**FIFTEENTH ANNUAL REPORT 2006**

# CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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

www.cjd.ed.ac.uk

Department of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
Keppel Street, London, WC1E 7HT

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# SUMMARY

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Surveillance Unit (NCJDSU) 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, which currently comprises a care coordinator and a secretary. It is based within the NCJDSU and was formed in response to concerns regarding the care of CJD patients.

The information provided in this fifteenth report continues to provide evidence of a good level of case ascertainment. There has been a lower number of referrals since 2003 but analysis suggests that much, if not all, of the decline is due to changes in the number of referrals who turn out not to be CJD cases. The number of sporadic cases remains relatively stable (the data for 2006 may still be incomplete). Detailed clinical and epidemiological information has been obtained for the great majority of patients. Although the post mortem rate for patients with suspected CJD has declined, in line with general autopsy rates in the UK, it remains high (around 60%). The number of brain specimens examined in the neuropathology laboratory for sporadic CJD declined from 52 in 2003 to 32 in 2004 but has remained stable (at 32) in both 2005 and 2006.

In 1990-2006 mortality rates from sporadic CJD in England, Wales, Scotland and Northern Ireland were, respectively, 0.89, 0.95, 0.95 and 0.57/million/year. The differences between these rates are not statistically significant ($p>0.6$). The mortality rates from sporadic CJD 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. The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR=132) and Northern Ireland (SMR=77). The variation in the observed mortality rates between the different regions within the UK is not statistically significant ($p>0.1$).

Up to 31 December 2006, there were 158 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 112 were confirmed by neuropathology. A further 7 probable cases were alive on 31st December 2006. The clinical, neuropathological and epidemiological features of these cases of vCJD are remarkably uniform and consistent with our 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 145 clinically affected cases of vCJD with available genetic analysis have been methionine homozygotes. The incidence of vCJD is higher in the north of the UK than in the south. Analysis of the incidence of vCJD onsets and deaths from January 1994 to December 2006 indicates that a peak has been 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 disease-related PrP in the spleen of a clinically unaffected blood recipient of PRNP-129 MV genotype is not inconsistent

with such an hypothesis. This case, along with the report of the prevalence of abnormal PrP in the large study of appendix and tonsil tissues, suggests the possibility of a greater number of preclinical or subclinical cases in the population than might be indicated by the present numbers of confirmed clinical cases.

The only statistically significant geographic cluster of vCJD cases in the UK was in Leicestershire. All geographically associated cases of vCJD are considered for investigation according to a protocol which involves the NCJDSU, colleagues at the HPA, HPS and local public health physicians.

The activities of the NCJDSU 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 $PrP^{res}$ in the spleen of a recipient of blood donated by someone incubating vCJD. In 2006 a further two cases of vCJD associated with blood transfusion were identified.

The success of the National CJD Surveillance Project continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. We are particularly grateful to the relatives of patients for their help with this study.

Section

2

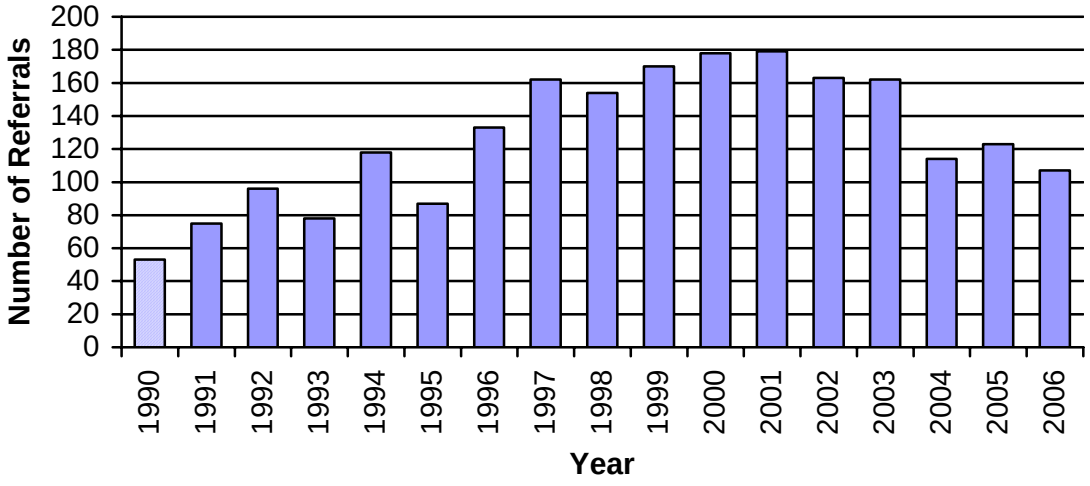
# CLINICAL SURVEILLANCE

The national surveillance of CJD in the UK was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the NCJDSU was to identify any change in the pattern of CJD that might be attributable to human infection with the agent responsible for the emergence of bovine spongiform encephalopathy (BSE) in cattle. Such a change was recognised in 1996 when vCJD was first described. The NCJDSU now aims to monitor characteristics of CJD, specifically sporadic CJD 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 sporadic, familial, iatrogenic and vCJD referred up to 31st December 2006 (with data ascertained up to 4th April 2007). Mortality data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective mortality data are available from 1985.

## *2.1 Referrals to NCJDSU*

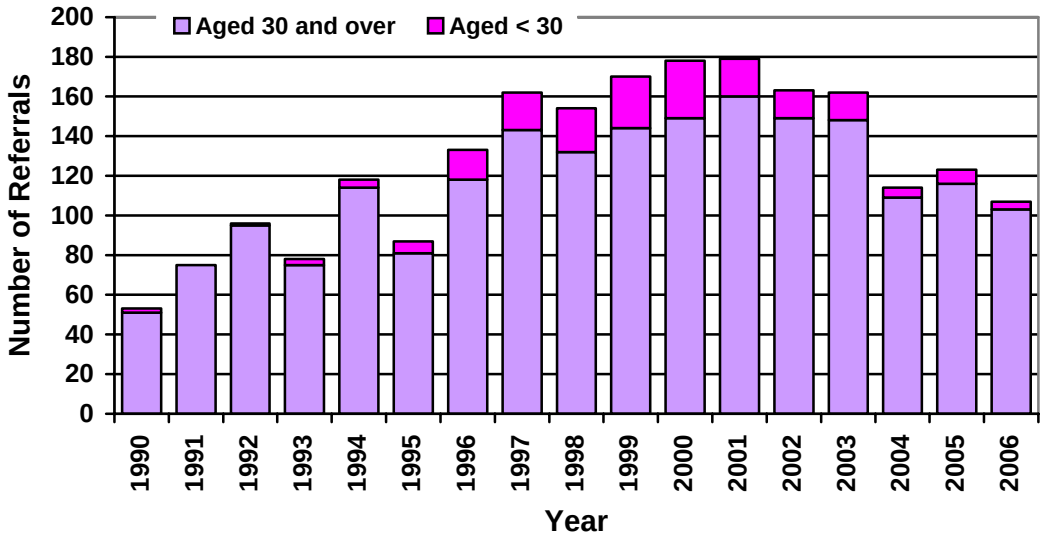
The NCJDSU receives referrals of suspect cases of CJD and a proportion of these will turn out not to have CJD. Referrals of suspect cases increased over the years after the present surveillance system began in 1990, particularly following the description of vCJD in 1996. Over the 1999-2003 period, the annual referral number varied little, between 162 and 179. In 2004, however, there were only 114 referrals, the lowest level since 1996, and they remained around this level over 2005-2006 (Figure 1a).

**Figure 1a Referrals to NCJDSU of patients with suspected CJD : 1 May 90 – 31 Dec 06**



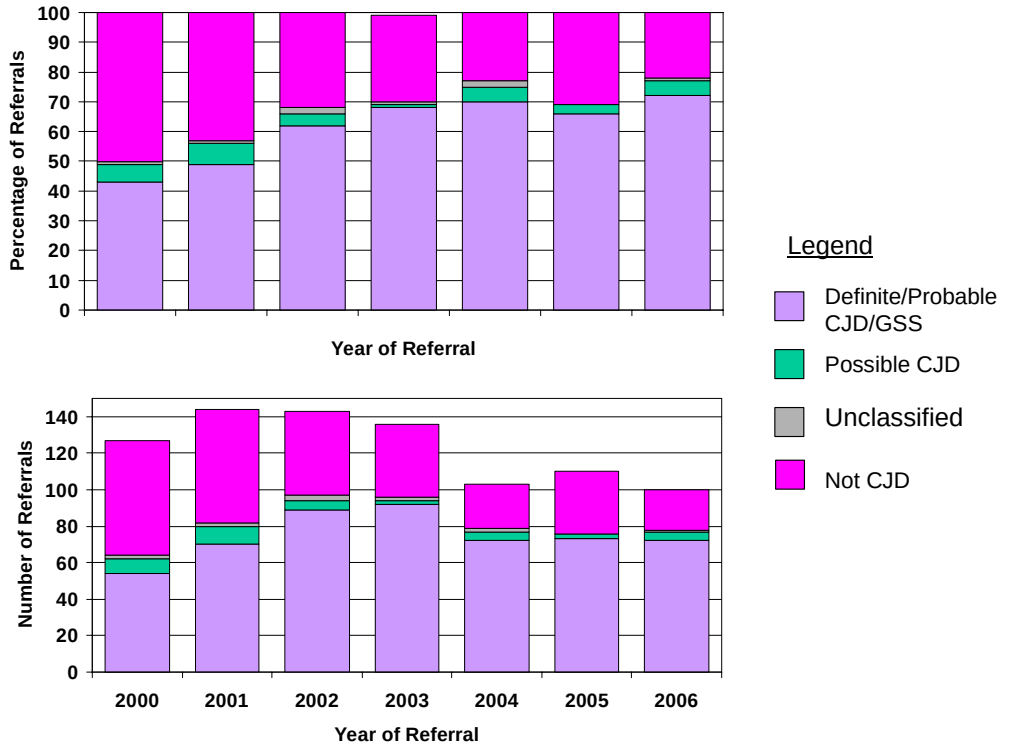
The number of referrals aged less than 30 has declined from a peak of 29 referrals in 2000 to 4-5 referrals per year in 2004-2006 (Figure 1b). At least part of this decline can be explained by the decline in vCJD cases over that period. The number of referrals aged 30-59 was very stable over the period 1996-2003 (range 49-60 individuals per year) but has dropped substantially since then (35, 34 and 29 referrals in 2004, 2005 and 2006 respectively). This age range includes more sporadic cases than the younger age group and the observed pattern does not fit particularly with the decline in vCJD cases. There is some evidence of extra-Poisson variation in the number of referrals per year ($p=0.03$ for the period 1996-2006); $p=0.06$ for the period 2000-2006). Referrals aged 60 and over were very stable immediately after 1996 (range 83-86 referrals per year between 1997 and 1999, were higher between 2000 and 2003 (range 96-106 per year) and then appeared to drop in 2004-2006 (74, 84, 74 referrals in each of the years). Over the entire period (1996-2006) there is at most weak evidence of extra-Poisson variation ($p=0.09$). A *post hoc* analysis comparing the period 2000-2003 with 2004-2006 suggests there has been a fall in referrals in this age group ($p=0.002$). Figure 1b shows number of referrals to NCJDSU split between age groups <30 and ≥30.

**Figure 1b Referrals to NCJDSU : 1 May 1990 – 31st December 2006: Age < 30 and age ≥ 30**




Over the period 2000-2006 the largest drop in referral numbers occurred in those whom eventually turned out not to be cases of CJD (Figure 1c). This suggests that the changes in numbers of referrals in the past couple of years is, at least in part, due to changes in the numbers of non-cases recorded as referrals.

**Figure 1c** **Diagnostic classification of referrals: 2000-2006* (shown as percentages and absolute numbers)**

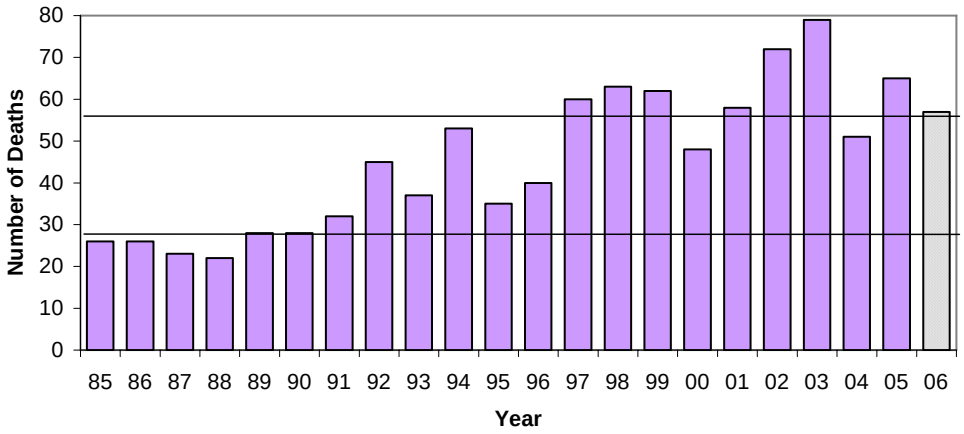



*excludes suspect vCJD referrals and vCJD cases

## *2.2 Sporadic Creutzfeldt-Jakob Disease*

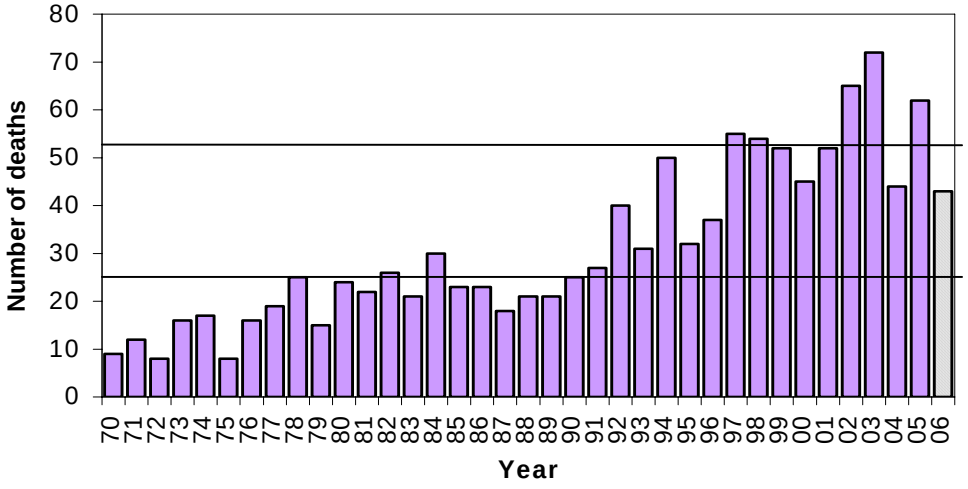
Between 1st January 1970 and 31st December 2006, 1286 cases of sporadic CJD were identified in the UK, of which 8 cases were alive on 31st December 2006. Two further cases were identified in Jersey but they are not included in the following UK analyses. Of these UK cases, 963 (75%) were classified as definite cases with the remainder classed as probable. Figure 2a shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2006, Figure 2b shows similar data for England and Wales between 1970 and 2006 and Figure 2c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2006. Table 2 shows data on cases of CJD (deaths and cases still alive as of 31st December 2006) according to age. In England and Wales the number of deaths identified each year increased from an average of about 10 per year at the beginning of the 1970s, to about 30 to 50 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are available for Scotland and Northern Ireland there is no clear secular trend. Over the period 1990-2006 the average crude annual mortality rates from sporadic CJD per million population were 0.89 in England, 0.95 in Wales, 0.95 in Scotland and 0.57 in Northern Ireland (Table 1). When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant ($p > 0.6$).

**Figure 2a Deaths from sporadic CJD, UK, 1985-2006**



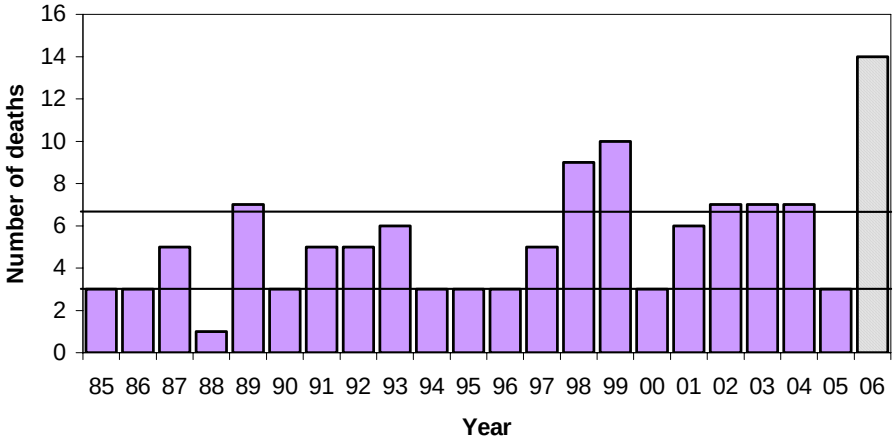

Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year. Data for 2006 may be incomplete.

**Figure 2b Deaths from sporadic CJD, England and Wales, 1970-2006**




Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year. Data for 2006 may be incomplete.

**Figure 2c Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2006 (please note different scale from Figs 1a and 1b)**




Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year. Data for 2006 may be incomplete.

**Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 1st January 1990 to 31st December 2006**

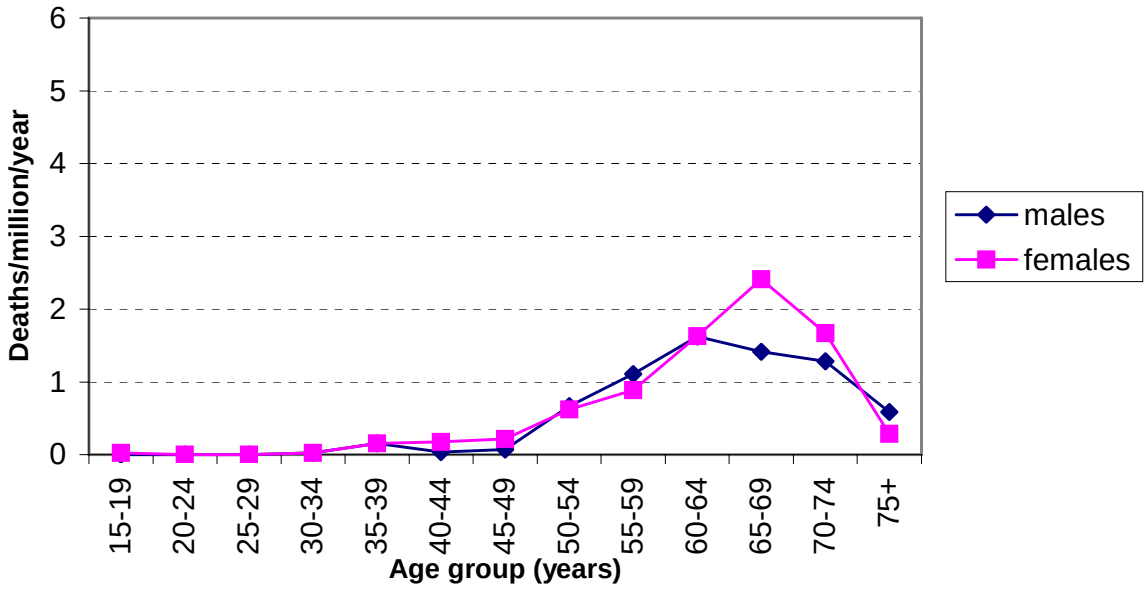
| | No of cases | Total no (mortality rate/million/ annum)* |
|---|---|---|
| **ENGLAND** | | |
| North | | |
| Cleveland | 7 | |
| Cumbria | 12 | |
| Durham | 6 | 47 (0.89) |
| Northumberland | 6 | |
| Tyne & Wear | 16 | |
| East Midlands | | |
| Derbyshire | 9 | |
| Leicestershire | 15 | |
| Lincolnshire | 9 | 51 (0.73) |
| Northamptonshire | 2 | |
| Nottinghamshire | 16 | |
| South East | | |
| Bedfordshire | 7 | |
| Berkshire | 10 | |
| Buckinghamshire | 5 | |
| East Sussex | 11 | |
| Essex | 33 | |
| Greater London | 87 | 253 (0.83) |
| Hampshire | 24 | |
| Hertfordshire | 13 | |
| Isle of Wight | 2 | |
| Kent | 19 | |
| Oxfordshire | 11 | |
| Surrey | 12 | |
| West Sussex | 19 | |
| North West | | |
| Cheshire | 14 | |
| Greater Manchester | 33 | 99 (0.91) |
| Lancashire | 27 | |
| Merseyside | 25 | |
| **WALES** | | |
| Clwyd | 7 | |
| Dyfed | 3 | |
| Gwent | 7 | |
| Gwynedd | 11 | |
| Mid Glamorgan | 11 | |
| Powys | 2 | |
| South Glamorgan | 3 | |
| West Glamorgan | 3 | |
| **TOTAL FOR WALES** | | **47 (0.95)** |
| **NORTHERN IRELAND** | 16 | **16 (0.57)** |

| | No of cases | Total no (mortality rate/million/ annum)* |
|---|---|---|
| **ENGLAND** | | |
| Yorkshire & Humberside | | |
| Humberside | 9 | |
| NorthYorkshire | 14 | |
| South Yorkshire | 25 | 79 (0.92) |
| West Yorkshire | 31 | |
| East Anglia | | |
| Cambridgeshire | 6 | |
| Norfolk | 15 | 35 (0.98) |
| Suffolk | 14 | |
| South West | | |
| Avon | 22 | |
| Cornwall | 14 | |
| Devon | 17 | |
| Dorset | 17 | 106 (1.30) |
| Gloucestershire | 12 | |
| Somerset | 14 | |
| Wiltshire | 10 | |
| West Midlands | | |
| Hereford & Worcs. | 8 | |
| Shropshire | 4 | |
| Staffordshire | 19 | 69 (0.77) |
| Warwickshire | 5 | |
| West Mids (Met) | 33 | |
| **TOTAL FOR ENGLAND** | | **739 (0.89)** |
| **SCOTLAND** | | |
| Borders | 3 | |
| Central | 5 | |
| Dumfries & Galloway | 1 | |
| Fife | 5 | |
| Grampian | 12 | |
| Highland | 1 | |
| Lothian | 19 | |
| Strathclyde | 30 | |
| Tayside | 4 | |
| Islands (Shetland) | 3 | |
| Islands (Orkney) | 0 | |
| Islands (Western Isles) | 0 | |
| **TOTAL FOR SCOTLAND** | | **83 (0.95)** |

* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 17-year period of the study.

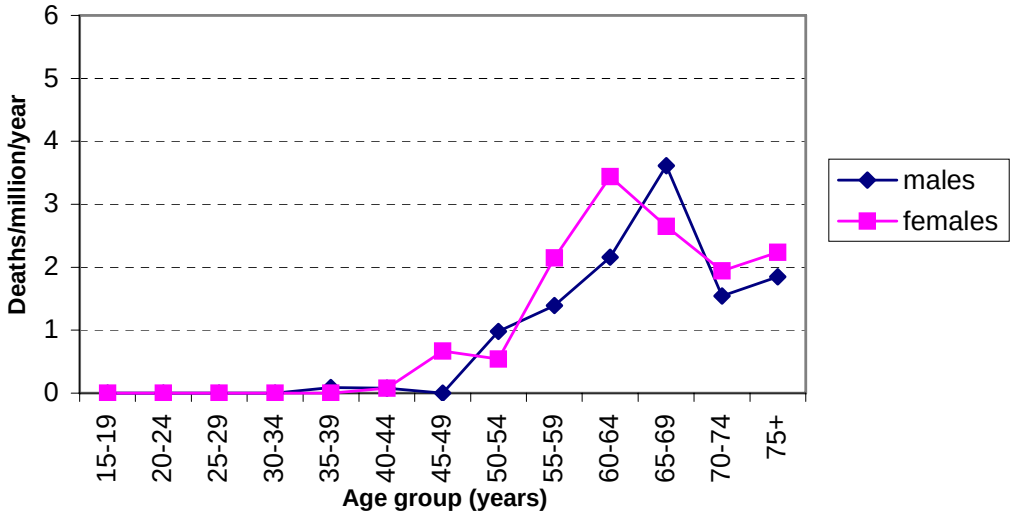
Figure 3a, 3b and 3c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-06, respectively. The median ages of cases at death during these time periods were 64, 66 and 68 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all three periods, the mortality rates increased up to ages 60-74 years and then declined. This decline might be explained by an under-ascertainment in the most elderly. The change in the sex ratio, affecting particularly older cases, with a male excess after 1995, was examined in the 2001 annual report. The explanation for this trend remains unclear.

**Figure 3a Age- and sex-specific mortality rates from sporadic CJD in the UK 1970-1989 (note: from 1970-1984 only England & Wales, thereafter UK)**



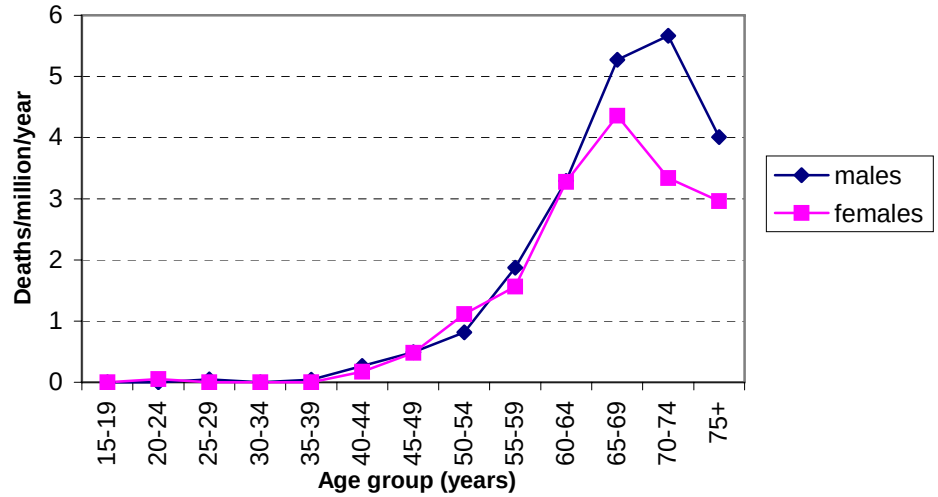

Mortality rates calculated using 1981 Census for GB and 1991 Census for NI

**Figure 3b Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1995**




Mortality rates calculated using 1991 Census

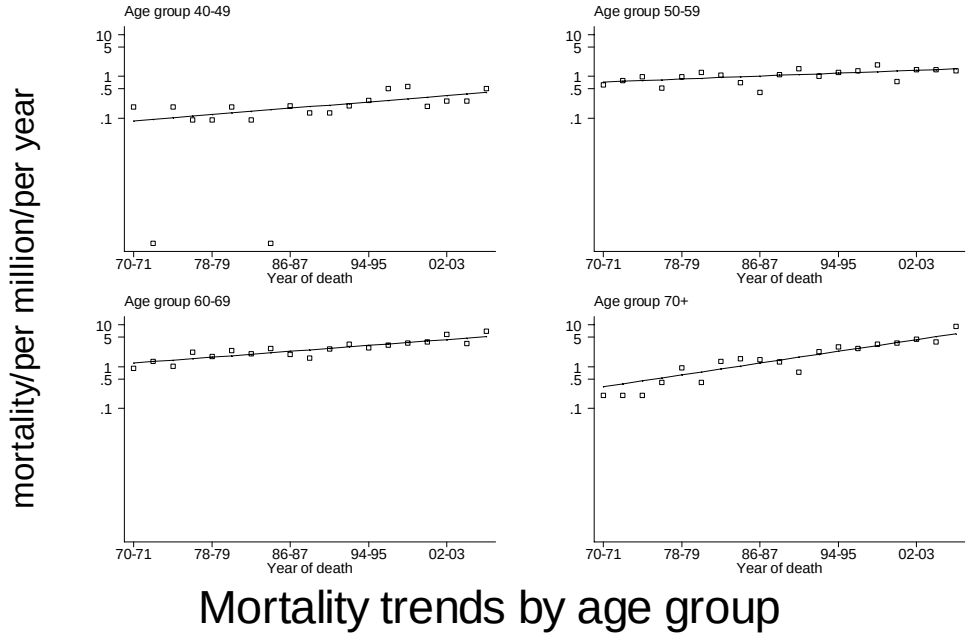
**Figure 3c Age- and sex-specific mortality rates from sporadic CJD in the UK 1996-2006**




Mortality rates calculated using 2001 Census

An analysis of age specific trends from 1970 to 2006 (Figure 4) shows there has been an increase in recorded mortality over time in all age groups, but that the greatest relative increase has occurred in those aged 70 years and above. Currently the mortality rate in this age group is similar to that in the age group 60-69 years. The temporal increases in mortality are statistically significant in all age groups ($p=0.003$, $p=0.001$, $p<0.001$, $p<0.001$ for age groups 40-49, 50-59, 60-69 and ≥70 years respectively). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

**Figure 4 Trends in mortality from sporadic CJD by age: 1970-2006**




Mortality rates calculated using 1981, 1991 & 2001 Census for time periods 1970-1985, 1986-1995 and 1996-2006 respectively.

Table 2 presents, by 2-year period, the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged <50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 25 per year in the UK in recent years.

**Table 2 Cases of sporadic CJD in England and Wales (from 1970) and the UK (from 1985) by two year period**

| Age at death (yrs) | Year of death | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 70-71 | 72-73 | 74-75 | 76-77 | 78-79 | 80-81 | 82-83 | 84-85[1] | 86-87 | 88-89 | 90-91 | 92-93 | 94-95 | 96-97 | 98-99 | 00-01 | 02-03 | 04-05 | 06[2] | **Total**[2,3] |
| 10-19 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| 20-29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | **2** |
| 30-39 | 1 | 0 | 0 | 2 | 2 | 1 | 1 | 4 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | **14** |
| 40-49 | 2 | 0 | 2 | 1 | 1 | 2 | 1 | 0 | 3 | 2 | 2 | 3 | 4 | 8 | 9 | 3 | 4 | 4 | 2 | **53** |
| 50-59 | 7 | 9 | 11 | 6 | 11 | 14 | 12 | 8 | 5 | 13 | 18 | 12 | 15 | 20 | 28 | 11 | 21 | 21 | 5 (2) | **247 (2)** |
| 60-69 | 9 | 13 | 10 | 22 | 17 | 24 | 20 | 28 | 22 | 18 | 30 | 39 | 32 | 35 | 40 | 43 | 65 | 39 | 19 (4) | **525 (4)** |
| 70-79 | 2 | 2 | 2 | 4 | 9 | 4 | 11 | 16 | 18 | 14 | 7 | 21 | 34 | 30 | 35 | 38 | 51 | 37 | 22 (2) | **357 (2)** |
| 80-89 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 7 | 3 | 6 | 10 | 11 | 9 | 15 | 9 | **76** |
| 90+ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | **2** |
| **Total** | **21** | **24** | **25** | **35** | **40** | **46** | **47** | **56** | **49** | **50[3]** | **60** | **82** | **88** | **100** | **125** | **106** | **151** | **116** | **57 (8)** | **1278 (8)** |

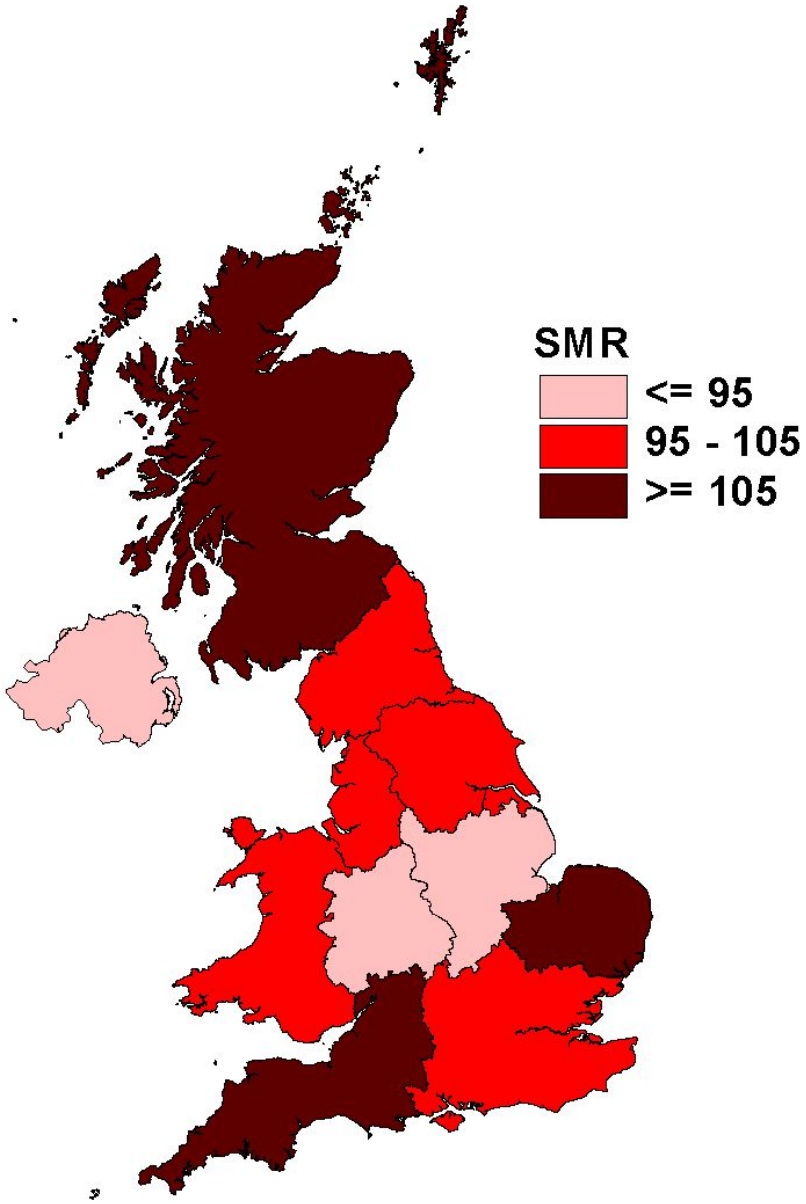
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included.

[2] Deaths up to 31st December 2006. Numbers in parentheses indicate additional cases alive on 31st December 2006. Data for 2006 not yet complete.

[3] Total includes one case whose age at death was unknown.

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st January 1990 to 31st December 2006 were calculated (Figure 5). An SMR of 100 equates to average mortality rate. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p>0.1$). Regions of relatively high mortality are South West (SMR=132), Scotland (SMR=107) and East Anglia (SMR=105). Low mortality rates were observed in Northern Ireland (SMR=77), East Midlands (SMR=82) and West Midlands (SMR=86). The highest SMR (132 in South West) arose from 106 cases observed compared with 80 expected, an excess of about 1.5 cases every year compared to the national average. For both Scotland and East Anglia the total numbers of excess cases was approximately 6 and 2 respectively.

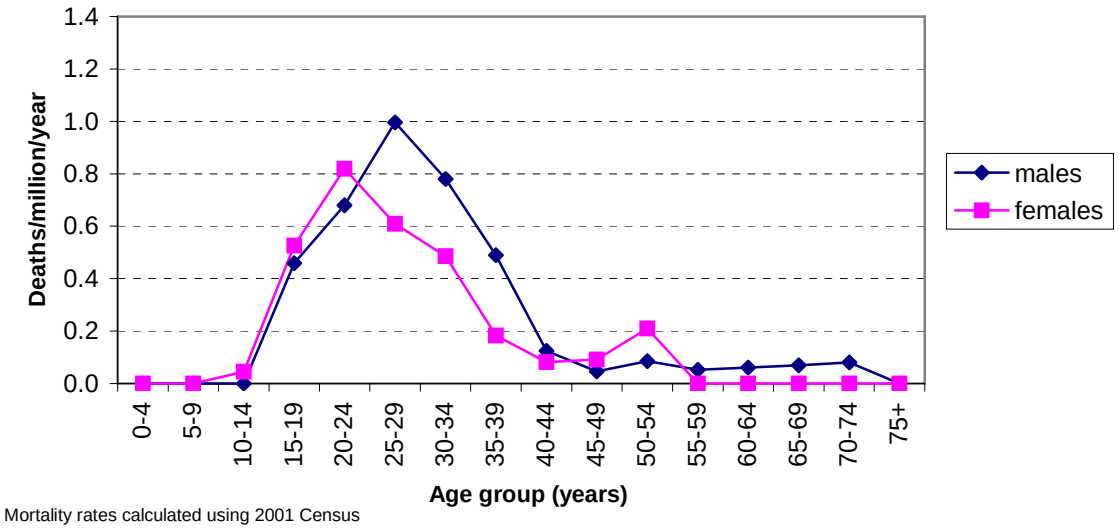
**Figure 5 Standardised mortality ratios (SMRs) by standard region, UK 1 January 1990 - 31 December 2006**



## 2.3 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2006, 165 cases of definite or probable vCJD had been identified in the UK (112 definite, 46 probable who did not undergo post mortem and 7 probable cases still alive). Seventy-three (44%) of the 165 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 66 years for the median age at onset and 67 years for the median age at death for sporadic CJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. To date, no case of vCJD has been identified in the UK in individuals born after 1989. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2006 are shown in Figure 6. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-40). The median duration of illness for cases of sporadic CJD was 4 months (range 1 to 74) during the period 1990-2006.

**Figure 6 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2006**




Mortality rates calculated using 2001 Census

### Incidence of vCJD onsets and deaths from January 1994 - December 2006

Each quarter data on diagnosed cases of vCJD in the UK are reviewed in order to investigate trends in the underlying rate at which disease onsets and deaths are occurring. The following analysis reviews the data to the end of December 2006.

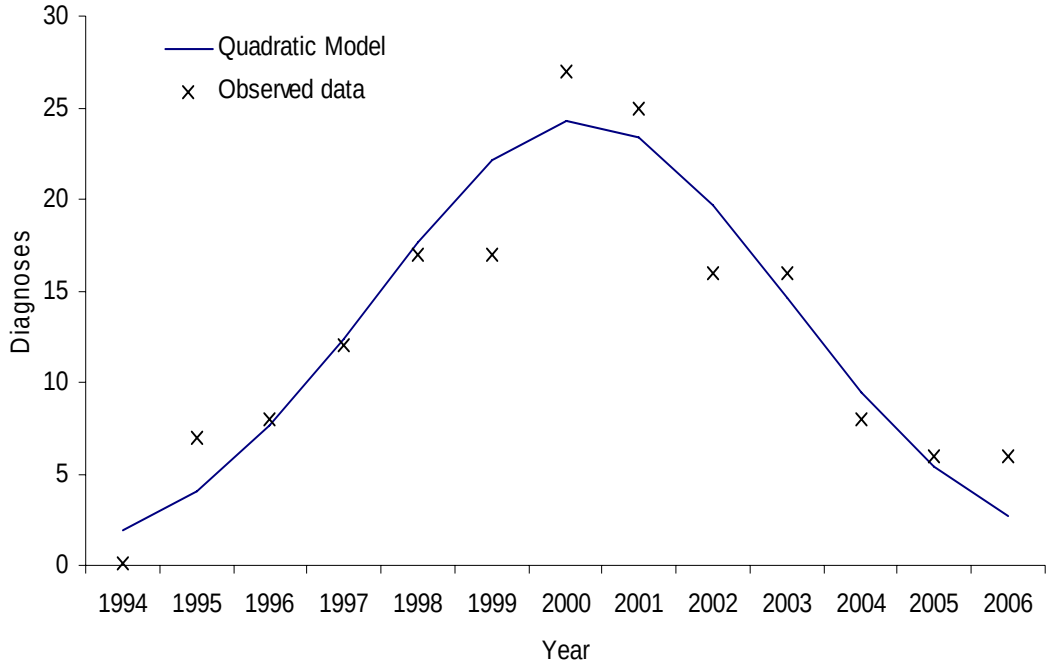
### Methods

The incidence of deaths and diagnoses was modelled by Poisson regression using polynomials. Most deaths and diagnoses are reported quickly so an adjustment for reporting delay is not necessary. With the exception of some increase in 2005 the age at death has not increased as might have been expected if exposure to BSE ceased by the early 1990s. In order to examine this further the cases were stratified by year of death and birth cohort (pre1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts.

## Results for Diagnoses

The quadratic trend model provided the best fit with a significant improvement on the simple exponential model ($p<0.001$). This model output is shown in Figure 7 and estimates that the current annual incidence of diagnoses is 2.7. If the quadratic model is correct then the peak is estimated to have occurred in mid 2000. A model with a cubic term was also fitted but did not provide an improved fit ($p=0.13$).

**Figure 7: Quadratic-exponential model for vCJD diagnoses incidence trend**



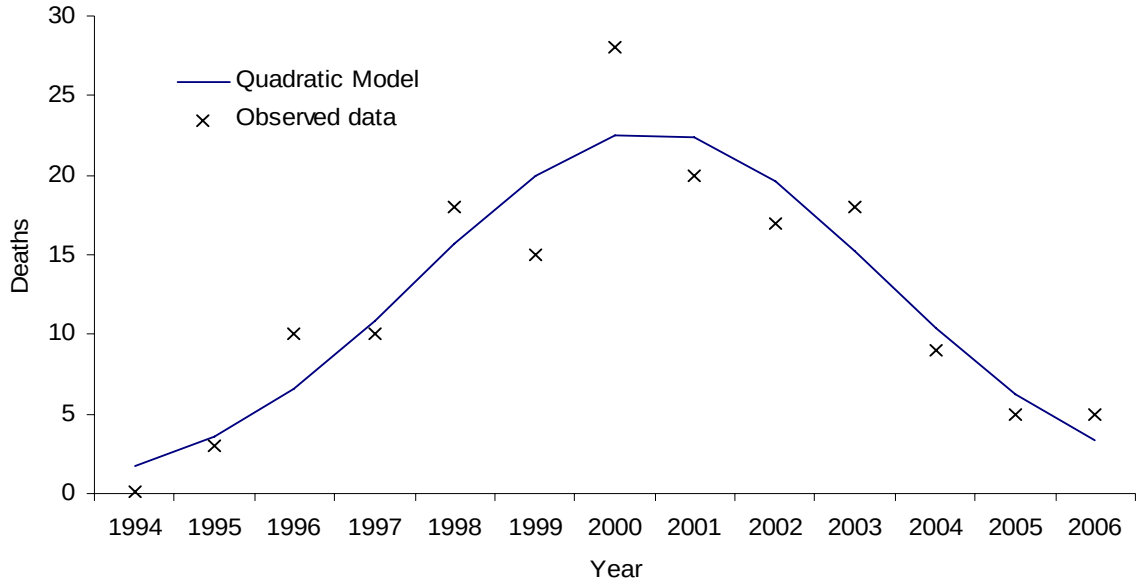

*Prediction for diagnoses in 2007*

Extrapolation of the model with the quadratic term predicts just one diagnosis in the next 12 months with a 95% prediction interval of 0 to 3. The cubic model predicts 3 diagnoses with 95% prediction interval of 0 to 6.

## Results for Deaths

The quadratic trend model provided the best fit with a significant improvement on the simple exponential model ($p<0.001$). The results from this model are shown in Figure 8 and it estimates that the current annual incidence of deaths is 3.3. If the quadratic model is correct then the peak is estimated to have occurred in mid 2000. A model with a cubic term was also fitted but did not provide an improved fit ($p=0.30$).

**Figure 8 Quadratic-exponential model for vCJD deaths incidence trend**




*Predictions for deaths in 2007*

Extrapolation of the model with the quadratic term predicts just 2 deaths in the next 12 months with a 95% prediction interval of 0 to 5. Note that 7 cases are alive so this may be an underestimate. The cubic model predicts 3 deaths with 95% prediction interval of 0 to 6.

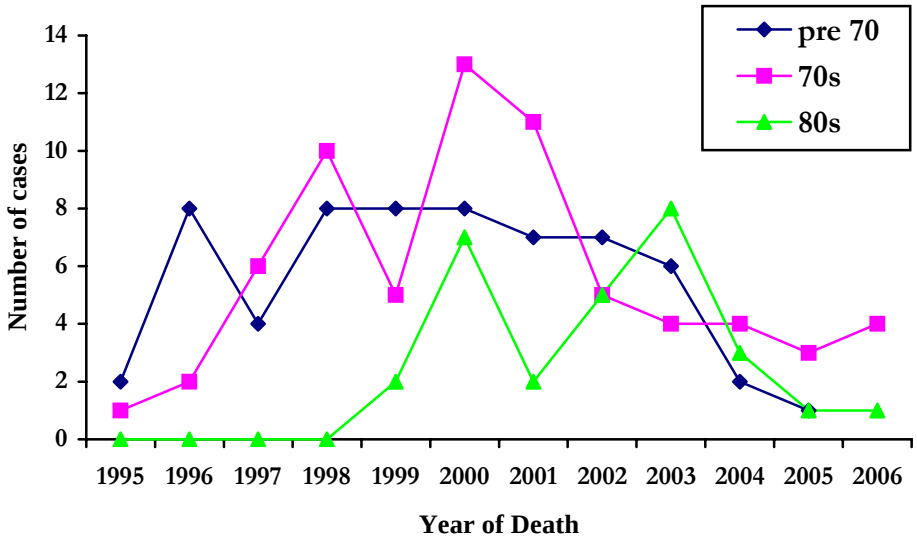
*Assessment of Predictions made at the end of December 2005*

The quadratic model gave a prediction of 2 deaths with a 95% prediction interval of 0 to 5. The actual observed number was 5, which is consistent with the quadratic model.

## Deaths by cohort

The age at death has so far remained stable, contrary to what might be expected given that most exposure to BSE is presumed to have ceased in the early 1990s. To examine this in more detail the epidemic curves (quadratic model) are compared in those born before 1970 with two other groups: those born in the 1970s and the 1980s. This analysis showed significant differences by cohort in the shape of the fitted curves ($p<0.001$). The main difference is due to the fact that in the 1980s cohort no deaths were seen prior to 1999 (Figure 9). This finding is consistent with those born in the 1980s being infected towards the end of the BSE epidemic when they were older rather than at the beginning. This requires a lower exposure/susceptibility in the very young, which is reasonable because no cases have been seen to date in individuals born in the 1990s. An alternative explanation of the stable age distribution could be shorter incubation periods in those exposed as teenagers/young adults than those exposed as young children. Note that both these explanations would only be expected to yield a temporary stable age distribution.

**Figure 9 Deaths by year and birth cohort**




## Summary

Results from modelling the underlying incidence of diagnoses and deaths indicate that the epidemic reached a peak in the year 2000 when there were 27 diagnoses and 28 deaths and has since declined to a current incidence of about 3 diagnoses/deaths per year. Extrapolating the best fitting model (the quadratic model) gives an estimate of 2 deaths in the next 12 months (95% prediction interval 0 to 5), however with 7 cases currently alive a prediction of 2 deaths is likely to be a slight underestimate.

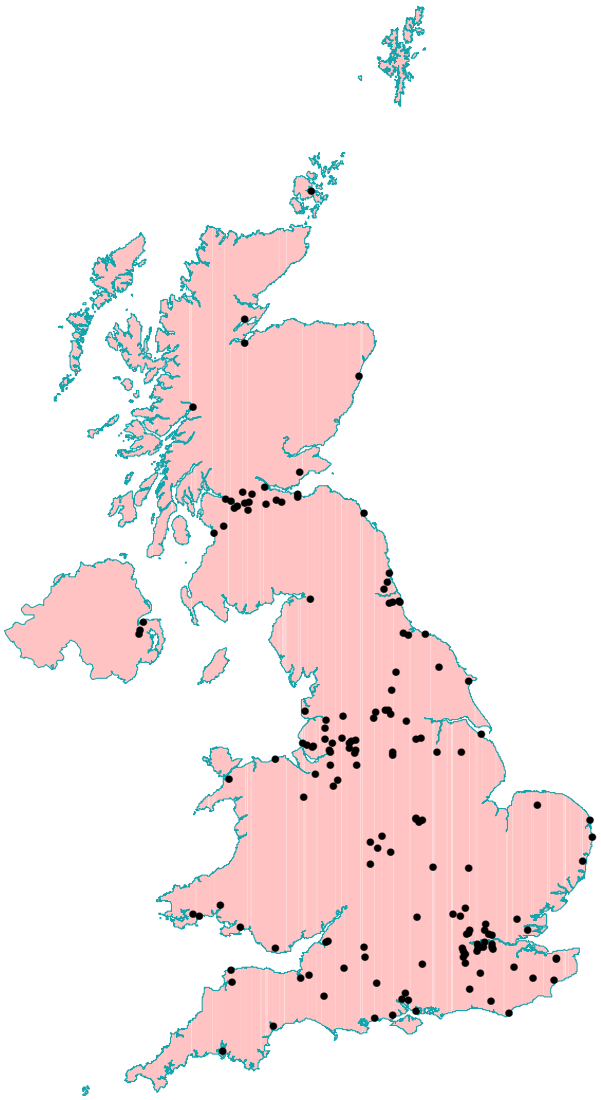
An analysis that looked at deaths by birth cohort (pre 1970, 1970s, 1980s) showed that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths of individuals born in the 1980s were only seen from 1999 onwards.

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 groups. There is also the possibility of ongoing person to person spread as seen with four instances of transfusion association vCJD infection to date, who received blood from earlier cases. Three of these individuals developed vCJD (one diagnosed in 2003 and two in 2006), whilst the fourth died from causes unrelated to vCJD, but was found on post mortem examination to have abnormal prion protein present in the spleen and a lymph node.

## Geographical distribution of vCJD

Figure 10 shows the geographical distribution, by place of residence at onset, of 164 cases of vCJD in the UK. For one additional case the address at onset is known only at county level. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution by county of residence at onset (for all 165 vCJD cases) and residence at death (for 155 vCJD cases who had died by 31st December 2006 and were resident in the UK at death), along with the crude mortality rate per million population per annum of each standard region.

**Figure 10 Geographical distribution of places of residence at onset of symptoms of vCJD (n=164*)**



* in one case only county of residence was known and could not be plotted.

**Table 3 Cases of definite and probable vCJD shown by region and county of onset (n=165†) and region and county of death (n=155‡)**

| | No of cases resident at onset | No of cases resident at death (mortality rate*) |
|---|---|---|
| **ENGLAND** | | |
| North | | |
| Cleveland | 3 | 3 |
| Cumbria | 1 | 1 |
| Durham | 1 | 2 |
| Northumberland | 3 | 4 |
| Tyne & Wear | 4 | 2 |
| **Total** | **12** | **12 (0.33)** |
| East Midlands | | |
| Derbyshire | 0 | 1 |
| Leicestershire | 4 | 5 |
| Lincolnshire | 2 | 2 |
| Northamptonshire | 1 | 1 |
| Nottinghamshire | 0 | 0 |
| **Total** | **7** | **9 (0.19)** |
| South East | | |
| Bedfordshire | 0 | 0 |
| Berkshire | 1 | 1 |
| Buckinghamshire | 0 | 0 |
| East Sussex | 2 | 2 |
| Essex | 2 | 2 |
| Greater London | 16 | 14 |
| Hampshire | 6 | 3 |
| Hertfordshire | 3 | 3 |
| Isle of Wight | 0 | 1 |
| Kent | 5 | 5 |
| Oxfordshire | 1 | 1 |
| Surrey | 6 | 4 |
| West Sussex | 1 | 1 |
| **Total** | **43** | **37 (0.18)** |
| North West | | |
| Cheshire | 7 | 8 |
| Greater Manchester | 10 | 8 |
| Lancashire | 4 | 4 |
| Merseyside | 4 | 4 |
| **Total** | **25** | **24 (0.32)** |
| **WALES** | | |
| Clwyd | 1 | 0 |
| Dyfed | 3 | 3 |
| Gwent | 0 | 0 |
| Gwynedd | 1 | 1 |
| Mid Glamorgan | 0 | 0 |
| Powys | 0 | 0 |
| South Glamorgan | 1 | 1 |
| West Glamorgan | 1 | 0 |
| **WALES TOTAL** | **7** | **5 (0.15)** |
| **NORTHERN IRELAND TOTAL** | **3** | **2 (0.10)** |

| | No of cases resident at onset | No of cases resident at death (mortality rate*) |
|---|---|---|
| **ENGLAND** | | |
| Yorkshire & Humbs | | |
| Humberside | 2 | 2 |
| NorthYorkshire | 4 | 3 |
| South Yorkshire | 5 | 5 |
| West Yorkshire | 6 | 7 |
| **Total** | **17** | **17 (0.29)** |
| East Anglia | | |
| Cambridgeshire | 1 | 1 |
| Norfolk | 2 | 2 |
| Suffolk | 3 | 2 |
| **Total** | **6** | **5 (0.20)** |
| South West | | |
| Avon | 2 | 1 |
| Cornwall | 2 | 1 |
| Devon | 3 | 4 |
| Dorset | 1 | 1 |
| Gloucestershire | 0 | 0 |
| Somerset | 4 | 5 |
| Wiltshire | 3 | 1 |
| **Total** | **15** | **13 (0.23)** |
| West Midlands | | |
| Hereford & Worcs. | 0 | 1 |
| Shropshire | 1 | 1 |
| Staffordshire | 0 | 0 |
| Warwickshire | 1 | 2 |
| West Mids (Met) | 4 | 6 |
| **Total** | **6** | **10 (0.16)** |
| **ENGLAND TOTAL** | **131** | **127 (0.22)** |
| **SCOTLAND** | | |
| Borders | 0 | 0 |
| Central | 1 | 1 |
| Dumfries & Galloway | 0 | 0 |
| Fife | 2 | 1 |
| Grampian | 1 | 1 |
| Highland | 3 | 2 |
| Lothian | 4 | 4 |
| Strathclyde | 12 | 12 |
| Tayside | 0 | 0 |
| Islands (Shetland) | 0 | 0 |
| Islands (Orkney) | 1 | 0 |
| Islands (Western Isles) | 0 | 0 |
| **SCOTLAND TOTAL** | **24** | **21 (0.35)** |

* mortality rate/million/annum based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the period 1st May 1995 to 31st December 2006.

† includes cases still alive at 31st December 2006. ‡ excludes 3 cases who died abroad.

Table 4 shows cumulative regional rates of vCJD based on cases' place of residence in 1991, rather than at onset, and the population aged 10 years and above resident at that time.

Age- and sex- standardised incidence ratios (SIRs) based on cases' place of residence in 1991 are shown in Figure 11 for the 11 standard regions of the UK.

**Table 4 Distribution of 165 vCJD cases by standard region of residence on 1st January 1991**

| Standard region (in order of latitude of the centre of the region) | Population aged 10 years and above at the 1991 census | Number (cumulative incidence/million) of vCJD cases by place of residence in 1991 |
|---|---|---|
| Scotland | 4,363,684 | 19 (4.35) |
| North | 2,635,785 | 11 (4.17) |
| Yorkshire & Humberside | 4,202,051 | 18 (4.28) |
| North-West | 5,326,333 | 25 (4.69) |
| East Midlands | 3,444,391 | 12 (3.48) |
| West Midlands | 4,464,592 | 10 (2.24) |
| East Anglia | 1,775,687 | 6 (3.38) |
| Wales | 2,466,669 | 5 (2.03) |
| South-East | 15,010,650 | 43 (2.86) |
| South-West | 4,055,268 | 13 (3.21) |
| Northern Ireland | 1,320,430 | 3 (2.27) |
| Total | 49,065,540 | 165 (3.36) |

**Figure 11 Standardised incidence ratios (SIRs) up to 31st December 2006 of vCJD by standard region on 1st January 1991**

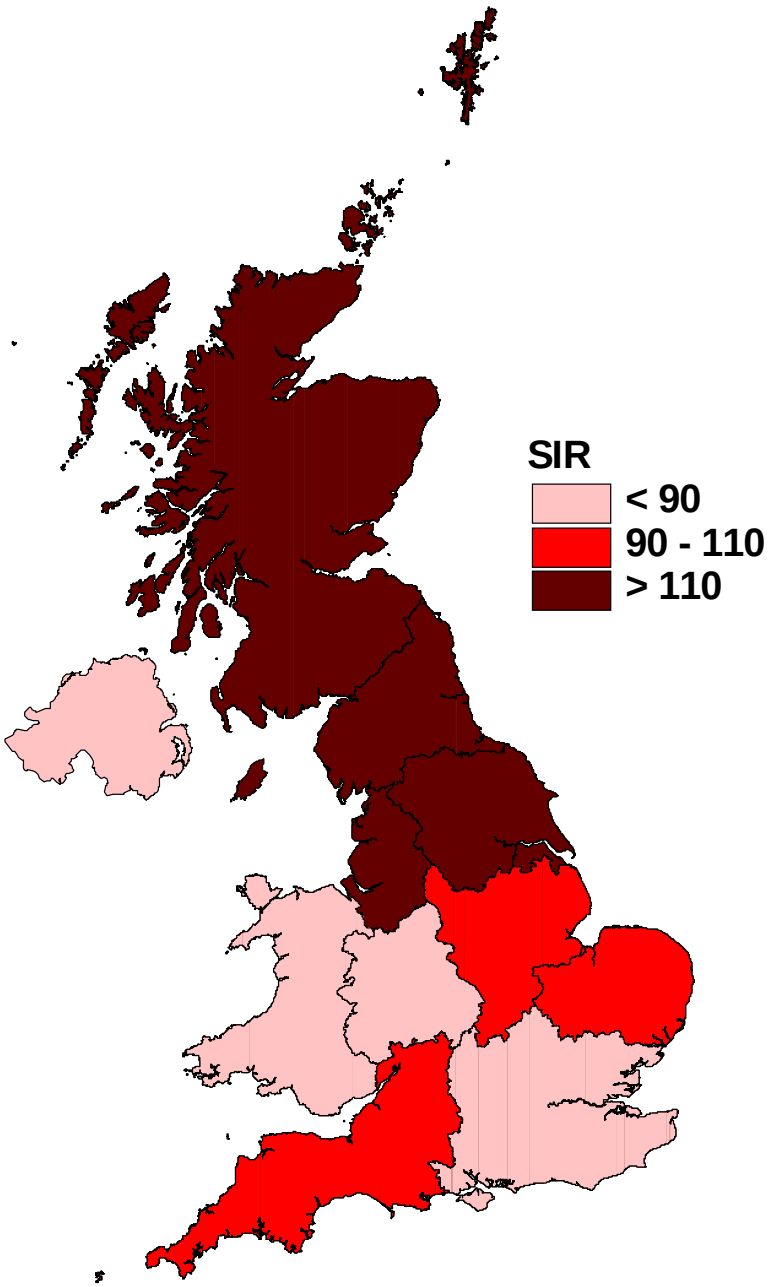



Table 5 shows the distribution of cases between the "North" and the "South" according to place of residence in 1991. We originally performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. The "South" comprised the remaining 6 regions: Wales, West Midlands, East Midlands, East Anglia, South West, South East. The excess of cases previously identified in the "North" (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) has declined somewhat as further cases have accrued, but remains statistically significant. The rate ratio controlling for age and sex is 1.55 (95% c.i., 1.14, 2.12), i.e. 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.

**Table 5 Comparison of cumulative incidence in the "North" of the UK (excluding Northern Ireland) with that in the "South"**

| Region | Population aged 10 years and above at the 1991 census | Number (rate/million) of vCJD cases by place of residence at 1st January 1991 | |
|---|---|---|---|
| | | First 51 cases | Total |
| "North" (North West, Yorks & Humbs, Northern, Scotland) | 16.6 million | 26 (1.57) | 73 (4.42) |
| "South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia) | 31.2 million | 25 (0.80) | 89 (2.85) |
| Total (rate ratio*) | 47.8 million | 51 (1.94) | 162 (1.55) |

*North versus South, adjusted for age and sex

Northern cases were slightly older at onset than southern cases (median of 27 years versus 26 years; p=0.5), a similar proportion were male (55% of both northern and southern cases).

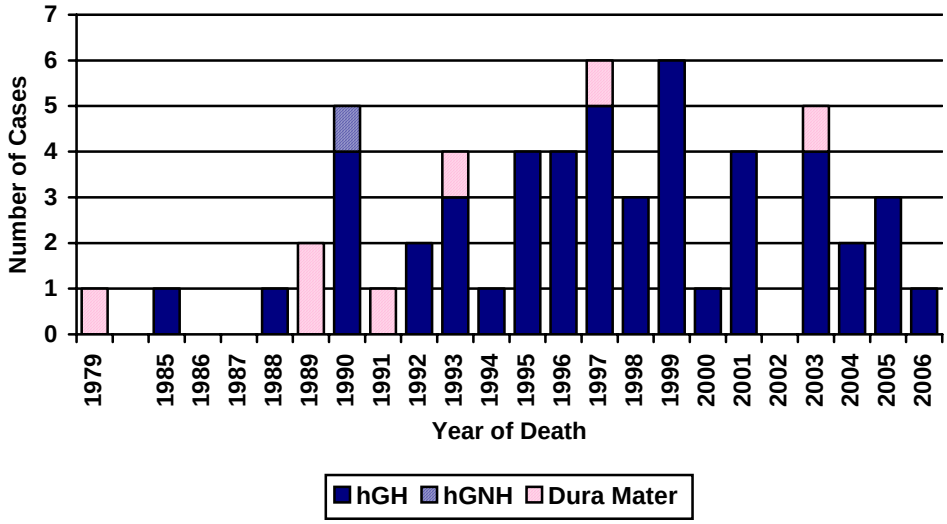
**Geographically Associated Cases of vCJD**

Geographically associated cases of vCJD are defined to be two or more cases of probable or definite vCJD with a geographical association, either through proximity of residence or through another link with the same location (occupational, educational or social/recreational). A total of thirteen investigations into geographically associated cases of vCJD have been conducted in the UK. The Leicestershire cluster of five cases remains the only statistically significant cluster of cases to date. None of the concluded investigations have revealed any suggestion of possible iatrogenic transmission. No evidence emerged from these investigations in any of the areas apart from Leicestershire of bovine heads being split or brains removed by local butchers in their shops during the relevant time period.

## *2.4 Iatrogenic Creutzfeldt-Jakob disease*

Since 1970, up to 31st December 2006, 60 cases of CJD attributable to iatrogenic exposure have been identified, 7 in individuals receiving dura mater implants, 52 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN). Fifty-seven of these individuals have died (Figure 12) and 3 were still alive as at 31st December 2006.

**Figure 12 Deaths from iatrogenic CJD, 1979-2006**




The mean age at death of the hGH/hGN group was 31 years (with a range of 20-46 years) and for the dura mater cases 42 years (range 27-59 years).

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, have been published in 2003.[1]

A study of the accumulated UK experience with dura mater-related CJD, including incubation periods, was undertaken and the results published in 2006.[2]

## *2.5 Transfusion Medicine Epidemiology Review*

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDSU 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. The following report is based on vCJD cases who donated or received blood and does not include data from the ongoing study of sporadic CJD.

### Methods

vCJD cases (definite and probables) are notified to the UKBS by NCJDSU; a search establishes whether any have acted as donors. Donation records are checked and all components traced through hospital records. Details of all identified recipients are forwarded to NCJDSU for subsequent checking.

In the reverse procedure, patients with vCJD reported to have received blood transfusions are identified by NCJDSU and notified to UKBS. Details of transfusions are traced through hospital

[1] 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.

[2] 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.

records and relevant blood donors identified. The identity of donors is notified to NCJDSU for subsequent checking.

**Results**

Thirty-one vCJD cases were reported to have been blood donors. Four additional cases who were not reported to have been blood donors were found to be registered with UKBTS. One of these cases was found to have been a blood donor while the other three cases were registered as a donor but never made any donations. Twenty-four of the cases have been traced at blood centres, including the four additional cases mentioned above. Components derived from donations made by 18 of these individuals were actually issued to hospitals. It has been established that 66 components were transfused to identified recipients.

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[3]. 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[4]; protease-resistant prion protein ($PrP^{res}$) was detected in the spleen but not in the brain. This is 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[5]. The fourth recipient (Case 4) who also 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 this donor (Donor 3) developed symptoms of vCJD[6].

In the reverse study, 14 vCJD cases were reported to have received blood transfusions in the past. A further case received a blood transfusion after onset of illness and is excluded from further discussion. Checks revealed that of these 14 cases, one was not transfused, 4 had transfusions which pre-dated available records (pre-1980), and 9 had records of transfusion which could be traced. These 9 individuals had received 207 donor exposures (with one patient given 103 components), which have been traced to 190 named donors (two of whom had vCJD as described above). No additional links between donors and recipients have been identified by the reverse study.

**Conclusion**

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 P.E. Hewitt, Dr C.A. Llewelyn, Ms M Malfroy).

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[3] 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.

[4] 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.

[5] 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.

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

## 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 of seven paediatric neurologists which allocates the cases to a diagnostic category[7-8].

As at 31st December 2006, after nearly 10 years surveillance, 2183 patients with suspected PIND have been reported. The Expert Group has discussed 1537 cases, of which 933 have a confirmed underlying cause other than vCJD, being categorised into 114 known neurodegenerative diseases. There have been 6 cases of vCJD; 4 definite and 2 probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest case of vCJD identified to date.

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

[7] 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.

[8] 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.

Section

3

# CASE-CONTROL STUDY

Since May 1990 a case-control study of CJD has been carried out in the UK to investigate potential risk factors for variant and sporadic CJD. Patients themselves are usually too unwell to answer questions when they are seen by members of the Unit. Therefore, relatives of patients with suspected CJD are approached and, with informed consent, interviewed about the patient using a standard questionnaire relating to possible risk factors for CJD, including residential, occupational, dietary and medical histories. To maximise the study's validity, this interview takes place as early as possible after a person is suspected of having CJD. We are indebted to the families of those with suspected CJD, who agree to be interviewed at what is an extremely difficult time in their lives.

The choice of the source of controls, with which to compare the information for cases, is extremely important in a case-control study. There are a number of possible choices each of which has its own advantages and disadvantages in terms of suitability as controls, practicalities of recruitment and cost. Since 1990 there have been some variations in control recruitment for the CJD risk factor study:

**1990-1997**

**Hospital controls:** For each suspect case, an age- and sex-matched patient with a non-neurological disease at the same hospital was identified as a control. Eighty hospital controls have been recruited for vCJD cases (between August 1995 to July 2006) and 227 for sporadic CJD cases (between May 1990 and June 1998).

**1998-2002**

**Community controls:** With the diagnosis of the first cases of vCJD, it was decided that in addition to hospital controls for variant cases, and instead of hospital controls for sporadic cases, sex and age-matched community controls would be recruited through general medical practices. Community controls are more suitable than hospital controls for the investigation of potential medical risk factors. However, major difficulties were encountered arising from the complex process of recruitment that we were required to follow for general practice based controls. Therefore, a revised strategy for control recruitment was devised and recruitment of controls through general medical practices ceased in 2002.

**2002-2006**

**General population controls:** During 2002/03 a one-off recruitment of approximately 900 general population controls throughout the UK was carried out on our behalf by the National Centre for Social Research, which is the largest independent social research institute in Britain.

These controls were selected across a wide age range so that their data could be compared with that from both variant and sporadic CJD cases.

**Friend nominated controls**: In addition, from 2003 to the end of 2006, a second group of controls comprising friends nominated by relatives of cases was recruited. Relatives of cases were asked to nominate a friend who would agree to be interviewed about a relative of theirs (the control), who was age- and sex-matched to the case. The degree of relative between control and friend was matched to that between the case and their relative. Consent of the control was sought before the friend was interviewed.

The recruitment of this control group was complex, involving relatives of cases at a difficult point in their lives. Often relatives needed time (sometimes many months, especially if their relative had recently died) to consider whether they wished to take part in the study and, of course, they could change their mind at any time in the process. Once they agreed to take part they then were asked to identify a suitable friend. The friend was contacted by the Unit's research nurse to seek agreement to take part in the study. If they agreed, a suitable relative of the nominated friend had to be identified, contacted and agree to participate. Finally if both nominated friend and their relative agreed to take part in the study, the interview could take place between the friend and one of the Unit's research nurses.

Table 6 summarises, to the end of 2006, the progress made in recruiting relative-nominated controls. The table shows that control recruitment has been completed for about a third each of variant (15/41) and sporadic (85/250) cases approached. Relatives of 78% (32) of variant cases and 73% (182) of sporadic cases agreed to participate in the study. However, of those agreeing, 8 (25%) of the relatives of variant cases and 49 (27%) of the relatives of sporadic cases were unable to nominate a friend. This was because either they had not told a suitable friend about the illness or they did not have a friend with a suitable relative. The recruitment of this control group has now ceased (as of 2007).

**Table 6: Relative nominated controls - recruitment process**

| | **Variant CJD** Number | **Sporadic CJD** Number |
|---|---|---|
| Relatives of cases approached | 41 | 250 |
| ▪ Relatives of cases agreeing to participate and able to nominate a friend | 24 | 133 |
| ▪ Relatives agreeing to participate but unable to nominate a friend | 8 | 49 |
| ▪ Relatives considering whether to participate* | 2 | 17 |
| ▪ Relatives of cases refused | 7 | 51 |
| Friend of relative contacted | 24 | 123 |
| ▪ Friend of relative agreeing to participate | 17 | 102 |
| ▪ Friend not replied | 7 | 6 |
| ▪ Friend refused consent | 0 | 15 |
| Control consented | 16 | 101 |
| Friend interviewed regarding control | 15 | 85 |

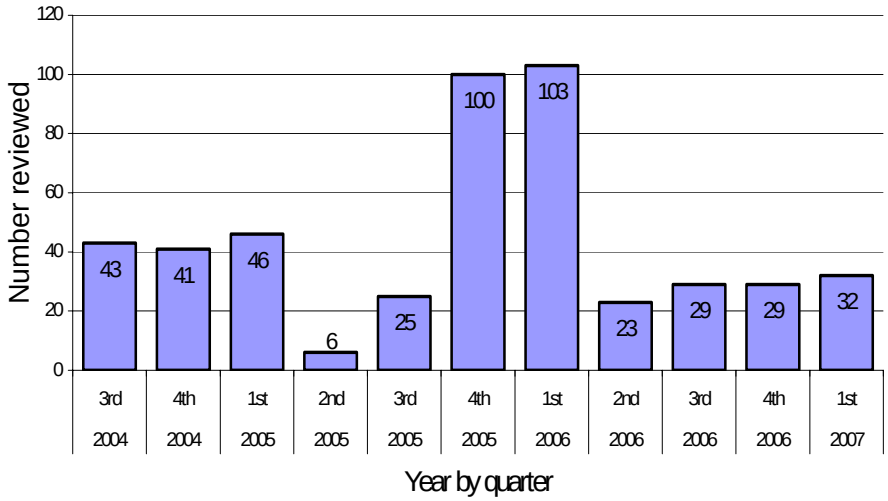
* these relatives have been contacted and informed that recruitment into the study has 'closed'

**2007 onwards**

In light of the declining numbers of cases of vCJD observed between 2000 and 2006, it was decided that on-going control recruitment would cease at the end of 2006. However, risk factor information continues to be collected for cases of CJD. In addition, because of the interest in the possibility of onward transmission of CJD through medical procedures, it was decided that efforts should be concentrated on collecting medical records of both cases and general population controls in order to investigate the possibility of secondary transmission of CJD. The data acquired from primary care records are likely to be more accurate than those obtained from relatives and not subject to recall bias.

For cases, records are obtained prospectively as they are identified. For the general population controls, we have written consent from three-quarters (approximately 600) to access their primary care medical and dental records. To assemble this information is a huge task and involves visiting practices throughout the UK. This work is in progress for primary care medical records and we have obtained records for 477 individuals to date. Figure 13 shows progress in obtaining control records over time.

**Figure 13 Number of GP records reviewed for NatCen Controls**




*It should be noted that during 4th quarter of 2005 and 1st quarter of 2006, there was a second research nurse employed who was dedicated to this task only. For the remainder of the time there was one research nurse with a number of other duties in addition to obtaining primary care records.*

**Results from the case-control study of risk factors for variant and sporadic CJD**

In 2004 we undertook the first comprehensive analysis of data from variant cases compared with general population controls.[9] Reported frequent consumption of beef and beef products thought likely to contain mechanically recovered and/or head meat, including burgers and meat pies, was associated with increased risk of vCJD, as was reported frequent chicken consumption. The reported histories of surgical operations were generally similar for cases and controls, with the exception of a small group of minor operations, possibly attributable to under-reporting in controls. Cases and controls had similar reported occupational histories and exposure to animals. These findings are consistent with dietary exposure to contaminated beef products being the main route of infection of vCJD, but recall bias cannot be excluded as an explanation for the findings

[9] Ward HJT, Everington,D, Cousens,SN, Smith-Bathgate,B, Leitch,M, Cooper,S, Heath,C, Knight,RSG, Will,RG. Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. Annals of Neurology 2006; 59: 111-120.

regarding diet. There was no convincing evidence of increased risk through medical, surgical or occupational exposure, or exposure to animals.

During 2006 we undertook analyses comparing cases of sporadic CJD with the group of general population controls in relation to surgical and medical risk factors. The results of these analyses have been submitted for publication in a peer-reviewed journal

## Dentistry

There is concern that dentistry may be a possible mechanism through which vCJD is transmitted between people. We have published data comparing the dental history of cases with hospital and with community controls. The results do not provide convincing evidence of an increased risk of vCJD associated with reported dental treatment[10]. However, these analyses were based on dental treatment as reported by relatives. This information is likely to be incomplete and therefore we are currently undertaking a pilot project with colleagues at Glasgow Dental School to investigate whether it is possible to trace dental records for cases and controls. Unlike GP records, when a person changes dentists, their records do not 'move' with them. We aim to apply for further funding to extend this to a full study in 2007.

[10] Everington D, Smith AJ, Ward HJ, Letters S, Will RG, Bagg J. Dental treatment and risk of variant CJD – a case control study. Br Dent J 2007; 202(8): E19.

Section

4

# LABORATORY ACTIVITIES

Laboratory investigations are part of the internationally-agreed diagnostic criteria for CJD, both during life (CSF protein analysis and PrP genetic studies) and post-mortem (neuropathology and protein studies). The NCJDSU 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.

## *4.1 Neuropathology – Statement of Progress and Surveillance Activities*

The neuropathology laboratory in the NCJDSU continues to maintain its diagnostic and research activities, including the work of the protein laboratory. 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. The laboratory is part of the NeuroPrion network of centres of excellence across Europe. Since 2001 the autopsy rates for sporadic and vCJD have declined, in keeping with national trends. This is reflected in the number of cases examined in 2006, with fewer cases of vCJD and cases with either no evidence of CJD or with other neurological disorders than in the previous year. These changes are small and compatible with random fluctuations. However, the number of cases of sporadic, iatrogenic and familial CJD/GSS is largely unchanged and the laboratory workload remains high (Table 7). In 2006 we identified, with colleagues in Plymouth, a case of GSS with a novel mutation in the prion protein gene (S132I). As in 2005, as a result of the Department of Health's guidelines for the examination of brain biopsy specimens, the increased number of cerebral biopsies referred to NCJDSU has continued. These samples require intensive investigation by conventional histology, immunocytochemistry, PET blot and western blot analysis. Many of these biopsy samples do not show any specific histological abnormalities, and so a conclusive diagnosis cannot always be reached, although a descriptive report is issued for each case. In 2006, the commonest alternative diagnosis to CJD was cerebrovascular disease, with smaller numbers of cases of Alzheimer's disease and Lewy body disease, which have been the commonest alternative diagnoses in the past.

The laboratory and its staff continue to participate in a range of EQA activities related to both technical and diagnostic neuropathology. The laboratory continues to develop more sensitive techniques for the detection of abnormal PrP in tissues, both within the CNS and in a wide range of non-neural tissues. 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 NCJDSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

**Table 7 Breakdown of Laboratory Activities: Period 1st January 2006– 31st December 2006**

| | CURRENT YEAR | PREVIOUS YEAR |
|---|---|---|
| **REFERRED CASES (UK)** | | |
| Sporadic CJD | 32 | 32 |
| Familial CJD | 2 | 1 |
| Variant CJD (vCJD) | 1 | 4 |
| Iatrogenic CJD (Growth Hormone) | 1 | 1 |
| Iatrogenic CJD (Lyodura) | 0 | 0 |
| Gerstmann-Straussler-Scheinker Syndrome | 2 | 3 |
| Fatal Familial Insomnia | 0 | 0 |
| No evidence of CJD (no alternative pathological diagnosis) | 23 | 25 |
| Alzheimer's disease | 2 | 3 |
| Dementia with Lewy Bodies | 2 | 1 |
| Other forms of brain disease† | 7 | 9 |
| | | |
| **REFERRED CASES (EU)** | | |
| Sporadic CJD | 2 | 2 |
| Familial CJD | 1 | 0 |
| Variant CJD | 0 | 4 |
| GSS | 0 | 0 |
| Other forms of brain disease | 5 | 4 |
| | | |
| **REFERRED CASES (ROW)** | | |
| Sporadic CJD | 0 | 0 |
| Variant CJD | 0 | 0 |
| Familial CJD | 0 | 0 |
| Other forms of brain disease | 1 | 0 |
| **TOTAL NUMBER OF CASES** | **81** | **89** |

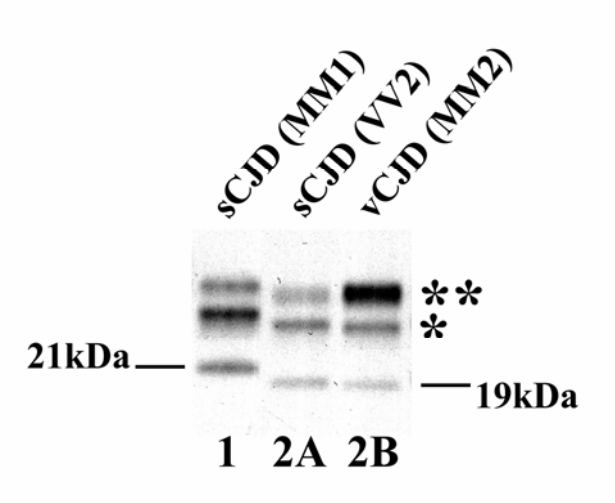
† Other forms of brain disease**:** meningoencephalitis (1); intracerebral haematoma (1); cerebrovascular disease, hypoxic/ischaemic brain damage and infarction (4); pituitary adenoma (1)

**Abbreviations:**
EU European Union
ROW Rest of World

## *4.2 Prion Protein Laboratory*

Prion protein typing is carried out as a routine diagnostic test on all suspected cases of CJD where fresh brain tissue is received by the NCJDSU. Small quantities of cerebral cortex are homogenized, treated with proteases and the size and relative abundance of the three $PrP^{res}$ glycoforms determined by Western blot analysis. The prion protein isotype is classified as type 1 if the nonglycosylated form has a molecular weight of ~21kDa or type 2 if the nonglycosylated form has a molecular weight of ~19kDa. The suffix B is used to denote a $PrP^{res}$ isotype where the diglycosylated band predominates. The remaining type 2 cases where the diglycosylated band does not predominate are termed type 2A. The type 2B isotype has previously found to be characteristic of vCJD. A typical result is shown in Figure 14.

**Figure 14: PrP$^{res}$ types in sporadic and variant CJD**




Western blot analysis of protease-resistant prion protein (PrP$^{res}$) in two cases of sporadic CJD (sCJD) of the MM1 and VV2 subtypes and in a case of vCJD (vCJD (MM2)). The size of the nonglycosylated (bottom band) is either 21kDa (termed type 1) or 19kDa (termed type 2). Diglycosylated PrP$^{res}$ (**) predominates in the vCJD and the pattern is termed type 2B to distinguish it from type 2 cases in which the monoglycosylated form (*) predominates (type 2A).

### *UK Referrals*

A total of 46 UK cases with frozen tissue were received and analyzed in 2006, representing a 12% decrease in the number of cases with frozen tissue referred to the NCJDSU for analysis compared with the previous year. The results of the analysis were as follows:

**Table 8 Breakdown of cases analysed in 2006**

| **Diagnosis** | **Type** | **PrP$^{res}$ +ve CNS** |
|---|---|---|
| CJD (n=31) | Sporadic | 28/28[1] |
| | Variant | 1/1 |
| | Familial | 2/2 |
| Gerstmann Straussler Scheinker disease (GSS) | | 2/2 |
| Alternative final diagnosis or not determined | | 0/13[2] |

[1]includes one brain biopsy
[2]includes six brain biopsies and one tonsil biopsy

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

**Table 9 $PrP^{res}$ type / *PRNP* genotype breakdown of CJD and GSS cases analysed in 2006**

| Diagnosis | *PRNP* genotype | Type 1 | Type 2A | Type 1+2 | Type 2B | <10 kDa | Total |
|---|---|---|---|---|---|---|---|
| Sporadic CJD | M/M | 14[1] | | | | | 14 |
| | M/V | 5 | 4 | 1 | | | 10 |
| | V/V | 1 | 2 | 1 | | | 4 |
| | Total | 20 | 6 | 2 | | | 28 |
| Variant CJD | M/M | | | | 1 | | 1 |
| Familial CJD | 4 repeat Insertion-MM | 1 | | | | | 1 |
| | E200K-MV | 1 | | | | | 1 |
| GSS | P102L-MM | 1 | | | | | 1 |
| | S132I-MM | | | | | 1 | 1 |

[1]includes one brain biopsy and two cases of sCJD of the panencephalopathic type

***Non-UK referrals***

Two requests for Western blot analysis were also received from non-UK referrals. One was found to be type 1+2 and was confirmed as a case of familial CJD (5 repeat insertion) in a Swedish patient homozygous for methionine and the other was a $PrP^{res}$ negative tonsil biopsy from Hong Kong.

## 4.3 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 2006 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. Funding from MRC was obtained in January 2007 to support the activities of the Bank for the next 2 years, under the direction of the Steering Group for the MRC Edinburgh Brain Banks. The local management of the bank has been modified accordingly and a revised request form is available for all potential users. The activities of the Bank comply with current guidelines from MRC and the Royal College of Pathologists, and the Human Tissue (Scotland) Act and the Human Tissue Act.

## 4.4 Molecular Genetics

**Familial CJD**

Eighty-two cases of familial CJD (excluding cases of GSS) have been identified since 1970 by the NCJDSU (these data are incomplete as formal investigation of familial CJD in the UK is undertaken by the National Prion Clinic in London). Of the 82 cases, 74 were resident in England, 6 were resident in Wales and 2 were resident in Northern Ireland. Twenty-one cases were still alive as at 31st December 2006. Forty-four of the cases had insertions in the coding region of the PrP gene, 19 carried the mutation at codon 200 (Glu-Lys), 3 at codon 178 (Asp-Asn, both with methionine at codon 129, ie FFI), 2 at codon129 178 (MV), one at codon 210 (Val-Ile),

one at codon D167G and one at codon V163STOP. The remaining 11 were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55 years (range 31-77 years).

**Codon 129 distribution in sporadic CJD**

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes in sporadic CJD is 64% MM, 18% MV, 18% VV (see Table 10). There appears to be evidence (p=0.011) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2006. The explanation for this remains unclear and is being investigated further. It should be noted that not all cases are genotyped (data available on 64%) and, therefore, changes in codon 129 distribution may reflect changes in the way in which cases are selected for analysis.

**Table 10 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2006**

| Deaths from sporadic CJD | MM(%) | MV(%) | VV(%) |
|---|---|---|---|
| Deaths from 1 May 1990 – 31 December 1995 | 97 (75) | 15 (12) | 17 (13) |
| Deaths from 1 January 1996 – 31 December 2006 | 260 (61) | 85 (20) | 83 (19) |
| Total | 357 (64) | 100 (18) | 100 (18) |
| **Genotype distribution for the normal population Pooling data from five studies** | (39) | (50) | (11) |

**Codon 129 distribution in vCJD**

All clinical cases for whom genetic data are available (n=145, 88%) were methionine homozygotes at codon 129 of the PrP gene.

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

## *4.5 CSF 14-3-3 and other brain specific proteins*

The laboratory received 300 cerebrospinal fluid (CSF) samples from January 2006 – December 2006. Of these, 245 were from patients residing in the United Kingdom (UK), 48 were from patients from non-UK countries and seven samples were blood-stained and as such unsuitable for analysis. The origin and numbers of these samples are given in Table 11.

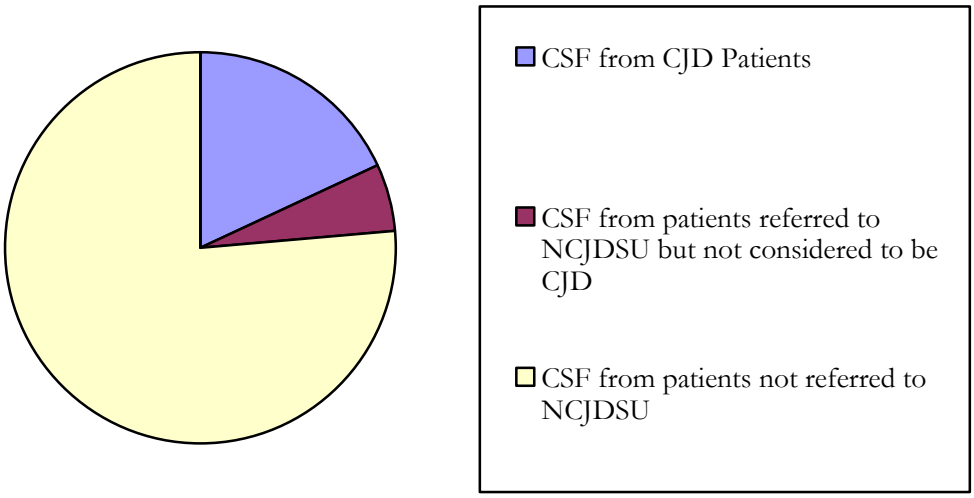
**Table 11 Origin of CSF samples sent to the National CJD Surveillance unit (NCJDSU) for CSF 14-3-3 analysis from January 2006 – December 2006**

| Origin of CSF samples | Total number CSF samples (%) |
|---|---|
| CSF from UK patients | 252 (84%)* |
| CSF from non-UK countries | 48 (16%) |
| Total number | 300 (100%) |

* Seven CSF samples were blood-stained and as such unsuitable for analysis.

Of the 245 analysable CSF samples received from patients within the United Kingdom, 44 were finally diagnosed with CJD or Gerstmann-Straussler-Scheinker disease, 14 were referred to the unit as suspect cases of CJD but did not satisfy the diagnostic criteria to be considered as a case of CJD and 187 patients did not have clinical features to merit formal referral as a suspect case of CJD (Figure 15).

**Figure 15 Source of CSF samples received from UK for CSF 14-3-3 analysis**




Of those patients diagnosed with CJD, 13 had neuropathological confirmation of disease, 26 were classified as probable sporadic CJD and 3 were classified as probable vCJD. One CSF sample was received from one vCJD patient undergoing therapeutic intervention. One patient was diagnosed as probable GSS associated with the P102L mutation in the PRNP gene. The CSF 14-3-3 results in these patients are given in Table 12.

**Table 12 The CSF 14-3-3 results in patients diagnosed with CJD and GSS**

| Diagnosis | Number of cases | Number of positive CSF 14-3-3 |
|---|---|---|
| Definite sporadic CJD | 13 | 12 |
| Probable sporadic CJD | 26 | 26 |
| Probable variant CJD | 4 | 2 |
| Probable GSS | 1 | 1 |

One patient with neuropathologically confirmed sCJD had a negative CSF 14-3-3. This patient was heterozygous for methionine and valine at codon 129 of the PRNP gene, a factor which is known to reduce the sensitivity of CSF 14-3-3.[11]

Of the patients with probable sporadic CJD, 16 died with no post-mortem, 7 have died and neuropathological confirmation of sCJD is awaited. The remaining 3 patients are still alive. Of the 16 patients who died without post-mortem examination, seven had EEG traces that were

[11] Sanchez-Juan P, Green A, Ladogana A, Cuadrado-Corrales N, Sanchez-Valle R, Mitrova E, Stoeck K, Sklaviadis T, Kulczycki J, Hess K, Bodemer M, Slivarichova D, Saiz A, Calero M, Ingrosso L, Knight R, Janssens ACJW, van Duijn CM, Zerr I. CSF tests in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology 2006; 67(4): 637-643.

considered typical for sporadic CJD whilst nine had either EEG traces that were not considered typical or EEG traces that were not reviewed by the NCJDSU. Therefore nine of the 16 patients with probable sporadic CJD who died without neuropathological confirmation have been classified as probable on the basis of the 14-3-3 result without independent EEG support.

Of the 187 CSF samples sent from patients who did not have enough signs and symptoms of CJD to merit formal referral to the NCJDSU, 11 had a positive CSF 14-3-3. In each of these patients an alternative diagnosis was identified and these are given in Table 13. Of the 176 patients with negative CSF 14-3-3 none were subsequently referred to the NCJDSU as a suspect case of CJD. It is improbable that this group contains unidentified cases of CJD but formal follow-up of all these patients would be required to confirm this.

**Table 13: The diagnosis in those patients with a positive CSF 14-3-3 who were diagnosed with an alternative diagnosis**

| **Diagnosis in CSF only referral cases with positive CSF 14-3-3** | **Number of cases** |
|---|---|
| Improved | 2 |
| Encephalitis | 3 |
| Stroke | 2 |
| Paraneoplastic syndrome | 1 |
| Hypoxic brain injury | 1 |
| Frontotemporal dementia | 1 |
| Awaiting PM result | 1 |

Section

5

# NATIONAL CJD CARE TEAM

The National CJD Care Team is based within the National CJD Surveillance Unit and was formed in response to concerns regarding the care of patients suffering from CJD. An initial national care coordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed. Between March 2003 and November 2004 there were two coordinators and since November 2004 there has been one coordinator. The present team consists of one care coordinator and a secretary with clinical neurological support from within the unit.

When a referral has been made to the NCJDSU of a likely case of CJD, the coordinator makes direct contact with the family and offers the opportunity to meet and to assist with care intervention. Referrals are also made to the Care Team from the National Prion Unit in London and Leah Davidson, who coordinates the care of iatrogenic CJD cases. Once contact is made, the coordinator can meet with the patient and family on a regular basis, depending on need, to provide support and to assist with coordination of local health and social care professions. Post bereavement support is offered to the family after the patient dies and assistance given with accessing more specialized counselling.

The National CJD Care Team works in close liaison with the Department of Health and provides access to the CJD Care Package, which is a sum of money available to assist local authorities with the care of patients suffering from all forms of CJD. The Care Fund is available to supplement local care provision for all strains of CJD rather than replace it – health and social services are still required to provide the necessary elements of the individual patient's care package. Care packages for individual patients will vary according to their individuals needs and it is not possible to be prescriptive about what each care package should contain. What is needed is a package that will provide the appropriate level of care at home both for the patient and for their family. The National CJD Care Team is also responsible for the management of the CJD Advice Network. This is a group of health and social services professionals who have had experience of working with patients and families affected by CJD and are available to share their experience and to provide advice to other professionals.

From the establishment of the first National Care Coordinator post in 2000 until 31st December 2006, the care team have been in contact with, and/or provided access to care funds, to 86 variant cases, 93 sporadic cases, 38 familial cases and 11 iatrogenic cases.

The National Care Coordinator undertook 158 patient visits and case conferences during 2006 (Table 14). In addition, 16 teaching sessions were provided to professionals involved in the provision of care to CJD patients. A further 5 teaching sessions were provided to 3 universities, which contributed to the courses being taught to student nurses.

**Table 14 Patient Visits and Case Conferences**
**1st January to 31st December 2006**

| Month | Cases Alive | Cases in contact with | Case Conferences and Visits |
|---|---|---|---|
| January | 36 | 17 | 9 |
| February | 34 | 18 | 19 |
| March | 33 | 19 | 12 |
| April | 28 | 14 | 11 |
| May | 32 | 18 | 16 |
| June | 32 | 18 | 14 |
| July | 34 | 21 | 9 |
| August | 32 | 20 | 15 |
| September | 30 | 19 | 15 |
| October | 31 | 21 | 19 |
| November | 30 | 21 | 9 |
| December | 30 | 21 | 10 |

One of the aims of the National Care Team is to provide and share information regarding CJD with all interested parties. This last year has seen the building up of important international contacts including professionals and support groups/agencies. After attending the yearly Washington Conference of the CJD Foundation, the Care Coordinator was invited to Australia by the CJD Support Organisation to discuss the important role of care coordination as part of their CJD Awareness Campaign with Commonwealth Department of Health Officials in Canberra. This was followed by meetings in Melbourne, Hobart, Sydney, Newcastle and New South Wales speaking to a wide range of professionals including the Health Departments, Infection Control Association, medical staff and support groups.

Expenditure from the National CJD Care Fund to the end of December 2006 is £1,595,138 comprising £387,225 in 2006, £296,572 in 2005, £311,547 in 2004, £323,722 in 2003, £304,631 to 2002. A breakdown of expenditure during 2006 is shown in Table 15.

**Table 15 Care Fund Payments**
**1st January to 31st December 2006**

| | |
|---|---|
| Adaptations | 103,850.59 |
| Alternative Therapy | 7,839.66 |
| Car Hire | 111,040.39 |
| Counselling | 1,881.60 |
| Equipment | 29,417.83 |
| Nursing | 107,460.70 |
| Physiotherapy | 13,894.80 |
| Respite | 1,356.00 |
| Social Care | 4,006.70 |
| Transport | 6,477.56 |
| **TOTAL** | **387,225.83** |

Section

6

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Section

7

***Staff based at the National CJD Surveillance Unit, Western General Hospital, Edinburgh in 2006***

| | |
|---|---|
| Dr RSG Knight | Director, NCJDSU |
| Professor RG Will | Consultant Neurologist |
| Professor JW Ironside | Consultant Neuropathologist |
| Dr H Ward | Consultant Epidemiologist, Deputy Director |
| Professor JE Bell, Dr C Smith | Honorary Consultants in Neuropathology |
| Dr M Gillies, Dr G Chohan | Clinical Research Fellows |
| Mrs B Smith-Bathgate | Nurse Practitioner |
| Ms M Leitch | National Care Co-ordinator |
| Dr MW Head | Senior Research Fellow |
| Dr A Green | Senior Clinical Scientist |
| Mr M Bishop | Molecular Biologist |
| Ms J Mackenzie | Study Coordinator |
| Mr A Hunter | Business Manager |
| Ms D Everington | Statistician |
| Mr N Attwood | Database Manager |
| Ms D Ritchie | Research Assistant |
| Mrs L McCardle | Chief Biomedical Scientist |
| Mrs M Le Grice, Ms S Lowrie, Mrs M Nicol | Senior Biomedical Scientists |
| Ms C-A Mackenzie | Tissue Bank Manager |
| Ms H Yull | Research Technician |
| Ms K Connolly | Research Technician |
| Mr G Fraser | Research Associate |
| Ms Elaine Lord | Administrative Co-ordinator |
| Ms K Forrest, Ms A Honeyman | Secretariat – Neuropathology |
| Ms G Stone | Secretariat - Clinical |
| Mrs S Macdonald | Secretariat - Care Team |
| Ms A Davies, Ms K Sewell | Secretariat - Case-control study |

Staff funded by Other Sources

| | |
|---|---|
| Ms T Lindsay (EU) | European Study Co-Ordinator |
| Mrs C Donaldson (EU) | Secretariat |
| Dr A Peden (CSO) | Postdoctoral Research Fellow |
| Dr M Jones (SNBTS) | Postdoctoral Research Fellow |
| Ms K Sherwood (UoE) | PhD student |
| Ms J Stott (UoE) | PhD student |

***Epidemiological and Statistical Support, London School of Hygiene and Tropical Medicine***

| | |
|---|---|
| Professor PG Smith | Epidemiologist, Department of Epidemiology and Population Health |
| Professor SN Cousens | Statistician, Department of Epidemiology and Population Health |