

[14] Bishop et al. *PRNP* variation in UK sporadic and variant Creutzfeldt-Jakob disease highlights genetic risk factors and a novel non-synonymous polymorphism. BMC Medical Genetics 2009;10:146-155.

3.5 CSF 14-3-3 and other brain specific proteins

Introduction

In August 2012 we published the results from a retrospective study we undertook, investigating a new technique for examining CSF samples from patients with suspected CJD, called Real-Time Quaking Induced Conversion (RT-QuIC).[15] The results were very promising with RT-QuIC having a sensitivity and specificity of 89% and 99% respectively, compared to 14-3-3 which had a sensitivity and specificity of 94% and 65% respectively. Since that time, we have been undertaking a prospective audit of how useful RT-QuIC is in clinical practice, therefore every CSF sample that is sent to us for 14-3-3 analysis from UK patients is also analysed for RT-QuIC, providing enough CSF is available.

The laboratory received 340 cerebrospinal fluid (CSF) samples from January 2014 – December 2014, from patients residing in the United Kingdom (UK) and from patients in non-UK countries. Two CSF samples were blood-stained and as such unsuitable for analysis. The origin and numbers of these samples are given in Table 7.

Table 7 Origin of CSF samples sent to the NCJDRSU for CSF 14-3-3 analysis from January 2014 – December 2014

Origin of CSF samples	*Total number CSF samples (%)*
CSF from UK patients	291[1]
CSF from non-UK countries	49
Total number	340

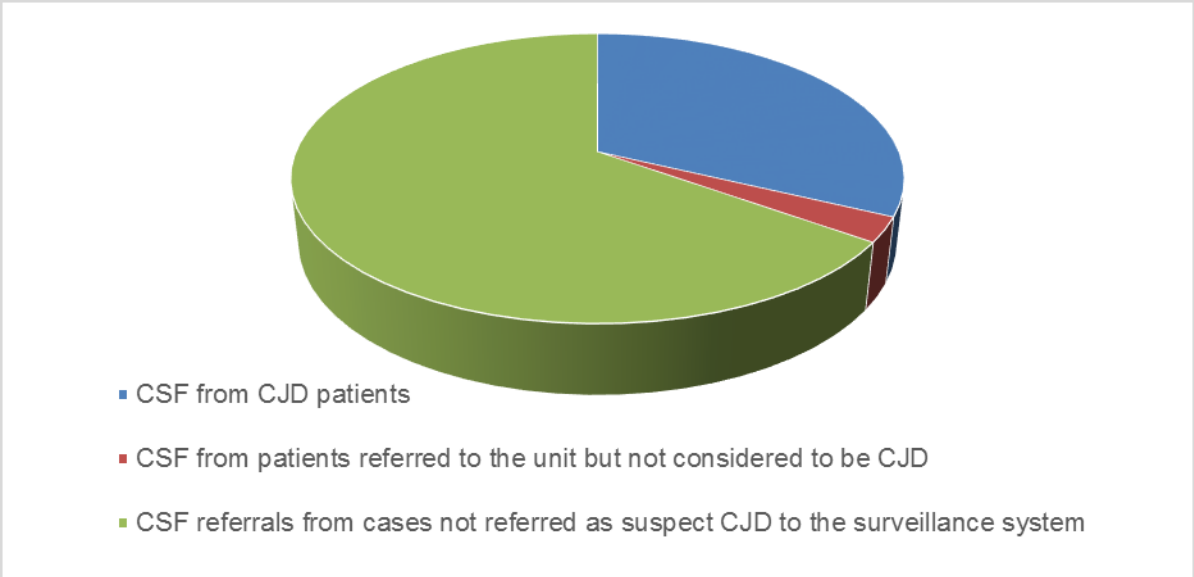
[1] Two CSF samples were blood-stained and as such unsuitable for analysis and 7 CSF samples were insufficient for analysis.

Of the 282 analysable CSF samples received from patients within the United Kingdom, 93 samples were from patients who were finally referred to the NCJDRSU as a suspected case of CJD. Of these, 86 patients were finally diagnosed as having definite, probable or possible CJD (Table 8). Of the remaining 7 patients, 4 have alternative diagnoses: one patient improved, one has a clinical diagnosis of Lewy body dementia, one patient died and the neuropathological examination showed no evidence of prion disease and in the final patient the diagnosis of CJD is no longer being considered. The remaining 3 patients are still alive and under review. None of these patients have a positive RT-QuIC, although one patient did have a positive 14-3-3.

The remaining 189 CSF samples were sent to the NCJDRSU for the analysis of 14-3-3 and S-100b but in none of these cases did the requesting clinician refer the patient to the NCJDRSU as a suspected case of CJD. Many requests for 14-3-3 and S-100b analysis are on patients where the clinical suspicion of CJD is low and the request is made to exclude the diagnosis. However, if a 14-3-3 request is made for a patient where CJD is reasonably suspected the referring clinician is encouraged to formally refer the patient to the NCJDRSU.

[15] McGuire LI, Peden AH, Orrù CD, Wilham JM, Appleford NE, Mallinson G, Andrews M, Head MW, Caughey B, Will RG, Knight RSG, Green AJE. Real time quaking-induced conversation analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease. Ann Neurol 2012; 72(2): 278-85.

Figure 9 Source of CSF samples received from the UK for CSF 14-3-3 analysis



The final diagnosis of the 86 patients referred to the NCJDRSU who were diagnosed with some form of CJD is given in Table 8.

Table 8 The CSF 14-3-3 results in patients diagnosed with CJD or prion disease

Diagnosis	Number of cases	Number of positive CSF 14-3-3 / Total number CSF 14-3-3 analysed	Number of positive CSF RT-QuIC / Total number CSF RT-QuIC analysed
Neuropathologically confirmed sCJD	35	22/33[1] (67%)	31/33[2] (94%)
Probable sCJD	37	28/35[3] (80%)	34/37 (92%)
Possible sCJD	7	0/7	2/5[4]
Definite genetic CJD	2 (E200K) 1 (D178N-M FFI)	2/2 0/1	2/2 0/1
Probable genetic CJD	1 (D178N-M FFI) 1 E196K 1 V210I	0/1 1/1 1/1	0/1 1/1 1/1
Probable Iatrogenic CJD[5]	1	1/1	1/1

1 Two samples were sent for RT-QuIC only and 14-3-3 analysis was not performed.
2 Two CSF samples were insufficient for RT-QuIC analysis and only 14-3-3 analysis was performed.
3 Two CSF samples were sent for RT-QuIC only and 14-3-3 analysis was not performed.
4 Two CSF samples were insufficient for RT-QuIC analysis and only 14-3-3 analysis was performed.
5 Secondary to administration of human cadaveric growth hormone.

Of the 37 patients with probable sCJD, 19 have died without undergoing a post-mortem, 3 have died and neuropathological confirmation of sCJD is awaited, 5 have died and it is unclear whether a post-mortem has been performed and 10 patients are still alive. Of the 19 patients who died without post-mortem examination, 18 had 14-3-3 analysis performed and all but one were positive. The RT-QuIC was performed in all 19 CSF samples and was positive in 18 of them.

Of the 189 CSF samples sent from patients who were not formally referred to the NCJDRSU, 3 were positive for 14-3-3 but none of the 189 CSF samples were positive for RT-QuIC. Of the 3 patients with positive 14-3-3, one recently had seizures, one had a paraneoplastic syndrome and one patient recovered.

Section

4

NATIONAL CJD CARE TEAM

Established by the Department of Health, the National CJD Care Team is based within the National CJD Research & Surveillance Unit and was formed in order to optimise the care of patients suffering from all forms of CJD. The national care coordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed. The present team consists of 2 care coordinators who are senior nurses with secretarial and clinical neurological support from within the Unit.

When a referral is made to the NCJDRSU the research registrar will take that referral and, if appropriate, ask the Care Co-ordinator to attend that first visit to meet with the family. Once a diagnosis of probable or possible CJD is made, if the co-ordinator has not already met the family, the coordinator makes direct contact with the family and offers the opportunity to meet and to assist with care planning. Referrals are also made to the Care Team from Leah Davidson (who coordinates the care of iatrogenic CJD cases) and the National Prion Clinic in London. Once contact is made, the coordinator can meet on a regular basis with the patient, family and professionals involved in care. This will depend on need and will provide support and assist with coordination of local health and social care professionals. The coordinators provide valuable expertise in nursing patients with CJD and can anticipate and prevent some problems that may arise by offering skilled advice and education. The care team enables local teams to provide high standards of care and continues to be involved as long as needed. This does not always involve a visit in person. Contact by telephone, text or email is just as important and may be preferred by families and other professionals involved. Post bereavement support is offered to the family after the patient dies and assistance is given in accessing more specialised counselling.

The National CJD Care Team works in close liaison with the Department of Health and provides access to the CJD Care Package. This is a sum of money from The Department of Health which provides funding to assist local authorities with the care of patients suffering from all forms of CJD. The Care Fund is available to supplement local care and equipment provision. Health and Social Services will provide the basic elements of the individual patient's care package. The Care package involves an individual assessment of need and will vary accordingly. It is essential that care packages are flexible and can change quickly to meet the rapidly changing needs of the patient. The aim is to provide a package of care that will meet the needs both for the patient and their family in a timely manner.

In addition to collaborations with national organisations in the United Kingdom, the Care Team liaises closely with international organisations, including the Australian and American CJD Support Groups and is an Official Friend of the CJD International Support Alliance.

A breakdown of patient visits, case conferences, teaching sessions and family contacts during 2014 is shown in Table 9. Care Fund payments from 1st January to 31st December 2014 are shown in Table 10.

Table 9 Patient Visits, Case Conferences and Teaching Sessions and Family contacts 1st January to 31st December 2014

Month	Patient Visits/Case Conferences/Teaching Sessions/Family Contacts
Patient Visits	137
Case Conferences	48
Teaching	14
Debrief	1
Emails	188
Texts	132
Telephone calls	1014
Other (letters etc)	26

Table 10 Care Fund Payments 1st January to 31st December 2014

Description	£
Adaptations	6,832.00
Alternative Therapy	3,288.00
Nursing	422,232.00
Social Care	2,130.00
Equipment	565.00
Accommodation	4,655.00
Transport	13,200.00
TOTAL	**452,902.00**

Section

5

PUBLICATIONS IN 2014

1. Barria MA, Balachandran A, Morita M, Kitamoto T, Barron R, Manson J, Knight R, Ironside JW, Head MW. Molecular barriers to zoonotic transmission of prions. Emerg Infect Dis. 2014; 20(1): 88-97.

2. Barria MA, Ironside JW, Head MW. Exploring the zoonotic potential of animal prion diseases: in vivo and in vitro approaches. Prion. 2014; 8(1): 85-91.

3. Bradford BM, Piccardo P, Ironside JW, Mabbott NA. Human prion diseases and the risk of their transmission during anatomical dissection. Clin Anat. 2014; 27(6): 821-32.

4. Choi YP, Head MW, Ironside JW, Priola SA. Uptake and degradation of protease-sensitive and -resistant forms of abnormal human prion protein aggregates by human astrocytes. Am J Pathol. 2014; 184(12): 3299-3307.

5. Davidson LRR, Llewelyn CA, Mackenzie JM, Hewitt PE, Will RG: Variant CJD and blood transfusion: are there additional cases? Vox Sang 2014; 107(3): 220-225.

6. Diack AB, Head MW, McCutcheon S, Boyle A, Knight R, Ironside JW, Manson JC,Will RG. Variant CJD: 18 years of research and surveillance. Prion 2014; 8(4): 286-295.

7. Diack AB, Ritchie DL, Peden AH, Brown D, Boyle A, Morabito L, Maclennan D, Burgoyne P, Jansen C, Knight RS, Piccardo P, Ironside JW, Manson JC. Variably protease-sensitive prionopathy, a unique prion variant with inefficient transmission properties. Emerg Infect Dis. 2014; 20(12): 1969-79.

8. Head MW, Yull HM, Törö K, Keller E, Rozsa C, Ironside JW, Kovacs GG. Pathological and biochemical investigation of a woman diagnosed with genetic Creutzfeldt-Jakob disease shortly after parturition. Neuropath App Neurobiol 2014 Dec 9. doi: 10.1111/nan.12204. [Epub ahead of print]

9. Ironside JW, Ritchie DL, Peden AH, Head MW. Human Prion Diseases. *In* Neuropathology of Neurodegenerative Diseases. Kovacs GG (Ed), Cambridge University Press, Cambridge, UK, 2014, pp176-194.

10. Ironside JW, Head MW. Variably Protease-sensitive prionopathy. Health Protect. Rep 2014 [http://www.hpa.org.uk/hpr/infections/ei_cjd.htm).

11. Jones M, Odunsi S, du Plessis D, Vincent A, Bishop M, Head MW, Ironside JW, Gow D. Gerstmann-Straüssler-Scheinker disease: novel PRNP mutation and VGKC-complex antibodies. Neurology. 2014; 82(23): 2107-11.

12. Krejciova Z, Barria MA, Jones M, Ironside JW, Jeffrey M, González L, Head MW. Genotype-dependent molecular evolution of sheep bovine spongiform encephalopathy (BSE) prions in vitro affects their zoonotic potential. J Biol Chem. 2014; 289(38): 26075-88.

13. Krejciova Z, De Sousa P, Manson J, Ironside JW, Head MW. Human tonsil-derived follicular dendritic-like cells are refractory to human prion infection in vitro and traffic disease-associated prion protein to lysosomes. Am J Pathol. 2014; 184(1): 64-70.

14. Moda F, Gambetti P, Notari S, Concha-Marambio L, Catania M, Park KW, Maderna E, Suardi S, Haïk S, Brandel JP, Ironside J, Knight R, Tagliavini F, Soto C. Prions in the urine of patients with variant Creutzfeldt-Jakob disease. N Engl J Med. 2014;371(6): 530-9.

15. Molesworth A, Yates P, Hewitt PE, Mackenzie J, Ironside JW, Galea G, Ward HJ. Investigation of variant Creutzfeldt-Jakob disease implicated organ or tissue transplantation in the United Kingdom. Transplantation. 2014; 98(5): 585-9.

16. Newman PK, Todd NV, Scoones D, Mead S, Knight RSG, Will RG, Ironside JW: Postmortem findings in a case of variant Creutzfeldt-Jakob disease treated with intraventricular pentosan polysulfate. JNNP 2014; 85(8): 921-924.

17. Peden AH, Sarode DP, Mulholland CR, Barria MA, Ritchie DL, Ironside JW, Head MW. The prion protein protease sensitivity, stability and seeding activity in variably protease sensitive prionopathy brain tissue suggests molecular overlaps with sporadic Creutzfeldt-Jakob disease. Acta Neuropathol Commun. 2014; 2: 152.

18. Will RG: Prions and agents of TSEs. In: Montarjemi Y, (ed): Encyclopedia of Food Safety. Waltham, MA, Academic Press, 2014, pp 12-17.

19. Will RG. Bovine Spongiform Encephalopathy. Reference Module in Biomedical Sciences. Elsevier 17 Oct 2014. doi: 10.1016/B978-0-12-801238-3.02540-X.

20. Xiao X, Yuan J, Qing L, Cali I, Mikol J, Delisle MB, Uro-Coste E, Zeng L, Abouelsaad M, Gazgalis D, Martinez MC, Wang GX, Brown P, Ironside JW, Gambetti P, Kong Q, Zou WQ. Comparative Study of Prions in Iatrogenic and Sporadic Creutzfeldt-Jakob Disease. J Clin Cell Immunol. 2014 Aug;5(4): 240.

Section

6

Staff based at the National CJD Research & Surveillance Unit, Western General Hospital, Edinburgh in 2014

Professor RSG Knight	Director, NCJDRSU, Consultant Neurologist
Dr MW Head	Deputy Director, Reader (Prion Protein Biochemistry)
Professor RG Will	Consultant Neurologist, Professor of Clinical Neurology
Professor JW Ironside	Professor of Clinical Neuropathology, Director MRC UK Brain Banks Network
Dr AM Molesworth	Senior Epidemiologist
Mr A Hunter	Operations Director
Dr C Smith	Honorary Consultant in Neuropathology
Dr P Urwin	Clinical Research Fellow
Dr B Waddell	Clinical Research Fellow
Dr A Green	Reader (CSF analysis)
Dr A Peden	Postdoctoral Research Fellow
Dr M Bishop	Molecular Geneticist
Ms J Mackenzie	Study Co-ordinator
Ms T Lindsay	European Study Co-ordinator
Mrs B Smith-Bathgate	National Care Co-ordinator
Ms M Leitch	National Care Co-ordinator
Mr N Attwood	Database Manager
Dr D Ritchie	Postdoctoral Research Fellow
Dr L McGuire	Postdoctoral Research Fellow
Dr Z Krejciova	Postdoctoral Research Fellow
Dr M Barria	Postdoctoral Research Fellow
Mr J Alibhai	Research Assistant
Ms S Lowrie	Senior Biomedical Scientist
Mrs M Le Grice	Senior Biomedical Scientist
Mrs M Andrews	Senior Biomedical Scientist
Ms H Yull	Research Technician
Mr G Fairfoul	Research Technician
Ms K Burns	Neuropathology Technical Officer
Ms Elaine Lord	Senior Administrative Co-ordinator
Ms A Honeyman	Secretariat
Ms F Frame	Secretariat
Mrs C Donaldson	Secretariat/Data Handler