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CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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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 on the surveillance, diagnosis 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.

The annual mortality rate for sporadic CJD (sCJD) was 2.07 cases/million in 2023. Although the data for 2023 may still be incomplete, detailed clinical and epidemiological information has been obtained for the great majority of patients. Although the autopsy rate in cases of suspected CJD has decreased in recent years, it remains relatively high in comparison to the general autopsy rate in the UK. The number of brain tissue specimens examined for sCJD in the neuropathology laboratory in 2023 was 6 cases (compared with 13 cases in 2022).

Over the period 1990-2023 average annual mortality rates from sCJD in England, Wales, Scotland and Northern Ireland were, respectively, 1.37, 1.66, 1.35 and 1.11/million/year. The mortality rates of sCJD in the UK are comparable to those observed in several other countries, including countries that are free of BSE.

Variably Protease Sensitive Prionopathy (VPSPr), is of uncertain nosological significance but is presently considered a form of sporadic prion disease, alongside sCJD. The NCJDRSU has so far identified a total of 20 such cases in the UK and is continuing to monitor this form of disease.

Up to 31st December 2023, 178 cases of definite or probable variant CJD (vCJD) had been identified in the UK (123 definite and 55 probable cases who did not undergo post mortem). All 178 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 – of 161 clinically affected definite and probable cases of vCJD with available genetic analysis, 160 have been methionine homozygotes and one methionine-valine heterozygous at Codon 129 of the *PRNP* gene. Previous analysis of vCJD diagnoses and deaths from January 1994 indicated that the peak has passed. While this is an encouraging finding, the incidence of vCJD may increase again, particularly if further cases in different genetic subgroups with longer incubation periods exist. The identification of an individual of the *PRNP*-129 MV genotype as a confirmed case of vCJD (in addition to the possible case of vCJD reported in the NCJDRSU 17th Annual Report, 2008) and the finding of 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 results of large-scale surveys of the prevalence of abnormal prion protein in appendix and tonsil tissues suggest 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 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 also continues to collaborate with government health departments and the UK public health authorities, including UK Health Security Agency and Public Health Scotland, in a range of activities in relation to the follow up of those identified as at increased risk of CJD.

The activities of the NCJDRSU has been strengthened by collaboration with other surveillance projects, including the Transfusion Medicine Epidemiology Review, Prion Surveillance in Primary Immunodeficiency Patients 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 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 positive results in UK individuals referred as suspected CJD but who had a final 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. We liaise with the National CJD Care Team based in NHS Lothian and also the National Prion Clinic in London and their associated Nursing Service. We are also particularly grateful to the relatives of patients for their collaboration.

Providing information to the public is an important aspect of the NCJDRSU's activities. We liaise closely with the CJD Support Network, providing articles for their newsletter, updating their information booklets and giving presentations to their Annual Family Day meetings. Professor Knight is the current Chair of the Network's Management Committee and is also a member of the CJD International Alliance of CJD support organisations.

Section

2

CLINICAL SURVEILLANCE

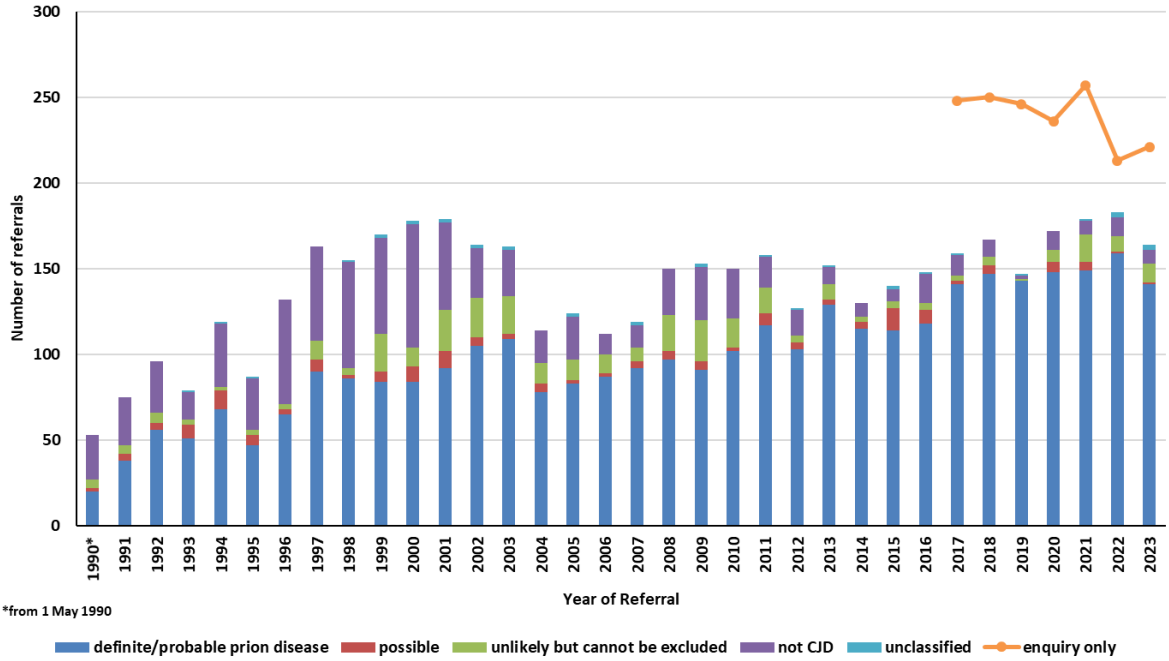
The national surveillance of CJD in the UK was initiated in May 1990. Surveillance is funded by the Department of Health and Social Care, UK and by the Scottish Government Health Department. The NCJDRSU aims to monitor characteristics of CJD, specifically sCJD and vCJD, to identify trends in incidence 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 2022 (based on data ascertained up to 18th September 2023). 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/sites/default/files/criteria.pdf. Cases classified as definite or probable are included in all analyses from Section 2.2 onwards.

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)

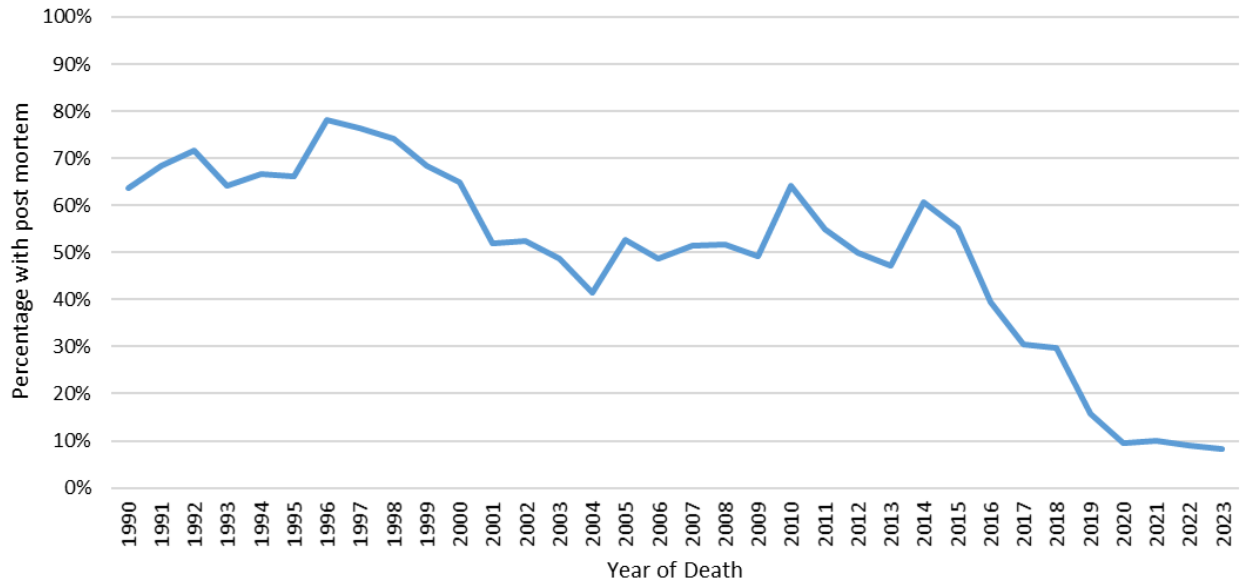
In addition to formal referrals of suspected CJD, the NCJDRSU also receives enquiries from clinicians for advice or to utilise the CSF tests available at the Unit. In Figure 1, these additional enquries are shown in an orange line from 2017 onwards. The NCJDRSU also receives a number of enquiries from relatives of patients, members of the public and professional bodies both in the UK and worldwide seeking advice in relation to CJD.

Figure 1 **Referrals (1990-2023) and Enquiries (2017-2023) to NCJDRSU**



Nationally across the UK rates of post-mortem examinations have been decreasing over time, and this includes for suspected cases of CJD (Figure 2). Although increasing diagnostic certainty can now be offered by biomarker tests (MRI, RT-QuIC), the fall in post-mortem rate may potentially impact on our ability to confirm the different types of prion disease, particularly in cases where prion disease may not have been considered or if otherwise atypical of CJD.

Figure 2 **Post-mortem rate in all referrals of suspected CJD to NCJDRSU: UK 1 May 1990 – 31st December 2023**



2.2 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2023, 3186 cases of sCJD were identified (268 in England and Wales from 1970-1984 and 2918 in the UK from 1985-2023), of which 28 cases were alive on 31st December 2023. Four cases moved abroad after diagnosis and are therefore lost to follow-up. Of these 3186 cases, 1654 (52%) were classified as definite cases with the remainder classed as probable; 1630 (51%) were female and 1556 (49%) were male. Ten further cases have been identified: 4 in Jersey, 3 in the Isle of Man and 3 cases who were repatriated to the UK when they became ill but had been living abroad. These 10 cases are not included in the following UK analyses.

Figure 3 shows the annual mortality rates from sCJD for the UK between 1985 and 2023. The number of deaths identified each year has increased over time. A similar phenomenon has been observed in several other countries, and may reflect improved case ascertainment, particularly in those aged over 70 years and following updated diagnostic criteria from January 2017, which demonstrated significantly improved sensitivity of the revised sCJD diagnostic criteria (with no change in specificity) which has enhanced the diagnostic accuracy for sCJD.[1] To date, there has been no evidence of another cause to explain the increased mortality rates.

Figure 3 Mortality Rates from sCJD, UK, 1985-2023

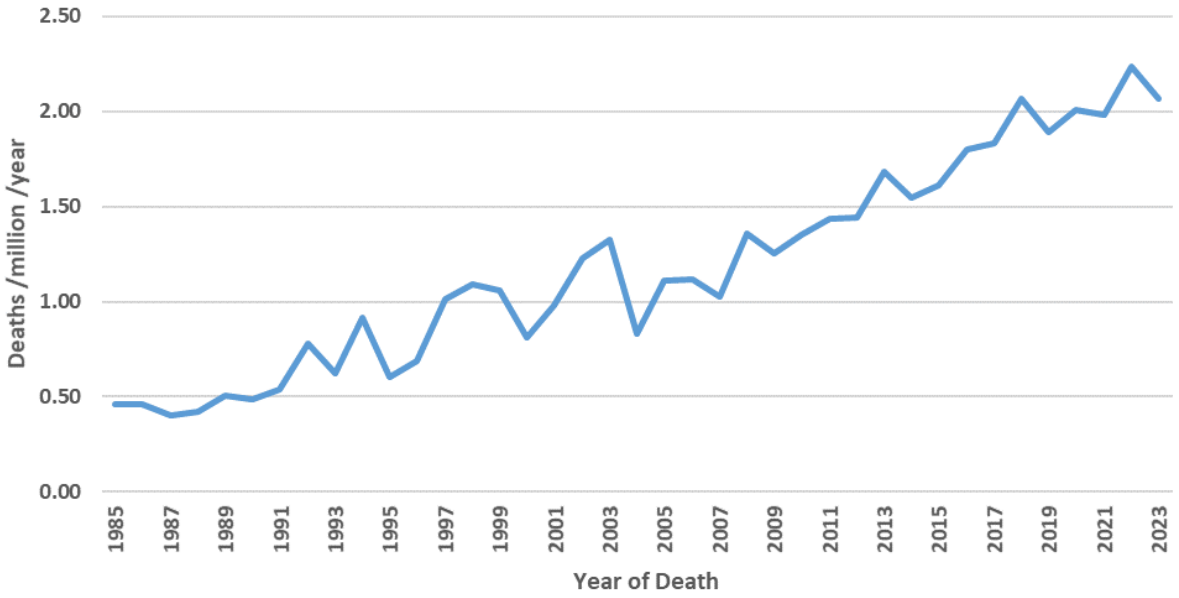
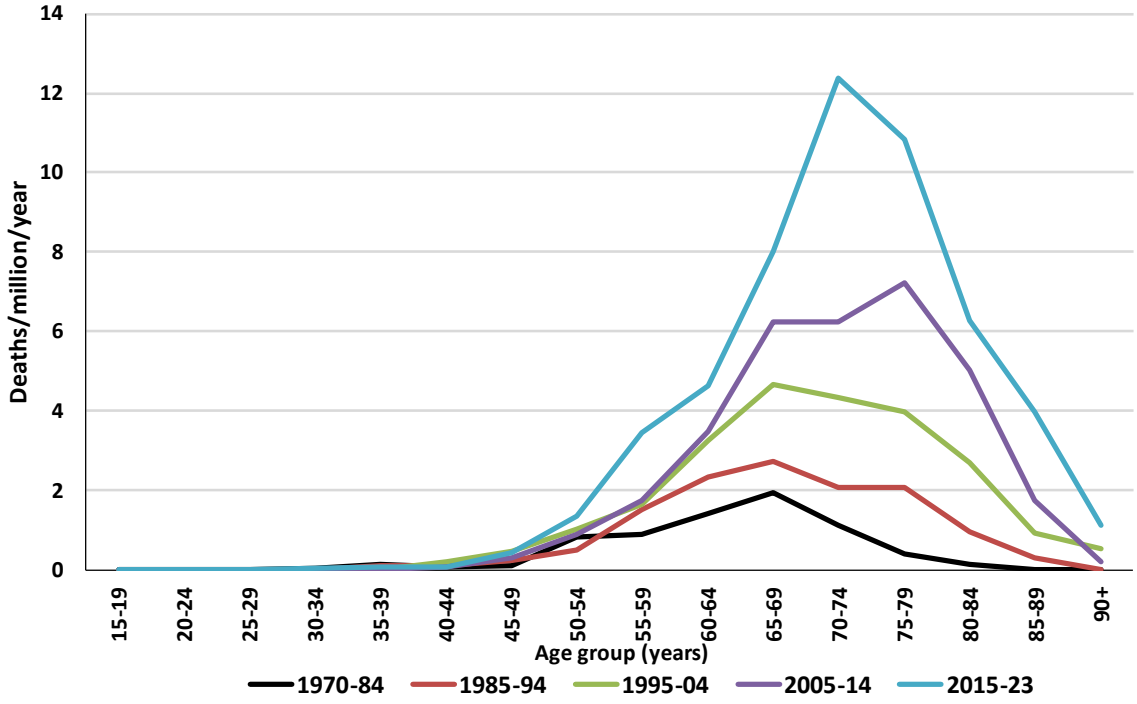


Figure 4 shows average annual age-specific mortality rates over the time periods 1970-1984, 1985-1994, 1995-2004, 2005-2014 and subsequently. These data also emphasise the very small numbers of cases of sCJD occurring in individuals aged <50 years. The median ages of cases at death during these five time periods were 63, 65, 67, 69 and 70 years, respectively. In all five time periods, the mortality rates below 40 years of age were low (< 0.04/million/year). Thereafter, in all five periods, the mortality rates increased up to ages 65-79 years and then declined. The reasons for this decline are unclear but might be explained in part 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.

[1] Watson N et al. Validation of revised International Creutzfeldt-Jakob Disease Surveillance Network diagnostic criteria for sporadic Creutzfeldt-Jakob disease. JAMA Network Open 2022;5(1):e2146319

Figure 4 **Age-specific mortality rates from sporadic CJD in the UK 1970-2023 (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
2015-2023 Mortality rates calculated using mid-2011 UK population estimates based on the 2011 Census

Geographical distribution of sCJD

Over the period 1990-2023 the average crude annual mortality rates from sCJD per million population were 1.37 in England, 1.66 in Wales, 1.35 in Scotland and 1.11 in Northern Ireland (Tables 1a and 1b).

Table 1a Deaths from definite and probable sporadic CJD in England (shown by region and local authority of residence at death). 1st January 1990 to 31st December 2023

ENGLAND	No. of cases	Mortality Rate*	ENGLAND	No. of cases	Mortality Rate*
North East	**107**	**1.24**	**East**	**278**	**1.47**
Darlington UA	5		Luton UA	3	
Hartlepool UA	3		Peterborough UA	5	
Middlesbrough UA	1		Southend-on-Sea UA	6	
Redcar & Cleveland UA	6		Thurrock UA	6	
Stockton-on-Tees UA	5		Bedfordshire	19	
Durham	19		Cambridgeshire	20	
Northumberland	18		Essex	86	
Tyne & Wear	50		Hertfordshire	45	
			Norfolk	45	
North West	**299**	**1.28**	Suffolk	43	
Blackburn with Darwen UA	9				
Blackpool UA	4		**London**	**260**	**1.02**
Halton UA	8		Inner London	82	
Warrington UA	14		Outer London	178	
Cheshire	25				
Cumbria	26		**South East**	**409**	**1.47**
Greater Manchester	93		Bracknell Forest UA	4	
Lancashire	55		Brighton and Hove UA	5	
Merseyside	65		Isle of Wight UA	5	
			Medway UA	7	
Yorkshire and the Humber	**229**	**1.32**	Milton Keynes UA	4	
East Riding of Yorkshire UA	13		Portsmouth UA	5	
Kingston Upon Hull, City of UA	7		Reading UA	8	
North East Lincolnshire UA	9		Slough UA	1	
North Lincolnshire UA	8		Southampton UA	6	
York UA	12		West Berkshire UA	12	
North Yorkshire	37		Windsor and Maidenhead UA	6	
South Yorkshire	63		Wokingham UA	6	
West Yorkshire	80		Buckinghamshire	17	
			East Sussex	27	
East Midlands	**194**	**1.32**	Hampshire	70	
Derby UA	14		Kent	86	
Leicester UA	13		Oxfordshire	40	
Nottingham UA	9		Surrey	51	
Rutland UA	2		West Sussex	49	
Derbyshire	46				
Leicestershire	28		**South West**	**302**	**1.75**
Lincolnshire	30		Bath & North East Somerset UA	9	
Northamptonshire	16		Bournemouth UA	10	
Nottinghamshire	36		Bristol, City of UA	13	
			North Somerset UA	17	
West Midlands	**217**	**1.19**	Plymouth UA	20	
Herefordshire, County of UA	10		Poole UA	8	
Stoke-on-Trent UA	8		South Gloucestershire UA	16	
Telford and Wrekin UA	6		Swindon UA	3	
Shropshire	13		Torbay UA	5	
Staffordshire	44		Cornwall and Isles of Scilly	36	
Warwickshire	12		Devon	42	
West Midlands (Met County)	94		Dorset	28	
Worcestershire	30		Gloucestershire	34	
			Somerset	35	
			Wiltshire	26	
TOTAL FOR ENGLAND	**2295**	**1.37**			

* number of deaths/million/annum based on mid-2005 population estimates in England (source: ONS) over the 34 -year period of the study. Postcode of residence obtained from AFD Postcode Plus.

Table 1b Deaths from definite and probable sporadic CJD: Wales, Scotland and NI 1st January 1990 to 31st December 2023

WALES†	No. of cases	WALES†	No. of cases
Isle of Anglesey	5	Neath Port Talbot	2
Gwynedd	8	The Vale of Glamorgan	8
Conwy	6	Cardiff	13
Denbighshire	2	Bridgend	4
Flintshire	8	Rhondda, Cynon, Taff	10
Wrexham	10	Merthyr Tydfil	4
Powys	16	Caerphilly	15
Ceredigion	3	Blaenau Gwent	2
Pembrokeshire	5	Torfaen	7
Carmarthenshire	8	Monmouthshire	5
Swansea	16	Newport	11
TOTAL FOR WALES (MORTALITY RATE*)	**168 (1.66)**	†unitary authorities	

SCOTLAND†	No. of cases	SCOTLAND†	No. of cases
Aberdeen City	7	Highland	8
Aberdeenshire	13	Inverclyde	3
Angus	3	Midlothian	5
Argyll & Bute	5	Moray	5
Clackmannanshire	3	North Ayrshire	7
Dumfries & Galloway	7	North Lanarkshire	12
Dundee City	10	Orkney Islands	0
East Ayrshire	6	Perth & Kinross	4
East Dunbartonshire	4	Renfrewshire	8
East Lothian	4	Scottish Borders	4
East Renfrewshire	4	Shetland Islands	3
Edinburgh, City of	28	South Ayrshire	7
Eilean Siar	1	South Lanarkshire	13
Falkirk	5	Stirling	7
Fife	14	West Dunbartonshire	5
Glasgow City	23	West Lothian	6
TOTAL FOR SCOTLAND (MORTALITY RATE*)	**234 (1.35)**	†council areas	

NORTHERN IRELAND†	No. of cases	NORTHERN IRELAND†	No. of cases
Antrim and Newtonabbey	3	Fermanagh and Omagh	2
Ards and North Down	4	Lisburn and Castlereagh	7
Armagh City, Banbridge & Craigavon	8	Mid and East Antrim	3
Belfast	14	Mid Ulster	5
Causeway Coast and Glens	5	Newry, Mourne and Down	6
Derry City and Strabane	8		
TOTAL FOR N IRELAND (MORTALITY RATE*	**65 (1.11)**	†local government districts	

* based on mid-2005 population estimates for unitary authorities in Wales, council areas within Scotland and local government districts in Northern Ireland (ONS) over the 34-year period of the study. Postcode of residence obtained from AFD Postcode Plus.

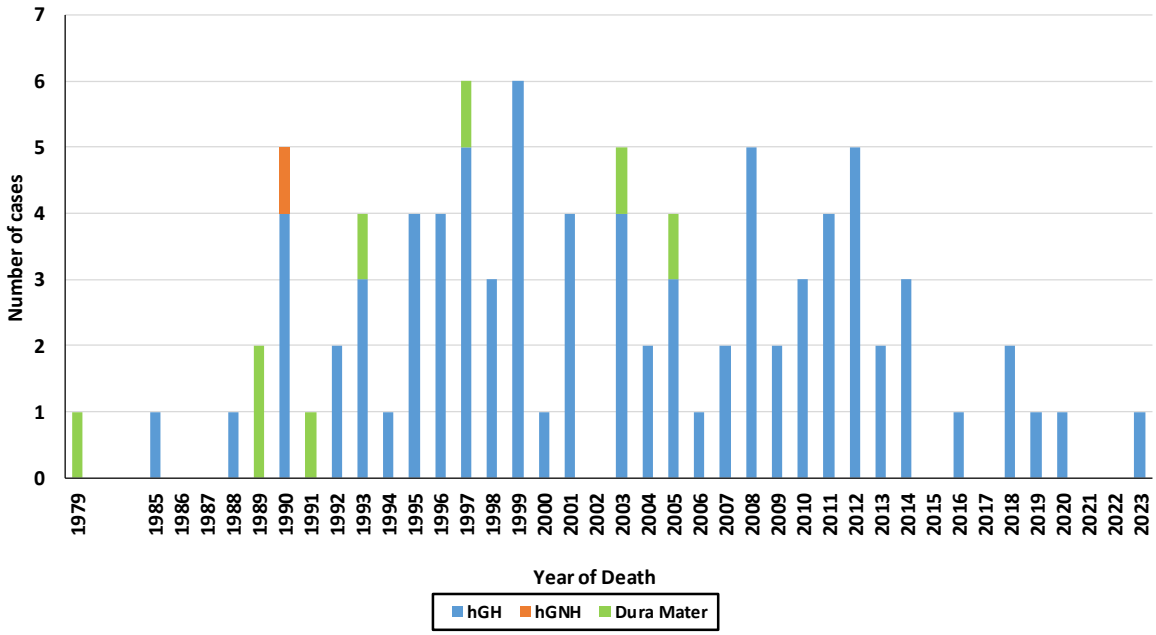
2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2023, 178 cases of definite or probable vCJD had been identified in the UK (123 definite and 55 probable cases who did not undergo post mortem). Seventy-five (42%) of the 178 cases were female and 103 (58%) were male. The median age at onset of disease was 26½ 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 last known UK case of vCJD was reported in 2016 with onset in 2014. Additional detailed information can be found in previous years' annual reports.

2.4 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2023, 90 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 81 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 of these individuals have died (Figure 5). The median age at death of the hGH/hGN group was 35½ years (with a range of 20-59 years) and for the dura mater cases 46 years (range 27-78 years).

Figure 5 Deaths from iatrogenic CJD, 1979-2023



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.[2] A study of the accumulated UK

[2] 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.

experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.[3]

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.

Results from the vCJD arm of the project identified four instances of probable transfusion transmitted infection in 3 cases of vCJD and pre-clinical infection in a recipient with post-mortem confirmation of abnormal prion protein deposition in the spleen (all previously reported[4567]). There have been no new cases of transfusion-associated vCJD since 2007.

Results from all other types of CJD included in the project have not so far shown any evidence of transfusion transmission[8]. This includes, to date, 708 blood component recipients identified from 81 sporadic CJD (sCJD) cases who were donors. None have been identified as CJD cases on the NCJDRSU database and death certificates from 371 of 376 recipients who have subsequently died did not reveal CJD as a cause of death. Thirty-four sCJD cases with a history of blood component transfusion were traced by the blood services from which 310 donors were identified. None of these donors have been identified as CJD cases on the NCJDRSU database and death certificates available from 12 of the 13 donors who have subsequently died did not reveal CJD as a cause of death. Thirty-two component recipients were identified from 6 genetic CJD cases who were donors. None have been identified as CJD cases on the NCJDRSU database and death certificates from the 21 recipients who have subsequently died did not reveal CJD as a cause of death.

(External collaborators on this project: Dr H Harvala Simmonds, Ms C Reynolds, Ms T Yawitch, Ms A St. John).

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3 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.

4 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.

5 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.

6 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.

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

8 Urwin PJ, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sang 2016; 110: 310-316.

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 and allocated to a diagnostic category by an Expert Neurological Advisory Group made up of consultants who have specialised knowledge of paediatric neurology, neurogenetics and metabolic disease, together with representation from the National CJD Research & Surveillance Unit.[9][10][11]

As of 28 of August 2024, after 27 years of surveillance, 5222 patients with suspected PIND had been reported. There have been six cases of vCJD in children aged 15 years or less: four definite and two probable. Three were reported in 1999, one in 2000 and two in mid-2001. The youngest UK case of vCJD identified to date was aged 12 at onset.

A total of 2369 cases had a confirmed underlying cause of neurological deterioration other than vCJD, being categorised into over 220 known neurodegenerative diseases. The clinical details relating to many of these disorders have been analysed and published as case series[12]. Thus, in addition to giving reassurance that vCJD has not re-occurred in UK children, the PIND Study has provided unique on-going surveillance of childhood neuro-degenerative diseases in the UK.

Having started surveillance in 1997, funding for the PIND Study ceases at the end of 2024, when the Study will close.

(External collaborators on this project: Dr C Verity, Mrs E Baker, Ms AM Winstone, Ms P Maunder)

2.7 Surveillance of potential occupational exposure to CJD

UK Health Security Agency (formerly 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. Two healthcare workers and one laboratory worker have 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 in the UK continues to be undertaken to determine if any exposure to prion disease occurred – there is no evidence to indicate the occurrence of occupational exposure to the prion agent in the UK.[13] [14]

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9 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.

10 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.

11 Verity C, Winstone AM, Stellitano L, Will R, Nicoll, A. The epidemiology of progressive intellectual and neurological deterioration in childhood. Arch Dis Child 2010; 95:361-364 deterioration in childhood. Arch Dis Child 2010; 95:361-364.

12 Verity C, Baker E, Maunder P, Pal S, Winstone AM. Differential diagnosis of progressive intellectual and neurological deterioration in children. Dev Med Child Neurol 2021; 63(3): 287-294.

13 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.

14 Mackenzie JM, Urwin P, Mackenzie G, Knight RSG, Will RG, Molesworth AM. Occupations of cases of vCJD in the UK. Poster presentation at Prion 2017, 23-26 May, Edinburgh.

The last two cases of vCJD recorded, both outside the UK, have been attributed to occupational exposure to the prion agent through laboratory work.[15]

(External collaborators on this project: K Sinka)

2.8 Prion surveillance in primary immunodeficiency patients

The study began in 2006 and aims 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.

By 31st December 2023, a total of 80 patients registered in 17 immunology centres across Great Britain had participated in the study. Of these, 46 remain alive. Participants have been followed up for approximately 1700 person-years following first exposure to UK-sourced immunoglobulin. In this time no participants have shown any clinical or pathological features suggestive of vCJD or evidence of abnormal prion protein in tissues tested.

(External collaborators on this project: M Turner, R McNairney, M Helbert, M Buckland, J Cooper, R Herriott, A Huissoon, M Gompels, S Jolles, C Chopra, G Hayman, P Wood, M Browning, T Garcez, A Herwadkar, D Lowe, M Thomas, C Bethune, S Goddard, A Anantharachagan, A Gururaj, S Mahabir, S Misbah)

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

The potential for secondary transmission of CJD has led to collaborative studies undertaken between the UK Haemophilia Centre Doctors Organisation, Institute of Child Health (London), NHS Blood and Transplant, National Prion Clinic, the UK Health Security Agency and Public Health 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[16].

As at 31st December 2023, 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. There have been no occurrences/diagnoses of CJD in individuals at risk through surgical exposures. Please see section 2.4 for figures relating to those at risk following treatment with pituitary derived hormones.

(External collaborators on this project: (H Ward, K Sinka, S Mead)

[15] Brandel, J-P et al. Variant Creutzfeldt-Jakob disease diagnosed 7.5 years after occupational exposure. NEJM 2020;383(1):83-85.

[16] Public Health England. Creutzfeldt-Jakob Disease (CJD) Biannual Update (February 2018). Health Protection Report, Vol 12, Number 5, 9 February 2018.

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 the majority of cases investigated referred from other centres across the UK (see Table 2). The laboratory maintains close links with other neuropathology centres across the UK and overseas, providing scientific, medical and technical advice in the handling and analysis of tissue from patients with a suspected prion disease. 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 2023, the numbers of cases diagnosed as prion diseases showed a decrease from the previous year but the overall number of referrals was lower than the previous year. No cases of vCJD were identified in the UK and none were referred from outside the UK.

In addition to the UK CJD surveillance work, the neuropathology laboratory is involved in a number of collaborative research and surveillance studies in relation to neuropathological diagnosis of CJD and other human prion diseases.

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 2 Breakdown of Laboratory Activities: Period 1st January 2023– 31st December 2023

	2023	2022
REFERRED CASES (UK)		
Sporadic CJD*	2*	13†
CJD, presumed sporadic[1]	4	0
Variant CJD	0	0
Iatrogenic CJD (GHT)	0	0
Iatrogenic CJD (Lyodura)	0	0
Gerstmann-Straussler-Scheinker Syndrome	0	0
Fatal Familial Insomnia	0	0
Variably protease sensitive prionopathy	0	0
No evidence of CJD	6	5
Alzheimer's disease	3	2
Lewy Body disease	1	4
Other forms of brain disease[2]	3	1
REFERRED CASES (EU)		
Sporadic CJD	4	3
Familial CJD	0	0
Fatal Familial Insomnia	0	0
No evidence of CJD	0	0
REFERRED CASES (ROW)		
CJD, presumed sporadic[1]	0	1
Other forms of brain disease[2]	0	1
TOTAL NUMBER OF CASES	**23**	**30**

NOTES

* The possibility of iCJD can not entirely be excluded for one of the cases who was treated with Merional OD, a urinary-dervied human gonadotrophin (hMG). However, to date, only human pituitary gonadotropin has been linked to latrogenic transmission of CJD, whereas hMG is considered low risk.

† Includes historical case (1) sent for prion evaluation

[1] Confirmed CJD that, in the absence of genetic testing for an inherited mutation, is presumed sporadic in origin.

[2] Other (2023) Cerebrovascular disease – 3

Abbreviations:
GHT Growth Hormone Therapy
ROW Rest of World
EU European Union

3.2 Protein Biochemistry 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 6 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 6

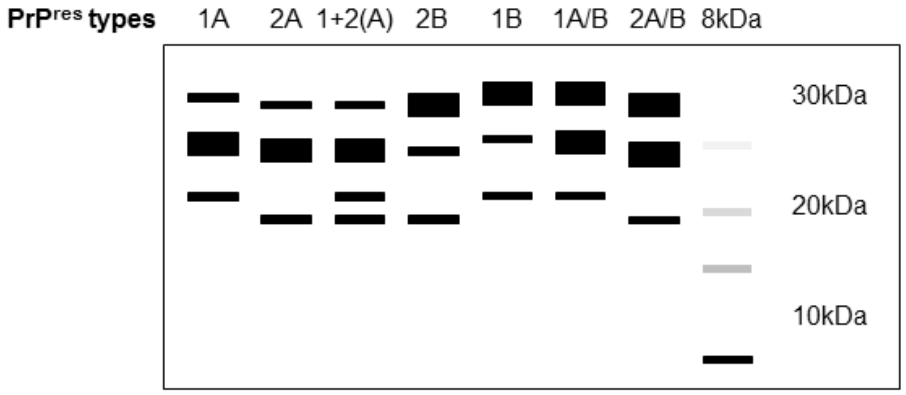

Figure 6 shows the diagrammatic representation of the main protease resistant prion protein (PrP^{res}) types found in the human prion disease brain as determined by proteinase K digestion and Western blot analysis. The classification of the banding pattern has two components, one numerical depending 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 and is a consistent feature present in all cases so far examined. However, a protein isotype resembling type 2B can also be found in cases of Fatal Familial Insomnia (FFI). Types 1B, 1A/B and 2A/B are often found in genetic CJD, Gerstmann-Sträussler-Scheinker disease (GSS) and FFI. The 8kDa pattern is characteristic of some cases of GSS and of Variably protease sensitive prionopathy (VPSPr).

UK Referrals

A total of 12 UK cases with frozen tissue were received and analysed in 2023. The results of the analysis were as follows:

Table 3 Breakdown of cases analysed in 2023

Diagnosis	Type	PrP^{res} +ve CNS
CJD	Sporadic	4/4
Alternative final diagnosis or CJD not determined		0/8

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

Table 4 PrP^{res} type / *PRNP* genotype breakdown of CJD cases analysed in 2023

Diagnosis	*PRNP* genotype	Type 1A	Type 2A
Sporadic CJD	MM	1	
	MV		2[1,2]
	VV		1

[1]One of the cases was reported as sCJD MV2K+C (according to the Parchi classification).
[2]The possibility of iCJD can not entirely be excluded for one of the cases who was treated with Merional OD, a urinary-dervied human gonadotrophin (hMG). However, to date, only human pituitary gonadotropin has been linked to latrogenic transmission of CJD, whereas hMG is considered low risk.

Non-UK referrals

There were 4 non-UK referral for Western blot analysis on frozen tissue. All four cases came from Sweden.

Table 5

Diagnosis	*PRNP* genotype	Type 1A	Type 2A
Sporadic CJD	MM	2	
	MV		1
	VV		1

3.3 Brain banking activities

The neuropathology laboratory houses the CJD Brain and Tissue Bank, which is part of the Edinburgh Brain and Tissue Bank, directed by Professor Colin Smith. The CJD Brain and Tissue Bank was used extensively in 2023 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. The Edinburgh Brain and Tissue Banks are part 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 (http://www.ed.ac.uk/clinical-brain-sciences/research/edinburgh-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

Two hundred and three 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 203 cases, 180 were resident in England, 12 were resident in Wales, 4 were resident in Northern Ireland and 7 were resident in Scotland. Twelve cases were still alive as at 31st December 2023 and one further case has been lost to follow-up after moving out of the UK after diagnosis. Seventy-eight of the cases had insertions in the coding region of the PrP gene, 66 carried the mutation at codon E200K, 21 at codon D178N, 6 at codon V210I, one at codon D167G, 2 at codon V163STOP, one at codon G54S, one at codon E211Q, 3 at codon E196K, 2 at codon P102L, one at codon P105S, one at codon Q112P, one at codon T188R and one at codon E220D. The remaining 18 were identified as genetic on the basis of relatives known to have had CJD. The mean age at death was 57, median 57 (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 60% MM, 21% MV, 19% VV (see Table 6). There appears to be evidence ($p<0.05$) of a change in the *PRNP* Codon 129 distribution in sCJD between the first and subsequent periods. The explanation for this remains unclear. It should be noted that not all cases are genotyped (data available on 65%) 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, 1990-2023

Deaths from sCJD	Percentage tested	MM (%)	MV (%)	VV (%)
Deaths from 1 January 1990 – 31 December 1999	63%	200 (70)	43 (15)	43 (15)
Deaths from 1 January 2000 – 31 December 2009	65%	255 (59)	90 (21)	87 (20)
Deaths from 1 January 2010 – 31 December 2023	65%	607 (57)	258 (24)	200 (19)
Total	65%	1062 (60)	391 (22)	330 (18)
Genotype distribution for the normal population[17]		(44)	(45)	(11)

PRNP Codon 129 distribution in variant CJD

In clinical cases for whom genetic data are available (n=161, 90%), 160 were methionine homozygotes at *PRNP* Codon 129 of the PrP gene and one case was heterozygous at *PRNP* Codon 129 of the PrP gene.

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

[17] 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 RT-QuIC

During the period January-December 2023, the laboratory received 253 cerebrospinal fluid (CSF) samples from suspected CJD patients residing in the UK, 10 samples from suspected CJD patients residing outwith the UK and 15 from young onset dementia patients (Table 7).

Table 7 Origin of CSF samples sent to the NCJDRSU for analysis January 2023 – December 2023

Patient Group	Number CSF samples received
Young Onset Dementia	15
Suspected CJD (non-UK)	10
Suspected CJD (UK)	253
Total number	278

Results of RT-QuIC analysis of 246 cases of suspected CJD in the UK are shown in Table 8. Testing was not not carried out on 7 samples: 6 testing not advised/no longer required and one not enough sample volume to test.

Table 8 CSF RT-QuIC results in 246 CSF samples from suspected CJD cases in the UK

Patient Group (n)	RT-QuIC number positive/total number analysed (% positive)
Neuropathologically confirmed sporadic CJD (2)	2/2 (100%)
Neuropathologically confirmed iatrogenic CJD (1)	0/1 (0%)
Probable sporadic CJD (118)	110/118 (93%)
Possible sporadic CJD (1)	0/1 (0%)
Probable genetic E200K (2)	2/2 (100%)
Probable genetic D178N (1)	1/1 (100%)
CJD unlikely but not ruled out (8)	0/8 (0%)
Not CJD (113)	0/113 (0%)

Section

4

PUBLICATIONS IN 2023

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2. Knight R. Overview on treatment of prion disease and decontamination of prions. In: Prions and Diseases, Eds: Zou & Gambetti, Springer Nature Switzerland 2023; Chapter 35: 727-74.

3. Peden AH, Libori A, Ritchie DL, Yull H, Smith C, Kanguru L, Molesworth A, Knight R, Barria MA. Enhanced Creutzfeldt-Jakob disease surveillance in the older population: Assessment of a protocol for screening brain tissue donations for prion disease. Brain Pathol. 2024 Mar;34(2):e13214. doi: 10.1111/bpa.13214. Epub 2023 Sep 28. PMID: 37771100; PMCID: PMC10901620.

4. Tam J, Centola J, Kurudzhu H, Watson N, MacKenzie J, Leitch M, Hughes T, Green A, Summers D, Barria M, Smith C, Pal S. Sporadic Creutzfeldt-Jakob Disease in the young (50 and below): 10-year review of United Kingdom surveillance. J Neurol. 2023 Feb;270(2):1036-1046. doi: 10.1007/s00415-022-11467-3. Epub 2022 Nov 5. PMID: 36334135; PMCID: PMC9886636.

5. Thomas S, Roberts B, Domanović D, Kramer K, Klochkov D, Sivasubramaniyam S, Miloslavich D, Plançon J-P, Rossi F, Misztela D, Kirkpatrick L, Turner M, Miflin G, Birchall J, Knight R. Safety profile of plasma for fractionation donated in the United Kingdom, with respect to variant Creutzfeldt-Jakob disease. Vox Sang 2023;118:345-353 [https://doi.org/10.1111/vox.13416]

6. Suleiman S, McGuire LI, Chong A, Ritchie DL, Boyle A, McManus L, Brydon F, Smith C, Knight R, Green A, Diack AB, Barria MA. Conservation of vCJD Strain Properties After Extraction and In Vitro Propagation of PrP^{Sc} from Archived Formalin-Fixed Brain and Appendix Tissues Using Highly Sensitive Protein Misfolding Cyclic Amplification. Mol Neurobiol. 2023 Nov;60(11):6275-6293. doi: 10.1007/s12035-023-03444-2. Epub 2023 Jul 13. PMID: 37442858; PMCID: PMC10533579.

Section

5

Staff based at the National CJD Research & Surveillance Unit, Edinburgh in 2023

Dr C Smith	Director, NCJDRSU, Professor of Clinical Neuropathology
Dr A Green	Reader (CSF analysis)
Dr S Pal	Senior Clinical Lecturer in Neurology and Honorary Consultant Neurologist
Dr M Barria	Group Leader/Research Fellow
Professor RSG Knight	Consultant Neurologist, Professor of Clinical Neurology
Dr D Summers	Consultant Neuroradiologist
Dr L Kanguru	Senior Epidemiologist
Ms J Ewins	Unit Manager
Mrs J Cavanagh-Anderson	IG Manager
Dr H Kurudzhu	Clinical Research Fellow
Dr J Centola	Clinical Research Fellow
Dr J Tam	Clinical Research Fellow
Dr A McDermott	Clinical Research Fellow
Dr A Peden	Postdoctoral Research Fellow
Ms J Mackenzie	Surveillance Co-ordinator
Mrs T Awe	National Care Co-ordinator and Senior Nurse
Ms J Jose	National Care Co-ordinator and Senior Nurse
Mr N Attwood	Database Manager
Dr D Ritchie	Postdoctoral Research Fellow
Dr N McKenzie	Postdoctoral Research Fellow
Dr S Suleiman	Postdoctoral Research Scientist
Ms S Lowrie	Senior Biomedical Scientist
Mrs M Andrews	Senior Biomedical Scientist
Ms H Yull	Senior Research Technical Officer
Mr G Fairfoul	Research Technical Officer
Ms K Burns	Laboratory Technical Officer
Ms A Chong	Research Technical Officer
Mrs F Frame	Secretariat
Mrs C Donaldson	Secretariat/Data Handler
Ms L Bond	Secretariat
Mrs K Karekwaivanane	Research Nurse
Dr S Cudmore	Research Associate
Ms C Wardhaugh	Research Assistant
Mr F Brydon	Research Technical Officer