The phenotype of sporadic CJD in the UK between 1993 – 2004, and a review of the diagnostic criteria and differential diagnosis

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Abstract

Background / Aims

Sporadic CJD is a rare but universally fatal neurodegenerative disease of unknown aetiology that occurs worldwide. This study aims to characterise UK sCJD cases between 1993 and 2004 looking for evidence of change over time. Transmission of cattle BSE to humans, with subsequent development of variant CJD, has raised concerns that other novel phenotypes of human prion disease may develop with potentially major public health implications. This study addresses this by reviewing suspect sCJD patients referred before and after the identification of vCJD, by evaluating the phenotype of young onset compared to older onset sCJD and by comparing UK cases with the sCJD databases in France and other predominantly European countries with lower BSE exposure.

This study also aims to review the WHO sCJD diagnostic criteria and hence explore the differential diagnosis of sCJD in the UK.

Methods

All suspected sCJD cases referred to the NCJDSU between 1993 and 2004 were evaluated by retrospective case note review using the NCJDSU archives. A more detailed analysis of clinical phenotype was performed on patients referred in 1993, 1994, 2003 and 2004, all cases with a negative 14-3-3 result and all patients aged 50 or less at disease onset. MRI, CSF, EEG and pathology results were analysed. UK data were compared with European sCJD data extracted from the EUROCJD database. Suspect sCJD cases that ultimately received an alternative, non CJD diagnosis were reviewed, and the WHO sCJD criteria were evaluated.

Results and Conclusions

There is no evidence to support emergence of a novel, BSE related phenotype of human prion disease. The sCJD demographic data and clinical phenotype are reassuringly similar between 1993/4 and 2003/4, between young and older onset cases and between UK and other European cases. The small number of changes that have been observed can largely be attributed to alterations in data collection and investigation use, plus improved case ascertainment. There is a suggestion that the proportion of *PRNP* MM cases is decreasing in the UK and France, most likely related to improved identification of atypical presentations. However, continued close observation of *PRNP* trends is important.

The current WHO diagnostic criteria for sCJD are a useful tool, both for research purposes and clinicians in daily practise. Incorporation of CSF 14-3-3 into the Probable sCJD classification has resulted in improved sensitivity of 72% but at the expense of moderate reduction in specificity to 79%. The positive predictive value remains high of 89%. Currently there is insufficient evidence to support inclusion of MRI in the diagnostic criteria.

The differential diagnosis of sCJD is wide but Alzheimer's disease is the condition most commonly mistaken for sCJD. However, a significant minority of individuals initially suspected of having CJD never receive a diagnosis, sometimes even after neuropathological studies. Accurate disease surveillance remains a priority, not only to ensure that atypical sCJD presentations are not misdiagnosed, but also to assess putative risk factors for developing sCJD and to identify any novel CJD phenotypes that may emerge in the future.

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Abbreviations

BASE Bovine Amyloidotic Spongiform Encephalopathy

BSE Bovine Spongiform Encephalopathy

CERAD Consortium to Establish A Registry for Alzheimer's Disease

CJD Creutzfeldt-Jakob Disease

CNS Central Nervous System

CSF Cerebrospinal Fluid

DNA Deoxyribonucleic Acid

DWI Diffusion Weighted Imaging

ECT Electroconvulsive Therapy

EEG Electroencephalogram

ELISA Enzyme-linked Immunosorbent Assay

EMG Electromyography

EUROCJD Europe and Allied Countries Collaborative Study Group of CJD

FFI Fatal Familial Insomnia

FLAIR Fluid Attenuated Inversion Recovery

GSS Gerstmann Straussler Scheinker syndrome

hGH human Growth Hormone

ICD International Classification of Diseases

LBD Lewy Body Dementia

LMN Lower Motor Neurone

LRS Lymphoreticular System

MM Methionine homozygous

MND Motor Neurone Disease

MRC Medical Research Council

MRI Magnetic Resonance Imaging

mRNA messenger Ribonucleic Acid

MV Methionine Valine heterozygous

NCJDSU National CJD Surveillance Unit

NEUROCJD Extended European Collaborative Study Group of CJD

NPC National Prion Clinic

NSE Neuron Specific Enolase

PCR Polymerase Chain Reaction

PD Proton Density

PIND Progressive Intellectual and Neurological Deterioration

PLEDS Periodic Lateralised Epileptiform Discharges

PPS Pentosan Polysulphate

PrP Prion Protein

PrP^C Prion Protein - cellular

PrP^{Sc} Prion Protein - scrapie

PRNP Prion Protein gene

RPD Rapidly Progressive Dementia

sCJD sporadic Creutzfeldt-Jakob Disease

SPD Slowly Progressive Dementia

SPECT Single Photon Emission Computed Tomography

SSPE Subacute Sclerosing Panencephalitis

TSE Transmissible Spongiform Encephalopathy

vCJD variant Creutzfeldt-Jakob Disease

VV Valine homozygous

WHO World Health Organisation

Chapter 1: Introduction

A. Aims and Objectives

The primary aim of this study is to evaluate the characteristics of UK cases of sporadic Creutzfeldt-Jakob disease (sCJD) and assess whether they have changed over a ten year period, and to evaluate possible explanations for any disparities.

The emergence of variant CJD has heightened concerns that we may be missing other human cases of prion disease, either related to BSE transmission or potentially from other animal TSEs. All vCJD cases to date have been homozygous for methionine at codon 129 of the prion protein gene, but we know that vCJD has been transmitted to a methionine valine heterozygote by blood transfusion and we do not know what the clinical picture might be in this context. It is possible that non methionine homozygotes might display a novel BSE phenotype. This study aims to analyse suspected sCJD patients in the UK before and after the identification of vCJD, searching for any evidence that might support emergence of a novel human prion phenotype. UK data will also be compared with European data extracted from the EUROCJD database to assess if any observed changes are restricted to the UK or reflect a more general Europe - wide shift. The BSE epidemic was maximal in the UK with far smaller numbers of cases elsewhere in Europe, and the majority of vCJD cases have also occurred in the UK. Any changes in sCJD characteristics that are confined to the UK and correlate with BSE exposure are of particular interest. French data is analysed separately as France occupies a position midway between the UK and the other EUROCJD nations with respect to BSE and vCJD. Whilst it did not experience a major BSE epidemic it had significant exposure to BSE via the UK export market and has had more vCJD cases than any other country with the exception of the UK (21 French vCJD cases as of February 2007).

Young onset suspected sCJD referrals are analysed in particular detail because vCJD tends to occur in younger individuals than sCJD. Therefore the differential diagnosis is particularly relevant in young adults with rapidly progressive dementia or other features suggesting prion disease. Whilst we cannot be sure that a novel human presentation of BSE would predominantly affect young adults it is reasonable to examine this group particularly closely.

The second principal aim of this study concerns the validity of the diagnostic criteria for sCJD. This is addressed by comparing National CJD Surveillance Unit referrals where a diagnosis of sCJD has been confirmed with those where an alternative diagnosis has been made. Thus the differential diagnosis of sCJD is reviewed. This is of interest for a number of reasons. On a practical, day-to-day basis the differential diagnosis of sCJD is what matters to the clinical neurologist, particularly the reassurance that a treatable alternative has not been overlooked. Secondly knowledge of the sensitivity and specificity of sCJD diagnostic criteria is useful for clinicians and relatives alike, to guide decisions regarding further investigation and to provide families with a measure of diagnostic certainty. Thirdly it is vital to assess the final diagnoses attributed to suspected sCJD referrals to ensure that potential novel CJD phenotypes are not being missed. This is especially relevant since a definitive neuropathological diagnosis is never made in a proportion of NCJDSU referrals in which sCJD is ultimately excluded.

The objectives of the study are as follows:

- To evaluate sCJD referrals for the period 1993 to 2004 inclusive and assess trends in absolute numbers, demographics and referral process.

- To perform more detailed analysis of all sCJD referrals in 2003/4 compared to 1993/4 with respect to clinical phenotype, referral process and investigations.

- To review the alternative diagnoses in non sCJD cases and identify which clinical features and investigations are most discriminating between sCJD and non-cases.

- To evaluate the current World Health Organisation (WHO) diagnostic criteria for sCJD and assess whether modifications are indicated in light of changes in diagnostic tools or the disease itself.

- To review all sCJD cases aged fifty or less at onset that were referred between 1993 and 2004 and compare their clinical phenotype and investigation results with a control older sCJD cohort.

- To compare UK data with European data to identify any changes in the characteristics of sCJD in the UK which may correlate with BSE exposure.

B. Introduction

1.1 Introduction to Transmissible Spongiform Encephalopathies

Sporadic CJD is a neurodegenerative, uniformly fatal human disease characterised pathologically by spongiform change within the brain. It is a member of a larger family of transmissible spongiform encephalopathies (TSE), which affect a variety of mammalian species (table 1.1). The aetiology of the different TSEs varies but in all cases the causative infective agent is believed to be a prion, a host encoded protein devoid of nucleic acid (1). It is notable for its small size and resistance to degradation by physical agents including heat, irradiation and chemicals. TSEs share three key pathological features, namely spongiform change, neuronal loss and astrocytosis. In addition amyloid plaque formation may occur within the brain. A pathological hallmark of TSEs is central nervous system deposition of an insoluble, protease resistant, cellular protein termed PrP^{Sc} (Sc for scrapie). A key feature distinguishing prion diseases from other neurodegenerative conditions is their ability to be transmitted, both experimentally and sometimes naturally.

Table 1.1 (2) Transmissible spongiform encephalopathies

Disease	Species	Geographical Distribution	Aetiology
Scrapie	Sheep, goats	Worldwide except New Zealand, Australia	Sporadic, infectious
Bovine spongiform encephalopathy (BSE)	Cattle, goats	Cattle epidemic UK; peak 1992. Small number of native cases elsewhere including the majority of European countries, USA, Canada and Japan. Imported cases only in Falklands, Oman. Goat: France 2005.	Source of infection unknown: ? sporadic BSE, ? scrapie. Propagated by cattle feed containing contaminated meat and bone meal
Atypical BSE including BASE* (3,4,5)	Cattle	Atypical BSE first identified in French cattle in 2004. BASE identified in Italy 2004. Subsequently identified in Germany, Japan, Poland, Belgium.	Unknown
Spongiform encephalopathy of captive zoo animals	Exotic ungulates eg. Kudu, oryx, tiger.	UK	BSE, via contaminated feed
Feline spongiform encephalopathy	Domestic cats	Mainly UK, isolated cases in France, Norway, Lichenstein	BSE, probably via contaminated feed
Chronic wasting disease	Mule deer, elk, moose	USA, Canada	Unknown – not clearly linked to other animal TSEs
Transmissible mink encephalopathy	Mink (farmed)	USA, Canada, Russia, Finland, Germany	? scrapie infected feed
Kuru	Humans	Highlands of Papua New Guinea	Perpetuated by cannibalism, origin of index case unknown
sCJD	Humans	Worldwide	Unknown
vCJD	Humans	Predominantly UK, smaller numbers in France, Ireland Netherlands, Italy, Spain, Portugal, USA, Canada, Japan, Saudi Arabia	BSE
Genetic CJD / GSS / FFI	Humans	Worldwide but higher incidence in Slovakia, Italy, Israel	Mutation in *PRNP* gene
Iatrogenic CJD	Humans	Variable; hGH cases most frequent in France and UK, dura mater in Japan. 4 cases or transfusion transmission of vCJD in the UK	CJD infected pituitary hormones, dura mater grafts, neurosurgical instruments, stereotactic EEG, corneal grafts, blood

*BASE bovine amyloidotic spongiform encephalopathy

1.2 Transmission experiments

The prototypical TSE, scrapie, was the first to be experimentally transmitted to a previously healthy sheep by inoculation of scrapie infected spinal cord in 1936. Further support for scrapie transmission came from a scrapie outbreak in sheep that had been vaccinated against the disease, louping ill, using a preparation containing brain from sheep exposed to natural scrapie (6). Hadlow, an American veterinary surgeon, noted the pathological similarity between kuru and scrapie in 1959 (7). This observation stimulated the successful transmission of kuru into chimpanzees by intracerebral inoculation in 1966 (8). Two years later CJD was transmitted to chimpanzees (Gibbs 1968) (9) and since then there have been numerous TSE transmission experiments including Gertsmann Straussler Scheinker syndrome to mice and Fatal Familial Insomnia to mice (10,11, 12).

The species barrier refers to the increased difficulty in transmitting infection between species as opposed to within a species (13). In prion disease this is by no means absolute, as demonstrated by BSE spreading to humans, ungulates and cats. The barrier is usually reflected in an increase in incubation time but, on some occasions, in failure of transmission altogether. E.g. BSE has failed to transmit to dogs, and rabbits appear completely resistant to experimental infection (14). However, if successful transmission occurs then sequential passage through the new species appears to allow the incubation time to shorten and stabilise (15). Ease of inter species transmission is believed to relate to PrP structure, with greater homology between donor and host PrP reflected in greater ease of TSE transfer. E.g. transgenic mice expressing hamster PrP are highly susceptible to infection with hamster prions unlike wild type mice (16).

This property of transmission is a key feature of prion diseases but such experiments are time consuming and expensive, even using mouse models with relatively short incubation periods. Therefore new techniques have been developed to diagnose and research TSEs, utilising detection of protease resistant PrP in infected tissue.

1.3 Prion hypothesis

Alper was first to suggest that the scrapie infective agent might lack nucleic acid following an experiment in 1957 where scrapie infectivity persisted despite high dose ionizing radiation. (17). Almost 20 years later this information was resurrected and

Stanley Prusiner postulated the prion hypothesis (18). He won the Nobel prize for medicine and physiology for his work in 1997, despite the fact it was controversial and not fully validated. The term prion derives from proteinaceous infectious particle (with the i and o reversed for ease of pronunciation), referring to the absence of nucleic acid in prions. PrP is encoded by a chromosomal gene in the host rather than nuclear DNA within the infecting particle itself, and PrP mRNA levels do not increase throughout the course of prion infection. These observations challenge conventional theories of infectivity. The normal PrP protein is PrP^c, a 33 – 35 kD protease sensitive protein that is structurally rich in α helices. It is anchored to the cell surface by a glycosyl phosphotidyl tail. PrP^c is present throughout most mammalian tissues but is particularly concentrated in the brain. Its normal role remains incompletely understood but interestingly PrP knock out mice appear relatively normal, with normal life expectancies although in one study circadian rhythm and sleep wake cycle were disrupted (19).

According to the prion theory an abnormal isoform of PrP termed PrP^{Sc} is derived by a post-translational process involving conformational change. One possibility is that spontaneous fluctuations in PrP^c structure could create a partially unfolded intermediate isoform (PrP^*) and this might either degrade, revert to PrP^c or occasionally undergo further conformational change to PrP^{Sc}. The disease associated PrP^{Sc} is rich in β pleated sheets and relatively protease resistant (20). It acts as a template for conversion of more PrP^c to PrP^{Sc}. It is believed that PrP^{Sc} is the principle and possibly the only agent required to catalyse this process. Each type of human prion disease can potentially be explained by this hypothesis. E.g. In sporadic CJD the initial formation of PrP^{Sc} is a rare, stochastic event; in acquired CJD (iatrogenic and variant) a seed of PrP^{Sc} is introduced acting as a catalyst for more to form; in genetic CJD underlying mutations mean PrP^c is inherently less stable and therefore more likely to form PrP^{Sc} (21).

There is some evidence to support this biologically eloquent hypothesis. PrP^c and PrP^{Sc} have identical amino acid sequences when analysed by mass spectrometry, but spectroscopy confirms they have different structures with respect to the proportion of α helices and β pleated sheets. Fluorescence and circular dichroism spectroscopy experiments have provided some support for an intermediate PrP isoform (284, 285). In another study mice inoculated with recombinant PrP died of neurological

dysfunction and brain extracts were positive for protease resistant PrP. Subsequently these brain extracts transmitted the disease to wild type mice with the creation of a novel prion strain, providing supportive evidence that prions alone are the infective agent (22). As predicted animals devoid of PrP^c are resistant to prion disease and fail to propagate infection. (23, 24, 25). The unique protein only explanation for prion propagation means that prions differ from all other known infectious agents.

However, many questions remain unanswered, not least how accumulation of PrP^{Sc} (or less likely absence of PrP^c) causes disease, and how PrP^{Sc} can catalyse conformational change. There is ongoing controversy as to whether PrP^{Sc} is really the infectious agent. Recently mouse models have demonstrated high infectivity in the absence of PrP^{Sc} in brain tissue (26), and conversely not all PrP^{Sc} is associated with infectivity. The prion theory also fails to satisfactorily explain the many strains of TSEs with the different, strain specific phenotypes. Therefore, the validity of the prion hypothesis continues to be debated (27, 28).

1.4 TSE strain variation

TSE strain variation refers to the fact that numerous different prion strains have been identified, mainly by mouse transmission experiments. Individual strains differ primarily in terms of incubation period and neuropathological lesion profile, but also in some cases by ease of transmission, clinical features and susceptibility to inactivation. The extent of strain variation in natural as opposed to experimental TSEs is less clear, and the number of different strains varies depending on the type of prion disease. For instance over 20 scrapie strains have been determined experimentally in mice whereas BSE is caused by a single strain whose features have remained constant, even after transmission into 7 species. Hence there appears to be strain specific information, which is independent of the host PrP genotype (15). What is remarkable is that prions, apparently composed of the same protein, can result in phenotypically distinct transmission states. The basis of prion strain variation at the molecular level is not completely understood nor adequately explained by the prion hypothesis but appears to relate to differences in PrP conformation and glycosylation (29, 30). However, PrP type may be a surrogate marker for TSE strain rather than the true determining factor.

1.5 Historical perspective on human prion disease

The CJD story dates from 1920 when H.G. Creutzfeldt, a German clinician with neuropathology training, described the case of a 22 year old female with a 6 year history of mild incoordination, culminating in 18 months of progressive dementia, spasticity, myoclonus and finally status epilepticus. Post mortem revealed moderate atrophy with degeneration of pyramidal tracts and scattered areas of partial necrosis.

Over the next 3 years A Jakob, a neuropathologist, described 5 further cases which shared some clinical features with Creutzfeldt's original patient and which he believed shared a common, novel clinical syndrome. They demonstrated a variable combination of dementia, pyramidal, extrapyramidal, cerebellar and psychiatric signs with death occurring between 6 and 13 months after illness onset. Pathologically all showed diffuse neuronal degeneration and, in some instances, astrocyte proliferation. Jakob denoted the clinical triad of cortical dysfunction, extrapyramidal signs and spastic-paretic pyramidal signs as 'spastic pseudosclerosis' (31).

In retrospect Creutzfeldt's patient probably did not represent a case of CJD, neither meeting the current clinical or major histological criteria. However, at least 2 of Jakob's 5 original cases are believed to be CJD, based on evidence of spongiform change on review of the pathology, with the remaining three probably representing forms of motor neurone disease and two toxic or metabolic encephalopathies. (32).

The eponymous term Creutzfeldt - Jakob Disease was first suggested in 1922 by Spielmeyer, a colleague of Creutzfeldt's, to describe these and similar cases. However, ongoing debate about the characteristic phenotype, pathology and aetiology led to a proliferation of synonyms including disseminated encephalomyelopathy (Jakob 1921), cortico-pallido-spinal degeneration (Davison 1932), presenile dementia with cortical blindness – Heidenhain's syndrome (Meyer et al 1954) and subacute spongiform encephalopathy attributable to vascular dementia (Nevin et al 1960 (33)). The term CJD only attained widespread acceptance in the 1960s following the seminal papers by Nevin and Jones (34).

Historically, cases with a combination of dementia and prominent lower motor neurone signs were thought to have an amyotrophic variant of sCJD, but this is no longer classified as prion disease due to largely unsuccessful transmission experiments (35).

1.6 Kuru

Kuru is a human TSE confined to the Fore tribe in the highlands of Papua New Guinea. It was first formally described by Gajdusek in 1957 but historically probably existed from the early 20th century (36). In the Fore language kuru means shiver, referring to the tremor which characterises this disease (37). Typically it presents with unsteadiness, followed by increasing ataxia, tremor, dysarthria, rigidity, involuntary movements and emotional lability (hence the term 'laughing death') (38). Frank dementia is believed to be unusual. Death usually occurs within a year, often with mutism being present in the final stages (39). Neuropathologically there is cerebellar atrophy, astrocytosis, mild spongiform change and, in over 70%, of cases striking PrP positive amyloid plaques, particularly concentrated in the cerebellum.

Kuru is believed to have been propagated by ritualistic cannibalism, which was practised amongst the Fore people in the first part on the 20th century, resulting in gastrointestinal, mucosal and skin exposure to CNS tissue. It is postulated that the index case may have been a chance occurrence of sporadic CJD but there is no evidence to support or refute this, although sCJD is certainly recognised in Papua New Guinea (40). The disease was more common in women and children (41), probably reflecting cultural practice where men were less exposed to CNS tissue during cannibal rituals (39).

Cannibalism was forbidden by the Australian government in 1954 and since then the incidence of kuru has markedly declined, although it has not, as yet, disappeared completely. 11 cases were identified between 1996 and 2004 and for these individuals the estimated incubation period ranged from 34 to 56 years (42). These recent cases were predominantly methionine valine heterozygous (MV) at codon 129 on *PRNP* analysis. The MV genotype is associated with reduced susceptibility to kuru compared with methionine homozygotes, but with a prolonged incubation period (43) (see section 1. 8 for discussion of effect of codon 129 genotype).

1.7 Creutzfeldt-Jakob disease

Prion diseases are unique in that they exist in sporadic, genetic and infectious forms. There are four distinct types of human CJD; sporadic, genetic, variant and iatrogenic.

Sporadic and variant CJD are described in detail later in this introduction (sections 1.9 and 1.10).

Genetic TSEs are associated with mutations in the prion protein gene (*PRNP*) and comprise genetic CJD, Gerstmann Straussler Scheinker syndrome (GSS) and fatal familial insomnia (FFI). However, increasingly genetic cases are being defined by the precise mutation as this is the dominant factor influencing clinical and pathological phenotype. For example the E200K insertion presents in a manner typical for sCJD (44) whereas codon 102 and codon 105 point mutations usually produce the GSS phenotype, characterised by a slowly progressive cerebellar syndrome with late cognitive decline (45). FFI occurs when a point mutation at codon 178 is coupled with methionine at codon 129 of the mutant allele (cis – 129 M). Clinically insomnia and dysautonomia are prominent features of FFI, associated with predominantly thalamic pathology (46, 47). Although particular mutations are associated with characteristic phenotypes there may be variability, even within a single family.

Genetic TSE inheritance is autosomal dominant and penetrance varies dependant on the mutation but is generally high. Despite this only one third to one half of inherited cases have a family history (44) and this may relate to non paternity, relatives dying of alternative causes prior to CJD onset or de novo mutations (as recently reported in some UK and other European families with the classic GSS P102L mutation (286)). This emphasises the need to offer *PRNP* gene sequencing in all suspected CJD individuals, irrespective of family history. Genetic TSEs are recognised throughout the world but the incidence varies, with Slovakia, Italy and Israel having particularly high levels (48, 49, 50). Overall it remains an extremely rare condition, comprising about 10% of all CJD cases (44).

Iatrogenic CJD is caused by inadvertent transmission of infection during medical or surgical procedures. The first reported case related to cadaveric corneal graft transplantation (51) but iatrogenic CJD is most commonly a result of human dura mater grafts or human pituitary growth hormone. Other implicated mechanisms include human pituitary gonadotrophin, neurosurgical instrumentation and depth electrodes (52, 53). The majority of the dura-related cases have been Japanese, probably reflecting their high use of dura mater during neurosurgical procedures (54). The resultant clinicopathological phenotype of iatrogenic CJD depends partly on the route of infection. Peripherally acquired growth hormone cases are associated with a progressive cerebellar syndrome and typically survive for over a year (55), whilst

intracranial infection sources such as dura mater cases are more variable in their clinical onset and duration. Some have cerebellar presentations (53, 56) whereas others have focal onsets, often corresponding to the site of dural graft placement (57). Illness duration in UK dura cases has ranged from 2 to 33 months (57). Incubation period is also influenced by route of infection. In growth hormone - related CJD the peak risk is estimated to occur 20 years after first exposure (58). In dura - related iatrogenic CJD the incubation period has ranged from 45 to 177 months with a mean of 7.75 years (93 months)(57). *PRNP* codon 129 genotype influences susceptibility and is discussed below (section 1.8).

1.8 Codon 129 polymorphism and CJD

The codon 129 locus of the human PRNP gene is a variable region encoding either methionine or valine. Thus three possible combinations exist: methionine homozygous (MM), valine homozygous (VV) and methionine valine heterozygous (MV). This locus has been identified as having a significant impact on disease susceptibility and expression in CJD.

All three codon 129 genotypes are potentially susceptible to sCJD but an excess of cases are MM suggesting this combination increases susceptibility (table 1.2). In addition codon 129 influences phenotype; atypical sCJD presentations are more likely to be non MM cases. All vCJD patients thus far have been MM. It remains unknown whether MV and VV individuals are resistant to vCJD or have a longer incubation period and therefore have yet to present. However, vCJD has been transmitted to a non MM patient. An individual heterozygous for methionine and valine was exposed to vCJD via blood transfusion and died 5 years later without CJD symptoms. PrP^{Sc} was detected in the lymphoreticular tissue (spleen) but not in the brain (59). Homozygosity for either methionine or valine is a risk factor for the development of iatrogenic CJD (53, 60). In genetic CJD codon 129 influences disease expression. E.g. Characteristically the combination of VV and a mutation at codon 178 results in a sCJD – like phenotype whereas the same mutation co-segregating with methionine at codon 129 results in FFI (61), with slight variation in disease duration and phenotype depending on whether the individual is homozygous or heterozygous for methionine (62). However, genotype / phenotype studies on Spanish D178N cases suggest the clinical picture may be less distinct, with a typical sCJD phenotype being recognised

in MM and MV patients. This suggests that factors other than codon 129 polymorphism influence disease expression of the codon 178 mutation (63).

Table 1.2 (64). Codon 129 distribution in the normal UK population and in sporadic and variant CJD

Codon 129 genotype	% MM	% MV	% VV
Normal UK population	39	50	11
sCJD (1990 – 2001)	69	15	17
vCJD	100	0	0

1.9 Sporadic CJD

Sporadic CJD has an annual incidence of 1 – 2 cases / million people and this figure is fairly constant between countries with an active surveillance system (65). An exception is Switzerland where the incidence has been unusually high at 2.2– 2.6 cases / million since 2001, although it is now declining to the norm (66, 67). There is no clear explanation for this and it may reflect an excellent surveillance system or a true increase in sCJD frequency, although no comparable rises have been reported in neighbouring countries such as Austria (68). Switzerland did have a higher incidence of BSE than the rest of continental Europe between 1995 and 1998 but none of their cases were clinically or pathologically suggestive of vCJD (66).

 The mean age of sCJD disease onset is 66 years (69) and the majority of cases occur between the ages of 50 and 75, although patients as young as 14 and as old as 86 have been recognised (70, 71). There is no significant gender difference. Disease duration is typically short with a median of 6 months from onset to death. Only 14% of cases survive longer than a year and only 5% live for two years or more (72).

The aetiology of sporadic CJD remains unknown. It occurs in a worldwide distribution with no sustained, statistically significant clustering to suggest particular environmental factors (73, 74). Numerous risk factor studies have been performed but recall bias is often a problem and no convincing risk factors have been identified (75, 76, 77, 78). It is postulated that it is caused by the spontaneous formation of PrP^{Sc} in the brain but if this were the case one might expect the incidence to increase with age, yet it decreases in the very elderly, although this may partially reflect limited case ascertainment in the elderly (69, 71).

1.9.1 Clinical Features of Sporadic CJD

The characteristic clinical picture in sCJD is one of rapidly progressive dementia with associated neurological features, particularly cerebellar ataxia, pyramidal signs and myoclonus. Visual disturbance, ocular movement disorders, extrapyramidal signs and hallucinations are all well recognised. The final stages are often characterised by an akinetic mute state. The illness may be preceded by a non specific prodrome including fatigue, low mood, weight loss, personality change and headaches. Some of these symptoms may reflect the early stages of dementia but potentially some may relate to recall bias.

Various studies have reviewed the clinical characteristics of sCJD and their findings are summarised in tables 1.3 and 1.4. The figures vary slightly from study to study but many of the inconsistencies are explicable on the basis of different definitions of symptoms and signs, and different methods of data collection (e.g. retrospective or prospective, proportion of cases seen in life).

Table 1.3 Clinical characteristics of sCJD: symptoms at presentation (expressed as percentage) (79)

Study	Eng and Wales 1970-79 (n = 124)	France 1968-77 (n = 124)	USA 1963-93 (n = 232)	UK 1990-94 (n = 144)
Dementia	21	29	48	19
Ataxia	19	29	33	39
Behavioural disturbance	18	30	29	15
Dizziness	11	8	13	n/a
Visual	9	17	19	10
Involuntary movements	5	1	4	2
Dysphasia	5	n/a	n/a	4
Sensory	4	2	6	n/a
Headache	3	10	11	n/a

Table 1.4: Clinical characteristics of sCJD: signs during course of illness (expressed as percentage) (79)

Study	Eng and Wales 1970-79 (n = 124)	France 1968-77 (n = 124)	USA 1963-93 (n = 232)	UK 1990-94 (n = 144)
Dementia	100	100	100	100
Myoclonus	82	84	78	85
Pyramidal	79	44	62	62
Dysphasia	62	n/a	n/a	58
Cerebellar	42	56	71	85
Akinetic mutism	39	n/a	n/a	75
Primitive reflexes	30	n/a	n/a	58
Cortical blindness	13	n/a	n/a	52
Extrapyramidal	3	60	56	34
Lower motor neurone	3	12	12	17
Seizures	9	9	19	13

The commonest sCJD presentation is with a rapidly progressive dementia but other onsets are recognised, including extrapyramidal, psychiatric and stroke – like presentations. Two clinical subtypes of sCJD deserve particular mention.

The Heidenhain variant presents with isolated visual disturbance and is named after Heidenhain who first described this phenotype in 1928 in an article describing three cases of CJD including two patients with prominent, early visual symptoms (80). The eponymous term was not coined until 1954 (81). Initial symptoms can be as diverse as pallinopsia, tunnel vision, peripheral field defects or simple blurring (82, 83). These visual problems persist in the absence of cognitive impairment for days to weeks. Then a typical sCJD course follows with rapid decline associated with dementia,

usually myoclonus and cortical blindness. Heidenhain cases are invariably methionine homozygous at codon 129 of the prion protein gene. They are rare representing less than 5% of all sCJD cases (82)

Brownell – Oppenheimer variant refers to the pure cerebellar presentation of sCJD where isolated cerebellar symptoms may persist for several weeks before dementia and a more typical CJD picture ensues (84). It was first described in the literature in 1955 under the heading 'The ataxic - cerebellar form of CJD' (85). Brownell and Oppenheimer went on to describe the clinical and pathological features in 1965, hence the historical eponymous name for this sCJD type (86).

The rapidity of deterioration in sCJD usually helps distinguish it from other dementias and neurodegenerative conditions.

1.9.2 Investigations in sporadic CJD

(i) Blood tests

There are no specific findings on blood tests in sCJD and their primary value is to exclude other diagnoses. Attempts are being made to identify a diagnostic blood test for sCJD (87) but no such test is currently available, although PrP^{Sc} has been detected in blood samples from hamsters with scrapie (88).

(ii) Cerebrospinal fluid

Routine examination of CSF in sCJD is usually unremarkable with normal glucose and no cells although protein may be modestly elevated (usually less than 1g / l) (89, 90). The most valuable CSF test is 14-3-3 analysis. 14-3-3 refers to a family of acidic, low molecular weight proteins that exist in mammalian tissue in 7 isoforms, 5 of which are present in neuronal cells. They have diverse roles including regulation of neuronal development, cell – cell signalling and production of neurotransmitters. In 1986 2 proteins entitled p130 and p131 were detected in the CSF of 21 sCJD patients (91). Subsequently they were identified as members of the 14-3-3 family and a diagnostic test for sCJD was developed utilising SDS / PAGE and immunoblotting techniques (92, 93). 14-3-3 analysis was introduced to the UK in Dec 1996. The World Health Organisation (WHO) diagnostic criteria for sCJD were modified in 1998 to include CSF 14-3-3, with a positive result classifying a possible case as probable (94). The assay sensitivity is 90 - 97% (95, 96, 97) and those cases with a

negative result appear to be clinically and pathologically atypical, often with a younger age of onset and prolonged disease duration (98). This may reflect the fact they are more likely to have unusual codon 129 – prion protein isotypes such as MM2 and MV2 (see section 1.9.4 for classification based on codon 129 – PrP isotype).

However, 14-3-3 detection in CSF is not unique to sCJD and is recognised in association with acute neuronal damage in diverse conditions including stroke, paraneoplastic disease, inflammation and post seizure activity (table 1.5) (99, 101). The value of the test is diminished when used as a screening tool for unselected patients with dementia (100, 101). The specificity of 14-3-3 in diagnosing sCJD varies depending on the population assessed but has been reported to be 87 – 100% in the context of CJD surveillance (96, 97, 99, 101). The aetiology of a positive 14-3-3 result is incompletely understood but it is assumed to relate to massive neuronal damage with leakage of brain proteins into the CSF (93, 101). The false positive 14-3-3 results seen in certain inflammatory conditions and following cerebral infarction would support this theory.

Other CSF proteins have also been investigated as diagnostic tools in sCJD. S-100 and neuron-specific enolase (NSE) are both elevated but are less specific or sensitive than 14-3-3. (102, 103, 104). A recent paper suggested tau has comparable sensitivity to 14-3-3 in sCJD diagnosis (104) and there is ongoing work assessing the sensitivity and specificity of total tau and phosporylated tau levels (105).

(iii) Magnetic Resonance Imaging

MRI is primarily performed to exclude alternative diagnoses but there is now evidence it can support the diagnosis of sCJD. The characteristic finding is hyperintensity of the putamen and caudate head (fig 1.1), usually present bilaterally but occurring asymmetrically in 10 – 20%. Sensitivity is reported at 60 - 80% with a specificity of around 90% (106, 107, 108, 109, 110). FLAIR and DWI sequences appear most sensitive, with DWI being particularly good at detecting early changes (111, 112). The hyperintensity is recognised most easily on axial views. The differential diagnosis for basal ganglia high signal includes Wilson's disease, carbon monoxide poisoning, mitochondrial disorders, haemolytic uraemic syndrome and variant CJD (although in the latter the posterior thalamic hyperintensity is more pronounced than the caudate / putamen signal change). However, most of these conditions should be readily clinically distinguishable.

Other radiological findings in sCJD include cortical hyperintensity (fig 1.2)(113), periaqueductal grey matter signal change, hippocampal hyperintensity and atrophy (probably correlating with disease duration).

Currently the WHO diagnostic criteria for sCJD do not include MRI features, because of limited information on specificity.
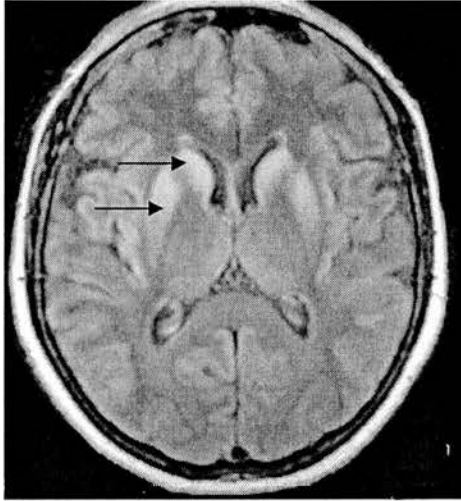
Fig 1.1   Fig 1.2
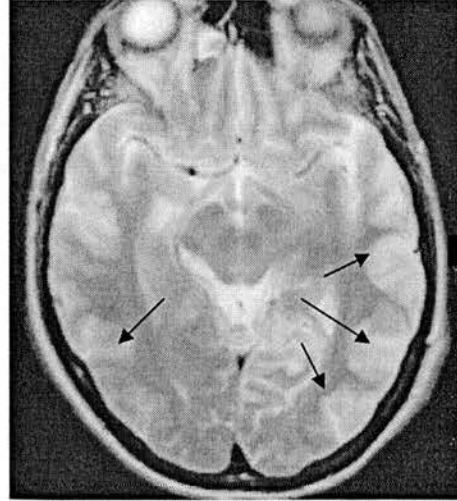
(iv) Electroencephalogram (EEG)

Fig 1.3
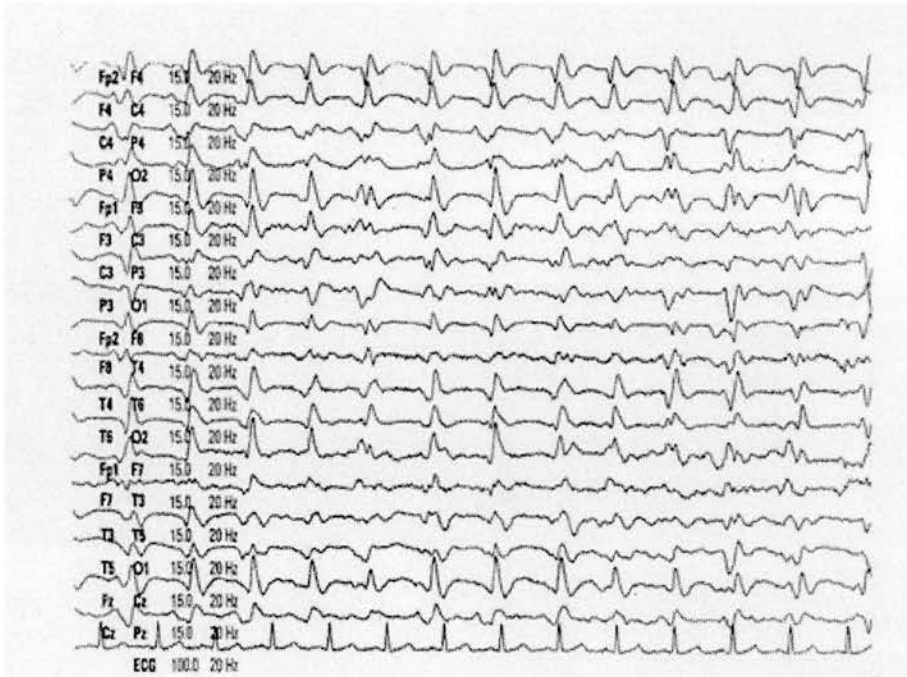
The typical EEG in sCJD shows periodic, triphasic sharp wave complexes occurring at about 1 / second, usually generalised throughout the trace (fig 1.3). Occasionally periodic lateralised epileptiform discharges (PLEDS) are seen initially but these are have a much wider differential diagnosis (114). Objective criteria have been published (115) and when these are applied sensitivity of the EEG is 64 - 67% and specificity 74 - 91% (115, 116, 117). However, sensitivity varies depending on the underlying codon 129 genotype / prion protein isotype combination with periodic complexes being detected most frequently in MM1 and MV1 cases and only rarely in valine homozygotes (118, 119, 120, 121). Sequential EEGs may be required to detect the typical pattern, but the triphasic complexes may disappear as the disease advances. The EEG is rarely if ever truly normal in established sCJD.

An apparently typical EEG even in the presence of dementia does not guarantee a diagnosis of CJD and false positive EEGs are recognised in Alzheimer's disease, Lewy Body dementia, vascular dementia (122, 123, 124), plus other less confusing clinical scenarios such as lithium toxicity (125).

Table 1.5. The differential diagnosis of basal ganglia hyperintensity on MRI, periodic complexes on EEG and a positive 14-3-3 CSF result

Differential diagnosis of a positive 14-3-3 result	Radiological differential diagnosis of basal ganglia hyperintensity	Differential diagnosis of periodic complexes on EEG
Acute stroke	Wilson's disease	Alzheimer's disease
Post seizure	Mitochondrial disease	Lewy body dementia
Variant CJD	Variant CJD (but pulvinar brighter)	SSPE
Paraneoplastic encephalitis	Huntingdon's disease	Lithium toxicity
Meningoencephalitis	Encephalitis	ECT
Hashimoto's encephalopathy	Haemolytic uraemic syndrome	Hepatic encephalopathy
Intracerebral malignancy	Hypoxic brain damage	
Alzheimer's disease	Carbon monoxide poisoning	
Lewy Body dementia	Hypoglycaemia	
Multi infarct dementia		
Down's syndrome		
Hypoxic brain damage		
Blood stained CSF		

1.9.3 Neuropathology of sporadic CJD

Macroscopically the sCJD brain may look normal but more often is atrophic, either diffusely or focally, although the hippocampi are usually spared in contrast to other degenerative dementias, particularly Alzheimer's disease. The three key histopathological features of sCJD are spongiform change, neuronal loss and gliosis, (astrocytes and microglia) (126). Neuronal loss and gliosis occur in many neurodegenerative conditions but spongiform encephalopathy is more specific and therefore a more useful diagnostic finding. Spongiform change is characterised by the presence of vacuoles in the neuropil of the deep cortical layers, cerebellar cortex or subcortical grey matter (fig 1.4). The vacuoles may become confluent, disrupting the cortical cellular architecture. The distribution of spongiform change is variable in sCJD but the most constant affected region is the head of the caudate nucleus whereas spinal cord and brainstem are rarely involved. The white matter can be involved but extensive white matter degeneration with necrosis distinguishes the 'panencephalic' variant of sCJD (127). This is rare outwith Japan. The regional distribution of spongiform change has been shown to be influenced by PrP glycotype and PRNP codon 129 genotype (128).

Fig 1.4

sCJD: confluent spongiform change
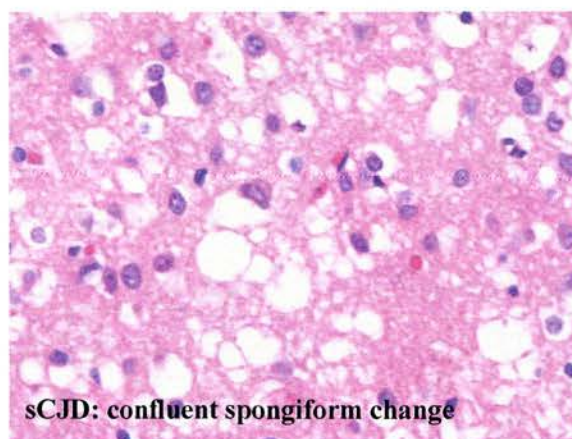
However, spongiosus is not specific to CJD. Focal changes indistinguishable from spongiform change in CJD are occasionally seen in Alzheimer's disease and diffuse Lewy Body dementia. Superficial 'spongy' alterations are associated with Pick's disease. and perineuronal vacuolation can occur secondary to hypoxia. Status

spongiosus can be the end result of extensive neuronal loss of various aetiologies including long duration sCJD and other, non PrP dementias (129).

Immunohistochemical identification of PrP^{Sc} has become a useful tool for diagnosis of sCJD. Normal brain contains only PrP^c which is fully degraded by proteinase K. PrP^{Sc} is either deposited in a diffuse, synaptic pattern, a patchy, perivacuolar distribution or in plaques (figs 1.5, 1.6, 1.7). True kuru like plaques are seen in only 10 – 15% of sCJD cases (130) and may be visible without immunohistochemistry, predominantly in the cerebellar cortex. Plaque-like PrP deposits are more common and require immunochemical staining to be visualised. There is increasing evidence that microglial cells play a crucial role in PrP plaque formation (131, 132). Similar to spongiform change the pattern and distribution of PrP is influenced by codon 129 genotype and PrP glycotype (120,128).

Fig 1.5

PrP: synaptic/perineuronal

Fig 1.6

PrP: perivacuolar

Fig 1.7

PrP: kuru plaques
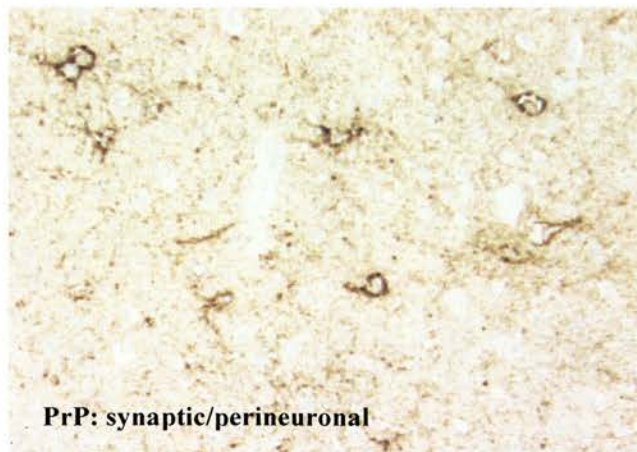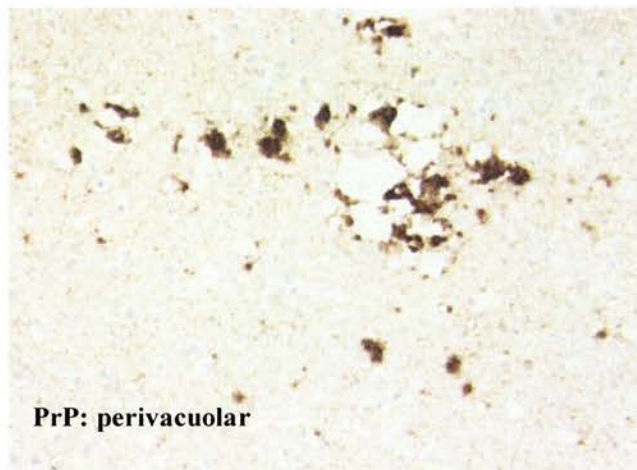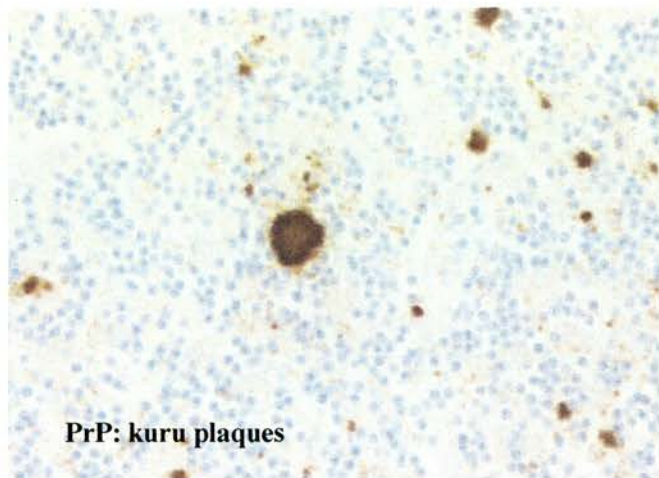
Western blot reveals two possible isoforms of PrP^{Sc} in sCJD, types 1 and 2A, differing in terms of electrophoretic mobility. This is determined by relative molecular mass, reflecting the degree of proteinase K-mediated truncation of PrP at the N terminus. (type 1 21 kDa, type 2A 19 kDa). PrP profile can be characterised further by glycosylation pattern on immunoblot. Diglycosylated, monogylcosylated and non glycosylated PrP occur but in sCJD the monoglycosylated protein predominates. A definite neuropathological diagnosis of sCJD requires either evidence of spongiform encephalopathy in cerebral and / or cerebellar cortex and / or subcortical grey matter, or an encephalopathy with PrP immunoreactivity. (133).

1.9.4   Sporadic CJD classification

It has been proposed that sCJD phenotypes are determined by the combination of host *PRNP* genotype and PrP^{Sc} isotype (characterized by molecular mass) (134, 135). Subsequently Parchi et al defined a classification system for sCJD subtypes, identifying six phenotypic variants with differing clinical features and neuropathology from a study of three hundred confirmed sCJD cases (120) (table 1.6).

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Table 1.6. sCJD classification based on codon 129 genotype and PrP isotype (Parchi classification)

Codon 129 / PrP isotype	Clinical profile	Neuropathology
MM1 / MV1	'Typical sCJD', RPD, myoclonus, visual symptoms	'Classic sCJD pathology', synaptic PrP staining
VV1	Young, dementia, cortical signs	Cerebellum largely spared, weak synaptic PrP
MM2 - Cortical	Main feature dementia, cortical signs	Cortical spongiosis and PrP staining, cerebellum relatively spared
MM2 - Thalamic	As FFI: progressive insomnia, psychomotor agitation	As FFI: prominent thalamic pathology, little PrP
MV2	Prominent ataxia and dementia	Kuru plaques and plaque like PrP deposits
VV2	Early ataxia, dementia often late	Similar to MV2 without kuru plaques

The commonest sCJD phenotype is associated with MM1 or MV1, accounting for 70% of cases. Such patients usually have the classic sCJD triad of rapidly progressive dementia, myoclonus and a typical EEG. The Heidenhain presentations are also contained within this subgroup. The second most frequently encountered phenotype (seen in 16%) occurs with VV2, the so called ataxic variant. The other codon 129 / prion protein isotypes combinations are all rare and are associated with long disease duration. MM2 has two characteristic phenotypes with different PrP gylcosylation ratios; MM - thalamic which is indistinguishable from fatal familial insomnia, and MM - cortical with prominent dementia. However, it should be noted that the pathological and particularly the clinical phenotypes associated with each codon 129 / PrP type are not absolute and are generalisations only. In fact other studies have shown only weak correlation between codon 129 / prion protein isotype and clinical phenotype and there is likely to be considerable overlap in clinical features between different Parchi subtypes (136).

To confuse matters further there are two other sCJD classification systems in use, both subdividing Parchi group MM1 into two. Collinge et al's system identifies three

rather than two PrP^{Sc} types, distinguished by gel electrophoretic mobility. Thus Collinge types 2 and 3 correspond to Parchi PrP^{Sc} types 1 and 2 respectively, but Collinge type 1 has a higher molecular mass than any PrP in the Parchi system and clinically it is suggested that Collinge type MM1 is phenotypically distinct with a shorter disease duration than Collinge defined MM2 sCJD (29, 128). Zanusso et al also identify two subtypes within Parchi sCJD MM1, in their case based on different pH dependant PrP^{Sc} gel migration and differences in disease duration (137). However, a recent study has re-evaluated these findings and the different classification systems and did not feel subdivision of Parchi sCJD MM1 was clinically, neuropathologically or experimentally justified (although admittedly the authors included Parchi and Gambetti, proposers of the original system) (138). In this thesis the Parchi system will continue to be used as it is currently the most widely accepted sCJD classification.

Codon 129 / PrP type also influences sensitivity of CJD investigations. EEG is most often typical in MM1 / MV1 patients. CSF 14-3-3 is positive in the majority of cases but the infrequent negatives are usually seen in association with PrP 2 (139, 140, 119). The relationship between MRI findings and *PRNP* / PrP type is less straightforward. The frequency of basal ganglia hyperintensity varies with molecular subtype but is recognised in all six Parchi types. Cortical hyperintensity is probably seen most commonly with MM1 and MM2 (141). Thalamic high signal has been associated with MV2, MM2 and VV2 (142, 143, 144).

Occasionally a mixture of PrP 1 and 2 is detected and recent evidence suggests that the harder you search for multiple PrP types the more likely you are to find them, although the true prevalence of multiple types is unknown (145). Conventional western blot analysis for the detection of PrP types is quantitatively limited and it is likely that the prevalence of PrP 1 / 2 co-occurrence is underestimated. Newer techniques using specific antibodies are proving more successful in detecting each PrP type. It is likely that as experimental techniques become more sensitive more sCJD patients will be identified as having both PrP type 1 and 2. This casts doubt on the current sCJD classification system based on the *PRNP* polymorphism and one or other PrP type. However, one PrP subtype usually predominates and this often correlates with the neuropathology and clinical presentation. (146, 147), but there is emerging evidence that when large sCJD cohorts are studied those cases with mixed PrP^{Sc} types may have a different clinical phenotype (121).

To date no sCJD case has been associated with PrP type 2B which is characteristic of vCJD (whereas it is type 2A in sCJD due to the different glycosylation pattern).

1.9.5 Diagnostic criteria for sporadic CJD

Diagnostic criteria for sCJD were first proposed in 1979 by Masters et al and have subsequently been revised three times (148). The current criteria were established in 1998, incorporating the CSF 14-3-3 result (94).

Current WHO criteria: Rotterdam 1998

I   Rapidly progressive dementia

II   A) Myoclonus

        B) Visual or cerebellar problems

        C) Pyramidal or extrapyramidal features

        D) Akinetic mutism

III   Typical EEG

1.0 Definite: Neuropathologically / immunocytochemically confirmed

2.0 Probable: I + 2 of II + III or I + 2 of II + positive 14-3-3 CSF protein

3.0 Possible: I + 2 of II + duration < 2 yrs

4.1 Unclear diagnosis, not meeting sCJD criteria

4.2 Clinical diagnosis not sCJD

4.3 Pathological diagnosis not sCJD

1.10 Variant CJD

1.10.1 BSE and vCJD

Variant CJD was first identified as a new disease entity in 1996 following identification in 1995 of three individuals under the age of thirty with an unusual clinical phenotype for sCJD and atypical pathology characterised by extensive amyloid plaque formation (149). As more cases followed and genetic CJD and alternative diagnoses were excluded it became apparent this was a novel phenotype, initially unique to the UK. Incidence continued to rise until a peak in 1999 and,

although there have been fewer cases since this time, new patients are still presenting each year (fig 1.8). To date (April 2007) there have been 199 cases worldwide, with 162 in the UK, 22 in France, 4 in Ireland, 3 in the USA, 2 in the Netherlands and single cases in Italy, Portugal, Spain, Canada, Japan and Saudi Arabia (150).

Fig 1.8

NUMBER OF ONSETS PER ANNUM OF vCJD IN THE UK
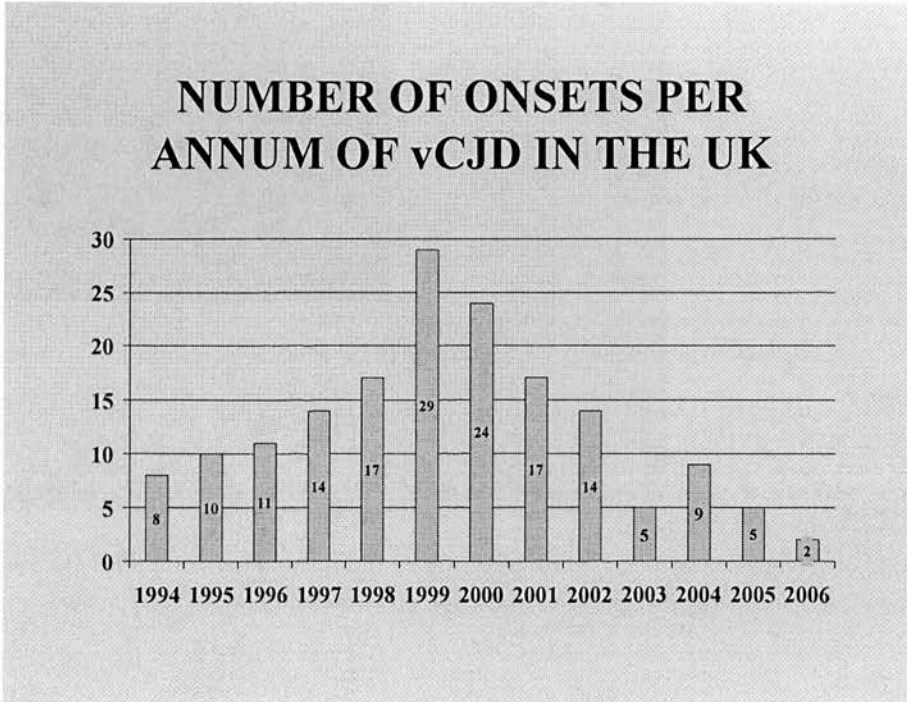
There is convincing evidence that the aetiological agent of vCJD is BSE. The origin of BSE in cattle is unclear with theories ranging from a sporadic onset, genetic mutation, via feed contaminated by a TSE - infected exotic ungulate or originating from scrapie. Scrapie strains can change their characteristics on transmission through a new species but currently strain studies do not provide positive evidence for scrapie as the source of BSE. Irrespective of its origin it seems likely BSE was propagated by the use of meat and bone meal in cattle feed (151). An alteration in the rendering process around 1980 probably allowed the infective agent in carcasses to survive and contaminate the feed, with subsequent recycling of the TSE. BSE was formally recognised as a novel disease in the UK in 1986 (152), although in retrospect the first cow died in December 1984. A full scale epidemic ensued, affecting nearly 200,000 cattle in total. The epidemic was slowly brought under control by the introduction of

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the ruminant feed ban in 1988 and the specific bovine offal ban a year later. In addition the public were further protected in 1996 by the 30 month rule whereby asymptomatic cattle over this age were pre-emptively destroyed (153). Numerous other countries have been affected by BSE but in far smaller numbers and probably as a result of imported livestock or food supplements.

The BSE epidemic immediately raised concern regarding the theoretical possibility of human transmission. This stimulated the reinstitution of active CJD surveillance in the UK in 1990 looking for evidence of a change in the pattern of CJD which might reflect a link to BSE. The evidence associating BSE and vCJD is three fold. In epidemiology terms the high incidence of vCJD in the UK compared to countries with similar surveillance systems mirrors the BSE problem and is consistent with the BSE theory. More convincingly transmission experiments inoculating mice with vCJD brain result in a similar incubation period and lesion profile as mice inoculated with BSE from cattle, confirming a common strain. (154, 155, 156). At a molecular level strain typing of vCJD has confirmed that the responsible agent is indistinguishable from that seen in BSE (29). This BSE glycoprotein 'signature' is a constant feature of vCJD and can therefore be used to distinguish it from other types of CJD.

BSE is believed to have entered the human food chain via beef products contaminated with central nervous system tissue e.g. meat pies and sausages containing mechanically recovered meat that is obtained by carcass compression and extraction and potentially contains spinal cord (157).

1.10.2 Clinical features of vCJD

The mean age at onset of vCJD is significantly younger than sCJD at 28 years and the mean disease duration is longer at 14 months (150, 158). The longest surviving case to date is 5 years and 7 months (April 07).

The clinical phenotype is remarkably stereotyped, consistent with the proposed aetiology from a single strain of infective agent. Typically the illness begins with non specific psychiatric symptoms including anxiety, loss of interest and behavioural change, often prompting referral to psychiatry (159, 160, 161, 162, 163). Around one third have early, persistent sensory symptoms such as dysaesthesia and numbness (162). A minority (around 15 - 30%) have a pure neurological onset (158, 162). Neurological features inevitably develop at some stage in all cases. Classically the

patient becomes ataxic and develops a movement disorder, most frequently myoclonus but sometimes dystonia, chorea or tremor (161). Other common late features include hallucinations, visual impairment and upper motor neurone signs. Progressive cognitive decline is universal, culminating in death. The possibility of a distinct vCJD neuropsychological profile has been explored, but ultimately most patients have global cognitive impairment with cortical and subcortical features (165, 166). Evaluation is limited by the fact many vCJD patients are unable to cope with the demands of rigorous neuropsychological testing.

1.10.3 Investigations in vCJD

(i) Blood tests

As with sCJD no prion specific blood test exists for vCJD and bloods are usually normal and not diagnostically helpful.

(ii) CSF

In variant as with sporadic CJD routine CSF examination is unremarkable with no lymphocytosis but possibly mildly elevated protein. 14-3-3 protein is positive in 40 - 50% of variant cases (167, 104, 161), making it a less useful diagnostic tool than in sporadic CJD, and it is postulated this relates to the slower disease course of vCJD. A positive result may be supportive but a negative assay by no means excludes the diagnosis. Various other CSF proteins including S100, Tau and neuron-specific enolase, have been evaluated in vCJD but to date none are sufficiently sensitive or specific for routine diagnostic use. Tau appears most promising with sensitivity greater than 90% in some studies, but it is frequently elevated in other neurodegenerative diseases limiting its utility as a specific diagnostic test for vCJD (167).

(iii) Magnetic resonance imaging

MRI is the most useful non-invasive investigation in the diagnosis of vCJD and is included in the diagnostic criteria, allowing a clinically possible case to be classified as probable (2). The characteristic finding is hyperintensity in the posterior thalamic nuclei relative to the basal ganglia, the so called 'pulvinar' sign (168). It was first described in 1996 on proton density and T2 sequences (169, 170) but FLAIR has been

found to be the most sensitive sequence (greater than 90% sensitivity) (171). A retrospective review in 2000 found the pulvinar sign was actually missed in 60% of cases at the referring centre (172), although this may well have improved with increasing awareness of the MRI findings in vCJD. Specificity is high at greater than 95% and many of the alternative causes of pulvinar hyperintensity are clinically readily distinguishable diseases. Also the hyperintensity often involves the thalamus generally rather than specifically the pulvinar nuclei. Alternative causes of thalamic hyperintensity include familial and sporadic CJD (172, 173) Alper's syndrome (174), Fabry' disease (but seen on T1-weighted images) (175), post infectious encephalopathy (176), idiopathic intracranial hypertension (177), 'tip of basilar' syndrome, Wernicke's encephalopathy (178), bithalamic glioma and paraneoplastic limbic encephalitis (179).

(iv) EEG

The EEG in vCJD usually shows non specific changes such as focal or generalised slow waves, and it can be entirely normal, particularly in the early stages of illness (161, 163). The typical sCJD pattern of periodic complexes has been reported in 2 cases of vCJD in Italy and Japan late in the clinical course but is not the usual finding (180, 181).

(v) Tonsil Biopsy

In vCJD PrP can be detected in the lymphoreticular system (LRS), in contrast to other human prion diseases where lymphoid PrP is undetectable by comparable methods. PrP^{Sc} is believed to replicate and accumulate in the LRS prior to neuroinvasion of the central nervous system, and this raised the possibility that lymphoid biopsy might provide an early diagnostic tool. Spleen, tonsil, appendix and lymph node have all been positive for PrP^{Sc} in vCJD at post mortem, and tonsil biopsy has proved to be a valuable diagnostic test in clinical practice (182). Analysis by western blot and immunohistochemistry demonstrates proteinase K digestion fragments identical in size to those in vCJD brain, but the glycoprotein ratios are slightly different. This probably reflects the role of tonsillar tissue in glycosylation, but the predominant type is still diglycosylated protein as in vCJD brain, as opposed to the monoglycosylated form in sCJD (183).

To date no definite or probable vCJD patients who have undergone tonsil biopsy have had a negative result (provided adequate tissue was available for analysis). Equally importantly no false positive tonsil biopsy assays have yet been identified. Like MRI tonsil biopsy is part of the current diagnostic criteria for vCJD.

However, there are a number of caveats related to tonsil biopsy. It is an invasive test with risks including haemorrhage, and may not be necessary in the face of a typical clinical picture and positive pulvinar sign on MRI. If the diagnosis of vCJD is really in doubt a tonsil biopsy can only confirm or refute this whereas a brain biopsy can potentially provide an alternative definitive diagnosis. It is not known how early tonsil specimens are positive for PrP^{Sc} but an appendix has been positive 8 months prior to symptom onset (184). Therefore lymphoid tissue could potentially be used as a presymptomatic screening test although this would not be indicated currently given the low disease incidence and lack of curative treatment. A retrospective study has evaluated PrP^{Sc} accumulation in tonsil and appendix tissues to guide estimates of vCJD prevalence. It identified 3 positive appendices out of over 12,000 appendix / tonsil specimens, giving an estimated prevalence of 237 per million (185). However, questions have been raised regarding the reliability of PrP^{Sc} detection in appendix tissue, even in the terminal stages of vCJD disease. In one study only one out of four appendices obtained at necroscopy from pathologically confirmed cases of vCJD was positive for PrP^{Sc} (186). Probably the most interesting finding from the retrospective, large-scale appendix review was that in both cases where *PRNP* codon 129 genotype was analysed the individual was valine homozygous (VV), providing the first indication that the VV subgroup are susceptible to vCJD infection.

1.10.4 Codon 129 genotype and variant CJD

The influence of codon 129 genotype on CJD susceptibility, incubation period and disease expression has already been mentioned in this introduction. All vCJD patients to date have been homozygous for methionine (MM) at codon 129. However, vCJD has been transmitted to a methionine valine (MV) heterozygous individual via blood transfusion, although at the time of death the patient was not clinically symptomatic. As mentioned above two presymptomatic valine homozygous (VV) individuals have been identified with detectable PrP^{Sc} in their appendices. There is much speculation as to whether clinical vCJD can occur in non-MM patients and if so what the clinical

phenotype will be. A recent paper on kuru highlighted the effect of *PRNP* 129 genotype on incubation period, with the very late onset cases being MV (42). This is potentially relevant in vCJD. We may not have observed non-MM vCJD cases because it is simply too early for them to present. Alternatively they may be truly resistant to infection, may be infected but never develop the clinical manifestations of vCJD, or be eluding diagnosis because clinically they differ from the MM patients.

1.10.5 Neuropathology of variant CJD

Neuropathology is required for a definitive diagnosis of vCJD and this usually involves routine microscopy plus immunocytochemistry for PrP^{Sc} using a range of monoclonal antibodies against PrP epitopes. Interestingly the neuropathological findings in vCJD are relatively uniform with less diversity than that recognised in sCJD, although this may simply reflect the fact that all vCJD patients to date have had the same *PRNP* genotype (methionine homozygous).

Cerebral atrophy is not generally a feature but long duration cases may have cerebellar atrophy. As with other prion diseases a characteristic finding is spongiform change throughout the cerebral cortex, but particularly involving the corpus striatum in vCJD. However, the extensive confluent spongiosus seen in the cerebral cortex in sCJD is not encountered. Neuronal loss is variable but often most pronounced in the cerebellar cortex associated with reactive gliosis. The most striking microscopic feature is the florid plaque, visible with haematoxlyin and eosin stains (fig 1.9). The term florid plaque was first used to describe the structures seen after experimental transmission of Icelandic scrapie to mice (187), and the plaques seen in vCJD appear similar microscopically. They are complex structures with eosinophilic centres surrounded by fibrils, with an outermost halo of spongiform change. They are scattered throughout the brain but are most prominent in the occipital and cerebellar cortex, basal ganglia and thalamus (188). Florid plaques are easily distinguished from the amyloid plaques seen in kuru and some cases of sCJD (usually *PRNP* codon 129 methionine valine heterozygotes), as amyloid plaques have a more restricted distribution , more compact morphology and lack the surrounding halo of spongiform change (fig 1.10).

Fig 1.9

vCJD florid plaque

Fig 1.10

sCJD kuru plaques
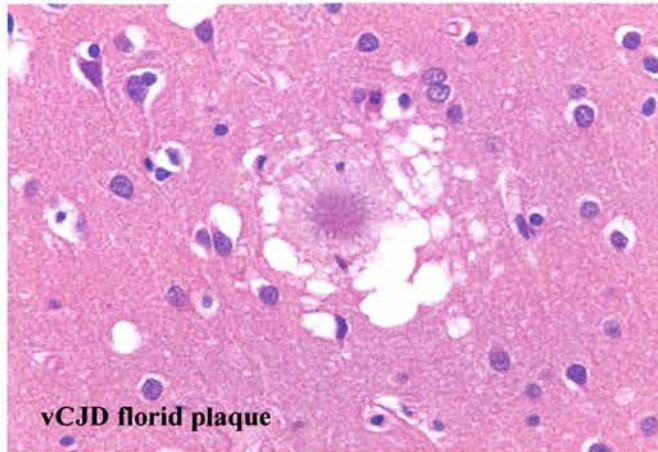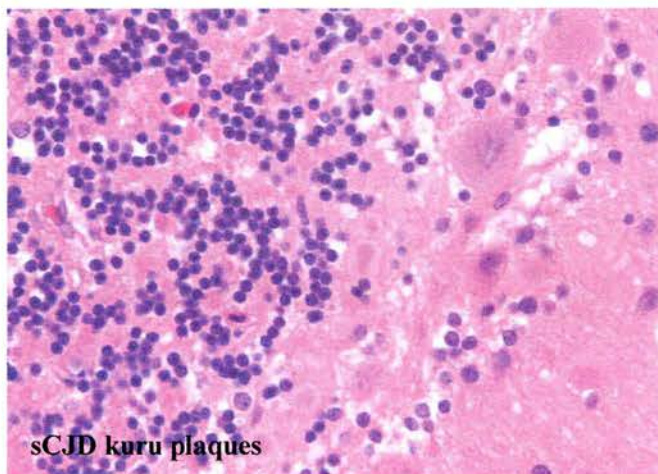
Immunocytochemistry confirms that florid plaques stain strongly for PrP, but PrP is more widely distributed in perivascular, pericellular and diffuse plaque-like patterns throughout the brain. Quantitatively PrP accumulation is greatest in the occipital and cerebellar cortices. Its pattern of distribution varies depending on the anatomical site. E.g. in the basal ganglia PrP tends to be linear and perineuronal with multiple small plaques, whereas in the thalamus it is in a more reticular pattern.

Western blot analysis of PrP extracted from vCJD brain confirms that it is different to PrP isotypes recognised in sCJD. Its distinct profile relates to fragment size following digestion with proteinase K and to glycosylation (with most of the PrP being diglycosylated as opposed to non glycosylated or monoglycosylated in sCJD). Some laboratories have reported different isoform mobility between PrP in vCJD and sCJD,

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classifying the variant isoform as type 4. However, this has not been a consistent distinction with most laboratories finding mobility indistinguishable from type 2 PrP in sCJD and therefore the vCJD isotype has been termed type 2B (and this latter nomenclature will be used throughout this study) (189). The glycotype appears to be modified by the tissue in which it accumulates, with slight differences noted between tonsillar and cerebral PrP[Sc] on western blots (200).

An important feature distinguishing vCJD from all other human forms of prion disease is the identification of PrP[Sc] outwith the central nervous system in lymphoid tissue. This has not been found using comparable techniques in sCJD. In vCJD PrP has been detected in follicular dendritic cells within germinal centres of the tonsil (the basis for the tonsil biopsy diagnostic test), in spleen, appendix and lymph nodes and possibly in Peyer's patches in the ileum (183, 189). These findings have major implications for the possibility of secondary transmission of vCJD, either via blood or surgical instrumentation.

1.10.5 Diagnostic Criteria for vCJD (2)

I   A Progressive neuropsychiatric disorder

        B Duration > 6 months

        C Routine investigations do not suggest an alternative diagnosis

        D No history of potential iatrogenic exposure

        E No evidence of a familial form of TSE

II   A Early psychiatric symptoms [a]

        B Persistent painful sensory symptoms [b]

        C Ataxia

        D Myoclonus or chorea or dystonia

        E Dementia

III   A EEG does not show typical appearance of sCJD [c]

        B Bilateral pulvinar high signal on MRI scan

IV   A Positive tonsil biopsy [d]

Definite: IA and neuropathological confirmation of vCJD [e].

Probable: I **and** 4/5 of II **and** IIIA **and** IIIB

        Or

        I and IVA

Possible: I and 4/5 of II and IIIA

[a] Depression, anxiety, apathy, withdrawal, delusions

[b] This includes both frank pain and / or dysaesthesia

[c] Generalised triphasic complexes at approximately one per second

[d] Tonsil biopsy is not recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect casesin which the clinical features are compatible

[e] Spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum

1.11   Secondary Transmission of CJD

The emergence of vCJD in 1996 heightened concerns about the possibility of secondary transmission of CJD. Experience with iatrogenic CJD demonstrated that sCJD could be transmitted to humans via contamination with brain tissue. However, there have not been any substantiated reports of blood borne transmission of sCJD and the weight of epidemiological evidence, including look back and case control studies, suggests this does not occur. Similarly there is no evidence supporting vertical transmission of sCJD. The situation is different with vCJD.

The lymphoreticular distribution of vCJD provides theoretical possibilities for blood borne spread. There is evidence of experimental transmission of BSE in sheep via intravenous transfusion of whole blood taken from pre-symptomatic sheep. There is now good evidence for blood borne transmission of vCJD relating to four individuals. In 1996 a neurologically well 24 year old donated blood. 3.5 years later the donor succumbed to vCJD. One unit of this donated blood was transfused into a 62 year old in 1996. 6.5 years later he developed the characteristic clinical phenotype of vCJD

and this was confirmed pathologically when he died at the age of 69. He was methionine homozygous at codon 129. At the time the probability of this being a chance occurrence was estimated at 1 in 30,000 (191).

In the second case a 27 year old donated blood eighteen months before developing symptoms of vCJD. One unit of this blood was transfused into an individual in 1999 and this recipient remained neurologically well up to her death in 2004 from unrelated causes. At autopsy the spleen and a cervical lymph node were positive for PrP^{Sc} but the brain and other lymphoid tissue including tonsil was negative. She was found to be a codon 129 heterozygote (59).

The third individual received a vCJD-implicated blood transfusion in 1997. 8 years later he developed painful parasthesiae of his lower limbs associated with fatigue, anxiety and personality change. He gradually deteriorated with development of ataxia and cognitive impairment, and died 10 months after symptom onset. Prior to his death MRI brain demonstrated the pulvinar sign and *PRNP* analysis confirmed he was methionine homozygous at codon 129 without any mutations. No tonsil biopsy was performed but autopsy confirmed the diagnosis of vCJD (192, 193). Recently a fourth case of transfusion - associated vCJD was identified, and again followed a typical disease course. In this case tonsil biopsy was performed and was positive for PrP^{Sc} (personal communication G Chohan).

To date there is no evidence that vertical transmission of vCJD can occur, based on a study of nine women who gave birth within one year of developing vCJD symptoms (194). However, this is limited by the small number of cases and relatively short period of follow up. BSE has been transmitted from ewe to lamb in an experimental sheep flock, although it is still not known if this was in utero vertical transmission or horizontal spread perinatally (195).

These secondary transmission issues have major public health implications, ranging from blood transfusion services to instrument sterilisation and the safety of bone grafts. A number of precautionary steps have been taken. Since 1999 all blood components have been leucodepleted. Fresh frozen plasma is imported from USA for all recipients born in or after 1996 and USA plasma is used for fractionation. Any transfusion recipient is banned from donating blood (implemented 2004) and all those who have received blood from a vCJD donor have been notified.

There are also concerns that the passage of the prion through one human prior to transmission could potentially modify the clinicopathological phenotype, making cases due to secondary transmission harder to detect.

1.12 Treatment of CJD

There is no known cure for CJD and treatment remains extremely limited. There are major challenges to identifying successful therapy for human prion disease. Most of the work has been on neuroblastoma cell lines or rodent scrapie models, with the therapeutic agent being introduced at the same time as prion infection. However, in real life CJD infectivity will predate treatment, probably by years. There is no pre-symptomatic diagnostic test so a successful drug needs to halt disease progression and ideally reverse pre-existing neurological damage. The rapidly progressive nature of the disease means any agent must act quickly. It also needs to penetrate the blood-brain barrier or be introduced directly into the cerebrum.

The principal therapeutic target has been conversion of PrP^C to PrP^{Sc} and subsequent aggregation of PrP^{Sc} (196, 197). Laminin receptor, a cell surface receptor for PrP^C and PrP^{Sc}, has been identified (198) and provides an alternative therapeutic option, either via production of competing antibodies (199) or by inhibition of laminin receptor production at the mRNA level (200). Numerous antiprion agents have been identified experimentally, including amphotericin B, congo red, polysulphated polyanionic substances such as dextran sulphate and pentosan polysulphate, chlorpromazine and quinacrine (both tricyclic compounds with aliphatic side chains), designer peptides like beta-sheet breaker and RNA aptamers (197). Unfortunately this has not translated into great clinical success.

Quinacrine and chlorpromazine impair de novo formation of PrP^{Sc} aggregates in cell and murine models, but are less effective at degrading pre-existing PrP^{Sc} fibrils (201, 202). Initially there was cautious optimism about the clinical prospects of quinacrine and chlorpromazine (203, 204, 205) but results have been disappointing (206, 207). An ongoing MRC - sponsored trial, PRION-1, is evaluating the efficacy of quinacrine in the UK CJD population. Results are not yet published but a decision has been made not to trial quinacrine in the rest of Europe.

Pentosan polysulphate (PPS) is a large polyglycoside molecule with weak heparin-like activity. It has been shown to prevent propagation of PrP^{Sc} in cell culture (208)

and prolong TSE incubation period in rodent scrapie models (209). Following promising preliminary animal studies it has been used experimentally in a number of individuals with variant, genetic and iatrogenic CJD (210). The numbers are small and the results to date are mixed. Several patients treated with PPS are still alive, including the longest surviving case of vCJD, and modest neurological improvement has been reported (211). However, others have been treated without any noticeable benefit and died within a few months (212). A major practical drawback is the requirement for intraventricular access. Further evaluation of PPS in a larger cohort is essential.

1.12   New developments in TSEs

There have been a number of recent interesting developments in the understanding of animal TSEs, with potentially important implications with respect to human prion disease.

The first naturally occurring case of BSE in a goat was confirmed in France in 2005, suggesting that BSE may have been accidentally transmitted to other ruminant species (213). Subsequently there has been a possible case of BSE in a UK goat (214). Previously BSE (and consequently vCJD) was thought to be caused by a single prion strain, in contrast to scrapie where multiple strains exist. However, there is now evidence that challenges this. Experimental transmission of BSE to transgenic mice expressing human *PRNP* MM has resulted in two distinct molecular phenotypes with differing PrP^{Sc} glycotypes and neuropathological profiles (215, 216). Transmission of human vCJD to chimeric mice with human and mouse PrP has produced two stable distinct prion strains (217). This suggests either the existence of two prion strains within individual cases of BSE and vCJD or potentially generation of a new prion strain on transmission. More recently two atypical strains of BSE have been identified with clinical features, PrP^{Sc} signatures and neuropathological lesion distribution distinct from BSE (3, 4, 218). Both of these atypical strains are experimentally transmissible and the inoculated transgenic mice exhibit strain-specific features clearly distinguishable from BSE. One of these strains is termed BASE (bovine amyloidotic spongiform encephalopathy) and is particularly interesting because it shares striking similarities with human sCJD of the MV2 subbtype, in terms of PrP^{Sc}

deposition and formation of amyloid plaques. It also has the intriguing ability to convert into a strain indistinguishable from classical BSE after serial passage through nontransgenic mice (219).

Other atypical TSEs have been identified in smaller ruminants, including atypical scrapie in sheep and goats (220).

What are the implications of all these findings to human prion disease? It is postulated that BASE might be the sporadic form of cattle prion disease, similar to sCJD in humans. Could sCJD be somehow related to BASE exposure, particularly in view of the pathological similarities with MV2 sCJD? The apparent conversion of BASE to BSE implies this could be the origin of BSE. Are these apparently novel atypical TSEs really new, or are they just being identified for the first time due to improvements in detection techniques and surveillance programmes?

Many questions remain unanswered but ongoing monitoring of human prion disease is vital.

1.14 CJD Surveillance

The word surveillance originates from the French and literally means 'to watch from above'. However, in medical terms it has been variously described as 'the collection, collation, analysis and dissemination of data' and 'a type of observational study that involves continuous monitoring of disease occurrence within a population.' In the context of transmissible spongiform encephalopathies, surveillance has a particularly important role because of concerns regarding transmission of prion disease, including animal to human and human to human spread. Thus individual cases may have far reaching implications for the population as a whole. Following the identification of BSE in British cattle the Southwood report was commissioned (221). This recommended that CJD was monitored in the UK population and shortly afterwards the NCJDSU was set up. CJD surveillance aims to identify all cases, collate clinicopathological data, monitor the epidemiology of the disease and inform health professionals, scientists, policy makers and the public of any relevant developments.

The NCJDSU was established in its current form in 1990 but CJD surveillance in the UK actually dates from 1970 and has occurred in four phases. A retrospective study in England and Wales covered 1970 – 1980. Between 1980 and 1984 a prospective study was undertaken in Oxford, again confined to cases in England and Wales. The third

phase was a retrospective review of all UK cases between 1985 and 1990. Prospective surveillance was instituted for the UK from 1990 and is currently ongoing. It is guided by the following eight principles, which are followed in order to optimally manage CJD in the UK:

- Provide care and support for patients and families
- Offer skilled clinical investigation to enable a reliable diagnosis to be made
- Early recognition of probable and possible cases of sCJD, vCJD, inherited and iatrogenic human prion disease
- Rapid reporting of such cases to the surveillance system
- Prompt gathering of information from and about patients to allow enhanced surveillance
- Maintenance of rigorous controls to minimise possible risks of secondary transmission via medical procedures or other means
- Quality assure existing controls on possible primary sources of transmission (e.g. the food chain) and keep under review the need for new controls
- Promote high quality research directed at various aspects of human prion diseases focussed on achieving early diagnosis and eventual effective treatment for these disorders

Numerous other countries run CJD surveillance programmes and there is a harmonised system for surveillance of CJD in Europe involving all major member states. EUROCJD (European and Allied Countries Study Group of CJD) was established in 1993 under the auspices of the European commission, and initially involved the national CJD registries of France, Germany, Italy, the Netherlands, Slovakia, Spain and the UK. It was extended in 1997 to incorporate Australia, Austria, Canada and Switzerland.

In 1996 the European clinical council recommended that epidemiological surveillance of CJD should be extended to all member states. Therefore NEUROCJD (the Extended European Collaborative Study Group of CJD) was established. It involves the CJD registries of Belgium, Denmark, Finland, Greece, Iceland, Ireland, Israel, Norway, Portugal and Sweden. Both NEUROCJD and EUROCJD are co-ordinated through the NCJDSU in Edinburgh.

In this study EUROCJD data on sCJD from 1993 to 2004 will be compared with UK figures for the same time period.

EUROCJD has a number of objectives including:

- Observation of trends in sCJD disease incidence across and within countries
- Assessment of putative risk factors for CJD
- Study of the clinicopathological variants and molecular biology of CJD with specific reference to genetic factors that influence susceptibility to disease
- Evaluation of diagnostic tests for sCJD.

Accurate data collection is vital if CJD surveillance is to be a reliable means of identifying novel disease phenotypes and identifying changes in disease incidence, both within one country and between countries. Virtually all national CJD registries have demonstrated an increase in sCJD incidence in the first few years after initiating a surveillance programme, presumably related to improved case ascertainment. However, the sCJD incidence rate in the UK has now been relatively stable since 1997 and is comparable with other developed countries with similarly established surveillance programmes (67). 100% case ascertainment is probably not realistic but current evidence suggests that the vast majority of sCJD cases are being detected in the UK (see discussion section 4.1).

Chapter 2. Methods

2.1 The study population

The principal study population was all suspect cases of sporadic CJD referred to the NCJDSU in 1993, 1994, 2003 and 2004. This included individuals who ultimately turned out not to have CJD or remained classified as Possible cases or 'Diagnosis Unclear', as one of the principal aims of the thesis was to identify novel 'atypical' phenotypes of sCJD. They were selected by year of referral rather than year of death because some of the non - sCJD cases and the Possible / Unclear diagnosis group recovered or remained unwell but alive, and it was important not to omit these individuals. In addition all UK Definite and Probable sCJD cases (as defined by their final classification by WHO diagnostic criteria) that died between 1st January 1993 and 31st December 2004 inclusive were reviewed. Basic demographic data and investigation results were extracted on all the study population. A more detailed review of clinical and pathological features was made on the 1993, 1994, 2003 and 2004 referrals and any patient aged fifty or under at onset and any pathologically confirmed case with a negative 14-3-3 CSF result.

Exclusion criteria were those referrals to the NCJDSU outwith the above timeframe, individuals referred and finally classified as having another type of CJD (genetic, iatrogenic or variant) and patients referred as suspect sCJD that were later identified as familial cases on the basis of *PRNP* mutations. One patient with a strong family history of genetic CJD in whom genetic analysis was not performed was also excluded. None of the study population was known to have a family history of CJD at the time of inclusion.

Data collection stopped at the end of July 2005. Therefore any of the study population that were alive at this stage were included but remain classified as 'alive' for the purposes of this study. Any additional information received after July 31st 2005 was not included in the analysis.

The UK data were compared with European sCJD data collected as part of the ongoing collaborative project, EUROCJD. All Definite and Probable sCJD cases notified to the relevant national CJD registries as having died between 1993 and 2004 were evaluated and compared with UK cases for the same time period. Annual

referrals were identified by date of death rather than date of referral because the EUROCJD database does not have referral dates for all patients.

Various subsets of sCJD patients were assessed in more detail and compared with appropriately selected 'control' sCJD patients. E.g. Definite sCJD referrals in 1993/4 and 2003/4 who underwent brain biopsy were compared with Definite patients for the same time period who did not have a biopsy. All young sCJD Cases with onset at age fifty or less between 1993 and 2004 inclusive were compared with Cases with onset over age fifty from 1993/4 and 2003/4 (the comparison cohort came from a more restricted time period because only these cases had sufficient information for a clinical comparison). All 14-3-3 negative pathologically proven patients from the time the test was introduced (December 1996) until 2004 were compared with 14-3-3 positive pathologically confirmed patients in 2003/4 (and again the comparison group were selected to provide sufficient detail to contrast clinical phenotypes).

2.2 The referral process

Referral of suspect sCJD cases to the NCJDSU occurs in one of three ways.

Clinical - passive ascertainment: neurologists, neuropathologists and neurophysiologists are reminded annually of the need to refer any individuals in whom sCJD or vCJD is considered a possible diagnosis to the NCJDSU.

Death certificates - passive ascertainment: the Office for National Statistics for England and Wales and the General Register Offices for Scotland and Northern Ireland supply all death certificates coded under rubrics A81.0 and F02.1 (10th ICD revision; and equivalent under the earlier 9th ICD revision).

Other sources - passive ascertainment: psychiatrists, paediatricians, geriatricians, other health professionals and members of the general public may refer cases to the NCJDSU. An enhanced surveillance system also exists for the paediatric population via the PIND study (Progressive Intellectual and Neurological Deterioration), in conjunction with the British Paediatric Surveillance Unit. This is primarily to avoid

missing childhood onsets of vCJD but will also apply to the very rare adolescent onsets of sCJD.

The majority of the study population were referred in one of these three ways with either a death certificate or pathology report / specimen reaching the NCJDSU, or a phone call from the clinician discussing and referring their patient. In July 2004, the Chief Medical Officer announced a new national reporting system centred on the National CJD Reporting Form (see appendix). This is faxed by the notifying clinician to the NCJDSU, the National Prion Clinic (NPC) and the local consultant in communicable diseases. However, very few of the study population were referred in this manner and all those that were had follow up phone calls prior to a visit to discuss the suspect case details further. Therefore this minor change in the reporting system did not impact on data collection.

All suspect sCJD referrals were given a unique NCJDSU number for anonymity and future identification. Occasionally a clinician informally discusses a doubtful case with the surveillance team but if this was not felt to reflect a referral and hence no number was allocated then the individual was not included in this study. Similarly, increasingly patients are being referred for CSF 14-3-3 analysis but this alone was not classified as a referral unless further contact was made with the unit.

2.3 Data collection

The NCJDSU archives were reviewed retrospectively for all individuals in the study population. However, in the majority of suspect cases the information was originally collected prospectively following referral when the patient was symptomatic but alive. Wherever possible such a referral prompted a meeting between the NCJDSU research registrar and the patient and their family, usually in hospital but occasionally at a nursing home or the individual's own home. This took place with the consent of the family and referring clinician. During the visit a detailed history was obtained from the family, a physical examination was performed and investigation results were reviewed. The examination included a neurological assessment recorded in a standardized fashion. The individual was classified as Definite, Probable, Possible, Diagnosis Unclear or Non Case using the current WHO diagnostic criteria as described in the introduction. (In this study capital letters will be used to denote these

classifications). All the information was recorded on a 'Patient review and examination form' with space to freely describe the history plus an additional section with specific questions regarding clinical features and investigation results. The questionnaire design and the specific questions were modified in 1997, so there may have been a slightly different emphasis in 1993/4 referrals compared to 2003/4 referrals (addressed in more detail in the discussion; see appendix for both versions of questionnaire).

One or two research registrars are employed at any one time at the NCJDSU, changing on average every two years, and therefore a number of different doctors visited the suspect cases over the time course of this study. A total of 10 doctors* were involved in CJD visits for the study population, but the majority of surveillance in 1993/4 was performed by two registrars (RS, MZ), and by three registrars in 2003/4 (SC, CAH, KM). To try and minimize inter-registrar differences the information was recorded on the questionnaire in a standardised manner. The history was acquired by allowing the family to freely describe their relative's illness, followed by a number of directed questions as to the presence or absence of particular symptoms and their timing. A new registrar usually accompanied a more experienced registrar on their first visit in order to learn how the history was taken and recorded, but some variability in the directed questions is inevitable depending on individual registrars and also different patients and families.

A research nurse usually accompanied the registrar and also interviewed the family in order to complete a risk factor and epidemiology questionnaire. This is part of a separate case-control study. A visit typically concluded with a discussion with the family regarding the certainty of diagnosis, its implications and prognosis. The family were offered information leaflets produced by the CJD support network and made aware of the National CJD Care package if appropriate. The possibility of genetic CJD was often discussed and genetic analysis offered.

Hospital notes were copied at the time of interview with the next of kin's consent, or if unavailable were requested by post. If an individual had been in several hospitals since their disease onset then all sets of notes were requested. General Practitioner

* RK, RS, MZ, GS, MAM, AL, CH, SC, CAH, KM

notes were not requested until after the suspect case had died. They were not used in this study as they were frequently unavailable or illegible and often did not provide any information over and above the hospital notes and data from the visit.

Details on the neurological examination at first presentation were obtained from the hospital notes. This was defined as the first documented neurological examination and usually occurred at admission or first clinic visit, but occasionally the GP referral letter was used if sufficiently detailed.

Where possible investigation results, particularly EEG and MRI, were reviewed at the time of the visit and either copied then or requested later by letter.

When data such as notes, information on date of death, EEG traces or MRI scans were missing attempts were made to rectify this via a further letter or phone call to the hospital or GP. The family were not contacted directly again.

Sometimes a suspect sCJD case was not visited in life, either because the referral was made when death was imminent and the registrar could not visit in time, or because the referral was made by death certificate or pathology, or the family were not happy for a visit to occur. In such cases attempts were made to visit the family at a later date if the diagnosis of sCJD was Definite or Probable and the local clinician and family gave their consent. This provided the opportunity to gather a detailed history although obviously no examination was possible. On these occasions a 'Late referral' questionnaire was completed (see appendix).

2.4 Definitions

(i) Dates

Information regarding dates of onset, death and timing of investigations was extracted from the hospital notes and relative interviews. Frequently accurate data were unavailable and therefore dates were recorded as the 1st of the month for all dates between the 1st and 10th inclusive, the 15th for all dates between the 11th and 20th, and 30th for all dates between the 21st and 31st. If only the month was given with no other indications this was recorded as the 15th. This strategy was used for all dates in the study.

- Notification date - defined as the date of referral to the NCJDSU, either by phone call, fax or when a letter was received. However, if the suspect case was referred after death, by pathology or death certificate, then date of death was taken as the referral date. This was to minimize artificial clustering due to death certificate referrals being sent in batches every few months.

- Date of onset – usually decided at the time of the visit by the interviewing registrar but if no decision was made at this time or new information came to light then the date was reviewed by the author.

- Disease duration – time interval in months between date of onset and death.

- Time to referral - calculated as the difference between the date of referral and the date of onset.

- Delay to referral - calculated as the difference between the date of referral and the date diagnosis of sCJD was first suspected.

(ii) Diagnosis / classification

- Final diagnosis – 'best guess' as judged by the author, not necessarily pathologically proven but taking into account all available information. If the final diagnosis was not clear it was discussed with one or both of the two consultant neurologists in the unit (RGW, RK).

- Final classification – classification according to the appropriate WHO diagnostic criteria when case closed or based on information available in July 2005 (Rome version for 1993/4 referrals, Rotterdam version for 2003/4 referrals).

- Initial classification – classification at time of NCJDSU visit. If no visit occurred then classification at time of referral was used.

- Who first suspected sCJD - established by examining the clinical notes to determine who first documented sCJD as a possible diagnosis and on what date.

(iii) Clinical parameters

The presence or absence of a large number of clinical features was recorded for the 1993/4 and 2003/4 referrals and all cases aged fifty or less at onset or those with negative 14-3-3 results. The symptoms and signs are listed and defined as follows.

Symptoms:

- Symptoms of impaired cognition including memory loss, disorientation and confusion (abbreviated on graphs to 'forgetful').
- Symptoms suggestive of cerebellar dysfunction. E.g. Unsteady gait, incoordination , clumsiness (abbreviated on graphs to 'unsteady').
- Visual disturbance – patient or family / friend reporting visual problems, including blurring, difficulty focussing, symptoms suggesting a field defect and colour, size or shape distortion. Diplopia as an isolated visual symptom was excluded as it might reflect brainstem or cerebellar pathology (and in fact there were no such cases).
- Language disturbance – speech problems including expressive and receptive dysphasia , excluding dysarthria (abbreviated on graphs to 'speech problems').
- Weakness – symptoms of limb or facial weakness, either of gradual or acute onset, but excluded non-specific descriptions such as 'generally feels weak all over' without any lateralising features.
- Sensory symptoms – included numbness, parasthesia, dysaesthesia and limb pain without any obvious non-neurological explanation such as trauma. When reviewing data on young onset sCJD sensory symptoms were subdivided into those that were painful and persistent. Painful sensory disturbance included dysaesthesia, painful parasthesia or any sensory symptom reported as being associated with discomfort or pain. Persistent sensory disturbance was harder to define as dates were rarely available, so any symptom reported on several occasions or prompting referral to hospital or GP was included, and any reported on only a single occasion or described as brief / transient were excluded.

- Psychiatric symptoms – including psychosis, depression, low mood, anxiety (judged by the visiting registrar to be abnormal rather than simply a normal reaction to their illness). A diagnosis of depression / low mood did not need to be formally confirmed by a psychiatrist.

- Hallucinations / delusions – hallucinations were defined as sensory experiences occurring without stimulation of the relevant sensory organ, and included visual and auditory hallucinations. Delusions were defined as false beliefs, firmly held despite evidence to the contrary. These could be reported by the patient, friend / family or medical / nursing staff.

- Headache.

- Seizure – history suggesting a seizure, not necessarily witnessed by medical staff.

- Dizziness – Non-specific dizziness or vertigo but not simply unsteadiness.

- Fatigue / sleep disturbance – included lethargy, fatigue, insomnia and excessive daytime sleepiness.

- Weight loss – either reported by the patient or family, or documented in the hospital notes.

- Other – prominent symptoms reported by patient / family / medical staff which did not fit into any of the above categories. Examples included new onset deafness, tinnitus, vivid nightmares and difficulty writing with no apparent cognitive, language or coordination problems.

Signs:

- Dementia – usually on basis of bedside mental state tests in hospital or neuropsychology testing but if described as confused and unable to cooperate with formal cognitive assessment then this was also included.

- Cerebellar signs – any of ataxic gait, heel-shin ataxia, finger nose incoordination or dysdiadochokinesis.

- Pyramidal signs – at least two of increased tone, sustained clonus hyperreflexia, extensor plantars and pyramidal pattern weakness.

- Signs of parkinsonism– at least two of rigidity, bradykinesia and parkinsonian type tremor, or described as having parkinsonian features.

- Lower motor neurone signs – at least two of muscle wasting, absent reflexes and fasciculation.
- Myoclonus – brief involuntary jerks were included if the description was consistent with myoclonus.
- Movement disorder other than myoclonus – included chorea, athetosis and dystonia but excluded tremor alone.
- Primitive reflexes – any of pout, snout, palmomental or grasp reflexes.
- Cortical blindness – if described as blind with no ocular explanation or if, on examination, patient appeared unable to see and did not blink to confrontation.
- Akinetic mutism – as judged by the visiting registrar or if the notes described patient as mute and unable to move (without alternative explanation such as sedation).
- Oculomotor abnormalities – included any opthalmoplegia and abnormal saccades and pursuit movements but excluded isolated nystagmus.
- Dyspraxia – defined as a disorder of planning and execution of learned tasks not explained by abnormal tone, power, coordination or sensation.
- Sensory signs – included altered sensation to light touch, pin prick, vibration or abnormal joint position sense but not a positive Romberg's test alone.

The presence or absence of each symptom was noted at onset and 'ever' (at any stage during the illness), and similarly each clinical sign was noted at first examination and at any stage in the disease course. There was also a 'don't know' category for those instances where information was unavailable.

Clinical presentation at onset:

- Rapidly progressive dementia – presentation with an encephalopathic illness with dementia and diverse other neurological features, progressing rapidly over weeks to a few months, with no individual physical or cognitive deficit being present for greater than two weeks alone.
- Heidenhain's – presentation with impairment of visual acuity and / or field, progressing into cortical blindness, without any other significant clinical deficit for the first two weeks of the illness.

- Pure psychiatric onset – presentation with psychiatric symptoms such as depression, anxiety, paranoia and delusions, without the presence of other features for at least four weeks.

- Slowly progressive dementia – presentation with a slowly progressive dementia, developing over months to years, without any other significant neurological features in the first six months.

- Pure cerebellar onset – presentation with a progressive cerebellar syndrome without other significant features, for at least two weeks.

- Extrapyramidal onset – Presentation with an extrapyramidal syndrome involving parkinsonian features with or without chorea, dystonia or athetosis, but without other significant features for at least two weeks.

- Stroke like onset – presentation sufficiently abrupt for stroke to be reasonably considered in the initial stages.

- Sensory onset – presentation with pure sensory symptoms, excluding vague aches and pains and special sensory symptoms (i.e. visual, olfactory, auditory, gustatory).

- Other – none of the above presentations applicable.

- Insufficient information.

2.5 Investigations

(i) MRI brain scans

MRI scans were requested on all patients who underwent this type of imaging. The MRI sequences available depended on the practice of the referring hospital, but included T1 and T2 sequences in all instances, and PD (proton density), FLAIR (fluid attenuated inversion recovery) or DWI (diffusion weighted imaging) in some. They were reviewed by one of two experienced neuroradiologists with an interest in CJD based at the NCJDSU (DC and DS). The neuroradiologists were aware the patients had been referred to the NCJDSU but had no other information regarding the type of CJD suspected or the likelihood of the diagnosis. MRI classification was as follows:

- Positive - defined as high signal in the putamen and caudate (usually bilateral but asymmetry allowed), with or without cortical hyperintensity.

- Cortical hyperintensity alone.

- Negative – no caudate / putamen / cortical hyperintensity. Other non – sCJD changes could be present. E.g. diffuse white matter disease, previous strokes.
- Scan unavailable or too poor quality to review.

(ii) EEGs

EEG tracings were requested and were reviewed by one of two experienced consultant neurologists based at the NCJDSU (RGW, RK). Similar to the MRI review process, the neurologists were blinded to any clinical details but were aware that the patient had been referred to the unit. The EEGs were classified on a five point scale: typical, highly suggestive, suggestive, non specific, normal (see appendix).

(iii) CSF

Protein and white cell count results from CSF analysis were obtained from the hospital notes. The 14-3-3 Western blot assays and S100 ELISAs were performed either at the NCJDSU or The National Hospital for Neurology and Neurosurgery using standardized methods (93, 165).

(iv) *PRNP* gene analysis

PRNP gene analysis was done to exclude familial CJD and to check genotype at codon 129 of the prion gene. This was performed either at the NCJDSU or National Prion Clinic, by DNA extraction, PCR amplification and gene sequencing using an automated analyser (220, 221).

(v) Neuropathology

Neuropathology was performed either at the NCJDSU by Professor J. Ironside, or by a local pathologist with tissue sections sent to the unit for review, or by a neuropathologist in London without any input from the NCJDSU. A pathology summary form was reviewed to identify the final pathological diagnosis, PrP type, codon 129 status if tested and presence or absence of kuru type plaques.

2.6 Database compilation and statistical analysis

All information was recorded on a database using the SPSS (version 12) package. Graphs were produced using the power point graphics programme. Statistical analysis utilised the SPSS programme. Student's t – test or Mann Whitney test were used to compare continuous variables, with Mann Whitney being selected if the variable was not normally distributed. The variables included disease duration, onset age, time to referral and time to investigations between the following cohorts:

- 1993/4 versus 2003/4 referrals
- sCJD Cases versus Non Cases
- sCJD patients aged fifty or less at onset versus those greater than fifty years
- pathologically proven sCJD patients with a negative CSF 14-3-3 result versus a positive result

Chi square (χ^2) analysis was used to compare categoric values including clinical features and investigation results in the same cohorts. The two tailed Fisher's exact version was used when the number of expected variables per cell was less than five. Logistic regression was used to assess trends with time.

For the purposes of graphs and statistical analysis clinical features that were recorded as absent or 'not known' were categorised together.

The diagnostic criteria and the value of specific clinical features were assessed by calculating sensitivities, specificities and positive and negative predictive values. Sensitivity was defined as the proportion of individuals with sCJD with a positive result (where a positive test was either fulfilling the diagnostic criteria or presence of a clinical feature). Specificity was the proportion of patients without sCJD with a negative test result. Positive predictive value referred to the proportion of patients with a positive test result who actually had sCJD. Negative predictive value was defined as the proportion of individuals with a negative test result who did not have sCJD.

Chapter 3: Results

3A. Overview of UK sporadic CJD 1993 - 2004

Suspected sporadic CJD patients that were either referred to the NCJDSU or died between 1993 and 2004 were evaluated. Fig 3.1 demonstrates the number of referrals finally classified as Definite, Probable and Possible each year whereas fig 3.2 shows the number of Definite, Probable and Possible sCJD patients dying each year. The figures are similar, irrespective of whether individuals were collated by date of referral or date of death. The overall trend has been an increase in the number of Definite, Probable and Possible referrals, albeit with an as yet unexplained drop in 2004. Using Poisson regression this annual increase is significant, both for Definite and Probable cases (average increase 1.05 / yr, p<0.001), and for Definite, Probable and Possible combined (average annual increase 1.04, p = 0.001). The proportion of Probable classifications in particular has increased with time, with an increase in 1998 following the introduction of 14-3-3 testing a year earlier, and a marked rise in 2002 – 2004, but with a decline in Definite, neuropathologically confirmed cases in 2003 and 2004. Only a minority of patients remain classified as Possible each year.

Fig 3.1

Number of Definite, Probable and Possible sCJD patients referred annually 1993-2004

72
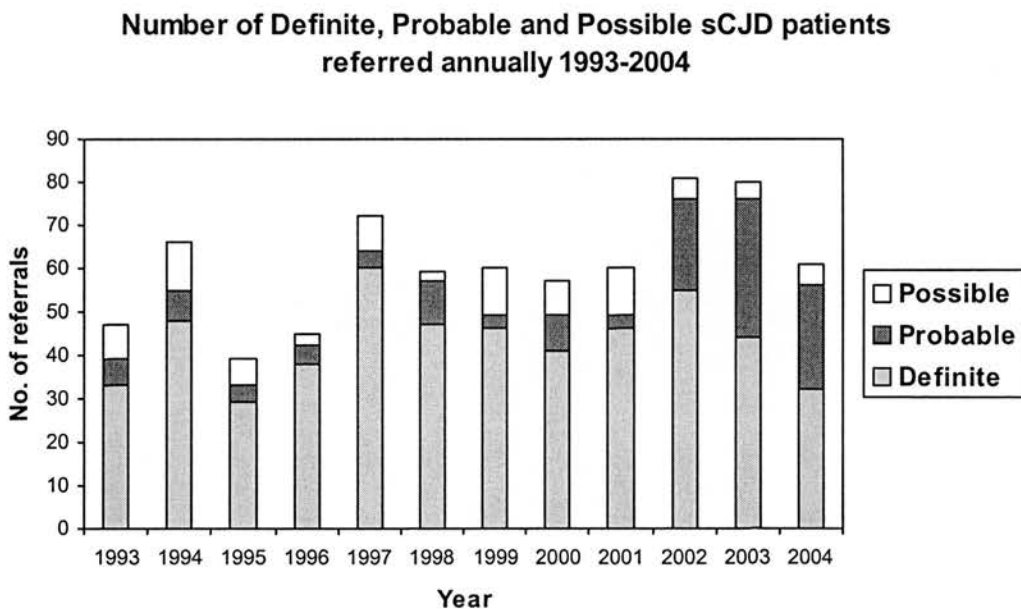
Fig 3.2

Definite, Probable and Possible cases of sporadic CJD by year of death 1993-2004
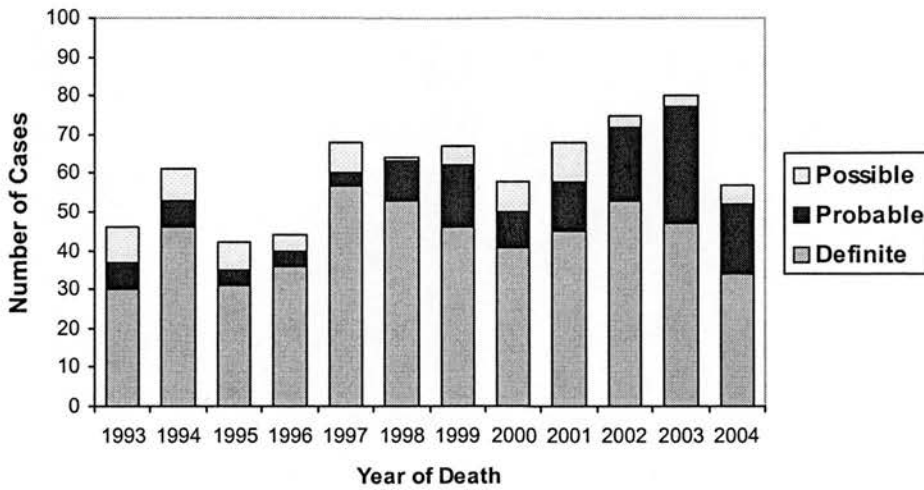
The mean age of onset of sCJD has remained constant at approx. 65 – 66 years (fig 3.3). Similarly mean age at death has remained stable at approx. 66 - 67 years (fig 3.4). Consistent with these findings median disease duration has not changed significantly with time and remains at 4 -5 months (fig 3.5).

Fig. 3.3

Mean age at onset of Definite and Probable sporadic CJD by year of death: 1993-2004
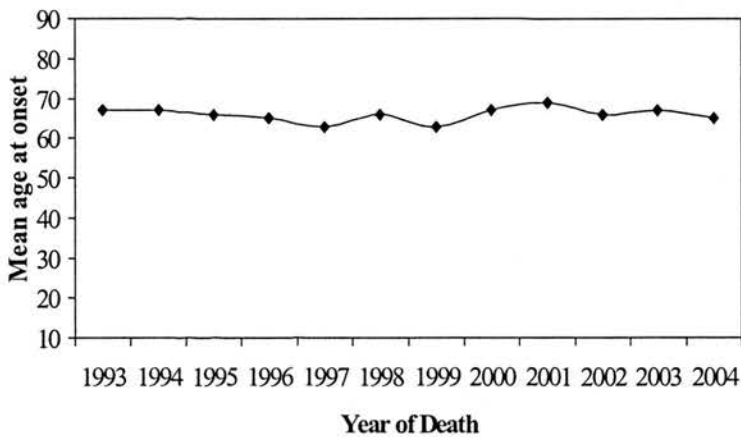
Fig.3.4

**Mean age at death of Definite and Probable sporadic CJD by
year of death: 1993-2004**
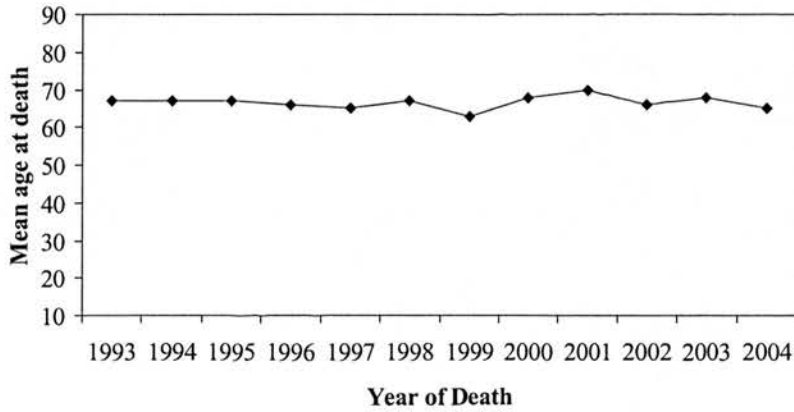
Fig 3.5

**Median duration of illness in sporadic CJD by year of
death: 1993 - 2004**
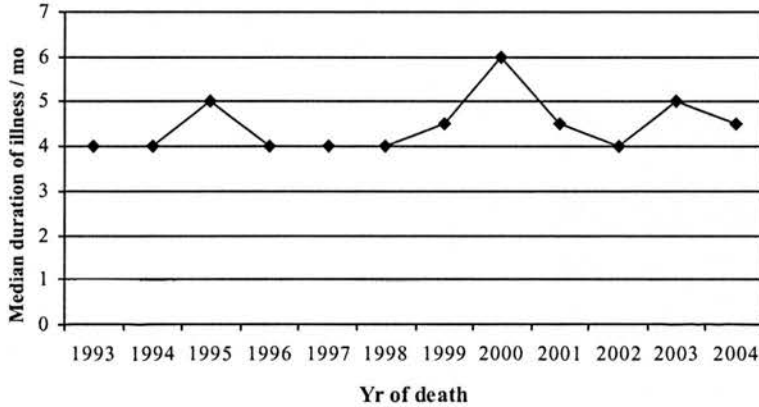
The proportion of sCJD cases undergoing autopsy was reviewed (fig 3.6). The autopsy rate was relatively stable with a mean of 85% until 2000 but since then has declined to a minimum rate of 61% in 2003. Whilst the post mortem rate shows significant heterogeneity from year to year, the data does not convincingly fit a linear

or curvilinear trend if logistic regression is applied. Thus there is currently insufficient evidence to support a statistically significant decreasing trend in annual autopsy rates.

Fig 3.6

PM rate in sporadic CJD Cases: 1993 - 2004
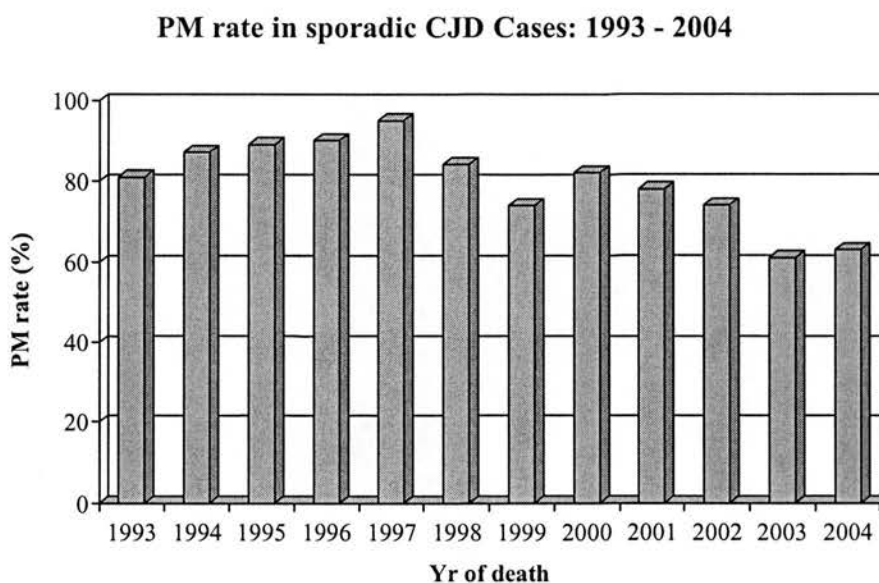
Referral source was evaluated for sCJD deaths during the period 1993 - 2004. The number and proportion of cases referred by death certificate was low throughout this time period at no more than 5 cases / year or usually 5% or less of the total referrals (the exception being 1993 when death certificate referrals made up 11%). Neuropathology referrals were also infrequent with a trend towards fewer pathology referrals with time. Before 1998 20 - 27% of cases were notified in this manner whereas after this date only 10 - 15% were. A minority (7%) of the referrals made by other sources also occurred after death. However, irrespective of the year the majority of referrals were made in life (figs 3.7 and 3.8).

When death certificate and pathology referrals are excluded it is apparent that between 70 and 85% of 'in life' referrals are made by neurologists, and this has remained relatively constant with time. Physician referrals are the next commonest comprising 10 - 20% of cases. Psychiatry, neurophysiology / EEG department and other referrals each comprise up to 10% of cases with no sustained significant differences with time.

Fig 3.7

Source of referral in Definite and Probable sporadic CJD by year of death: 1993-2004
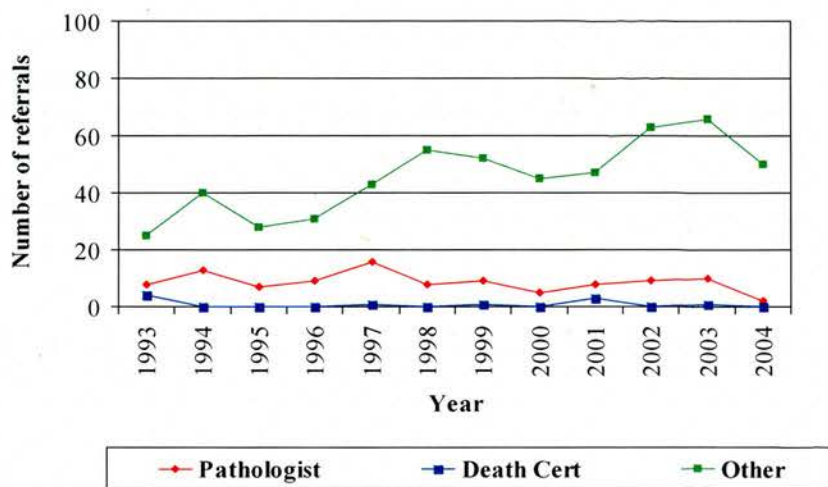
Fig 3.8

Source of referral in Definite and Probable sporadic CJD by year of death and % of referrals: 1993-2004
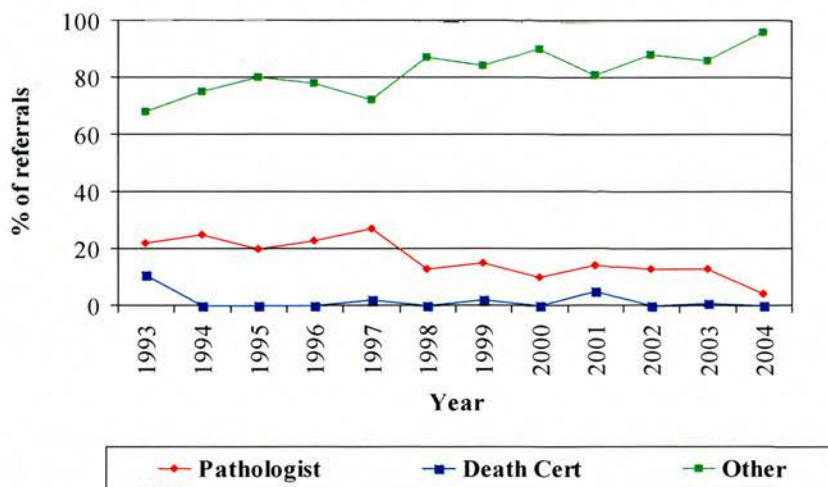
Fig 3.9

Source of referral in Definite and Probable sporadic CJD by year of death (excluding pathology and death certificate referrals): 1993-2004
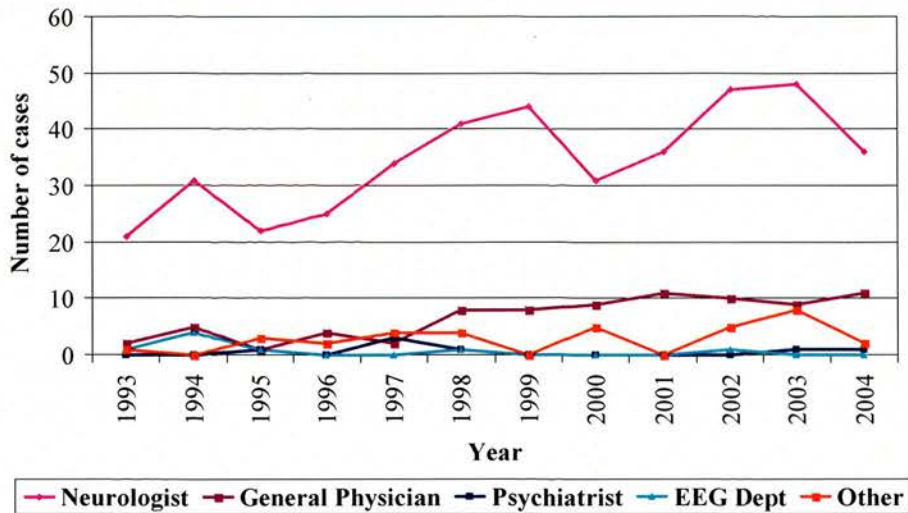
Fig 3.10

Source of referral in Definite and Probable sporadic CJD by year of death and % of referrals (excluding pathology and death certificate referrals: 1993-2004

77
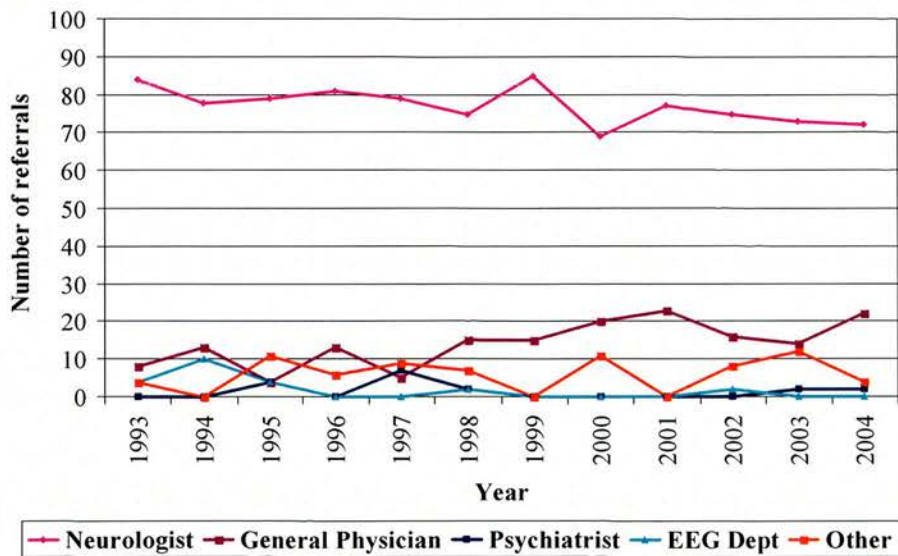
The distribution of *PRNP* codon 129 genotype was analysed over time. The total number of Definite and Probable sCJD patients increased with time, as did the number where codon 129 genotype was known. However, a significant proportion each year did not have genetic analysis performed and this ranged from 20 – 48% with an average of 35% untested annually, limiting data interpretation. When the unknown genotype cases are excluded it is apparent that methionine homozygotes (MM) predominate, but there is a trend towards fewer MM cases with time with correspondingly more heterozygotes and valine homozygotes. This result did not reach statistical significance, possibly because of the relatively small numbers (χ^2 p = 0.07 when the data was analysed for *PRNP* type in 4 year subgroups). The remaining 20 - 40 % of individuals are fairly equally divided between MV and VV genotypes.

PrP isotype distribution with time was also reviewed (concentrating on Definite sCJD patients only as PrP typing requires neuropathology). PrP type 1 comprised between one half and two thirds of tested Definite cases each year, without any sustained changes in time. Initially the remainder of patients were PrP type 2A but in 1996 the first individuals with mixed PrP types (1 and 2A) were identified in the UK. The number of mixed isotype cases has increased with time but they remain infrequent (to date maximum 5 / year).

Fig 3.11

Codon 129 distribution in Definite and Probable sCJD by year of death

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Fig 3.12

Codon 129 distribution in Definite and Probable sCJD by % and year of death

Fig 3.13

Codon 129 distribution in Definite and Probable sCJD by % and year of death excluding Cases where codon 129 unknown
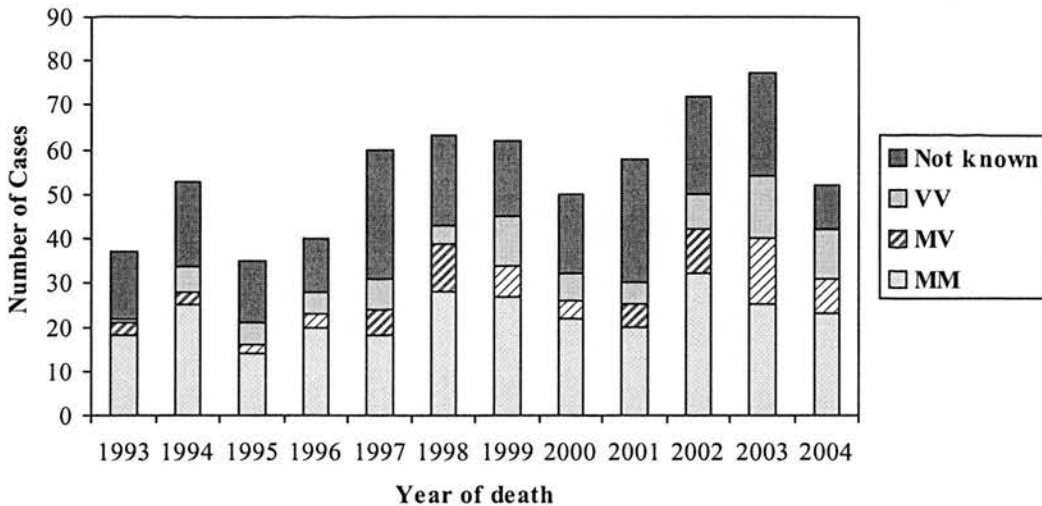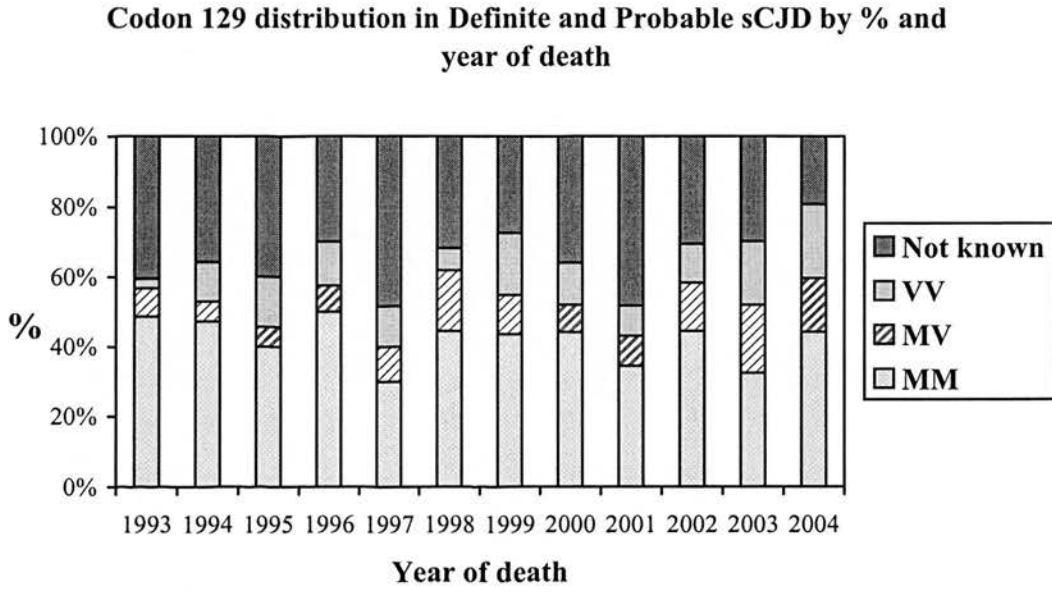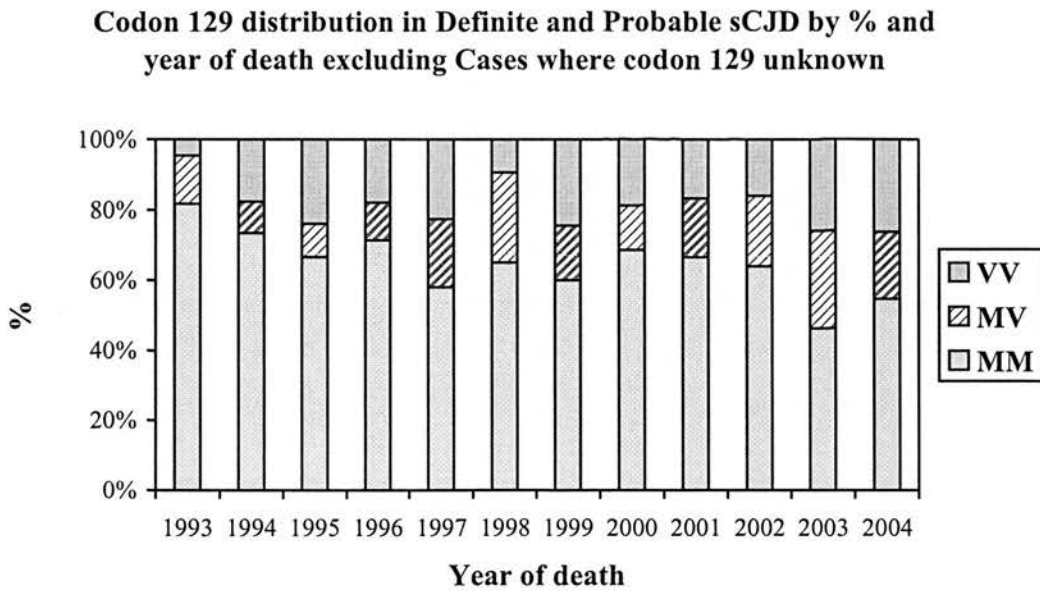
Fig 3.14

PrP isotype in Definite sCJD by year of death[*]
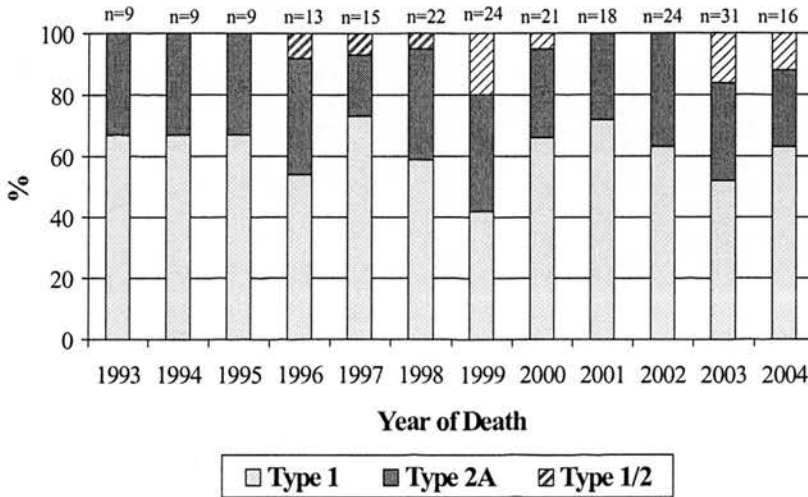
*PrP isotype is available for 32% of the UK sporadic cases

Table 3.1 summarises the Parchi subtypes for Definite sCJD cases over three time periods: 1993-96 prior to and up to the identification of vCJD, 1997 – 2000 when vCJD emerged and peaked, and 2001-2004 when vCJD numbers began to decline. The percentages of each subtype are relatively similar for each time interval, with MM1 being most common, followed by VV2 and MV2. If MM1 and MV1 are combined as 'typical' sCJD and compared with the other Parchi types ('atypical' sCJD) for each of the three time periods there is a non significant trend towards more atypical subtypes with time.

Similar findings are expressed graphically in fig 3.15 looking at the distribution of Parchi subtypes by year of death. The absolute numbers of the rarer Parchi types are small so even minor differences each year may impact significantly on annual percentages. Despite this there is no significant sustained trend with time and it is apparent that MM1 remains the commonest Parchi subtype each year.

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Table 3.1 Distribution of codon 129 / PrP type in pathologically confirmed sCJD by year of death

	1993 - 1996	1997 - 2000	2001 - 2004
MM1	60% (24)	47.5% (38)	51.7% (46)
MM2	7.5% (3)	8.8% (7)	4.5% (4)
MV1	0% (0)	8.8% (7)	4.5% (4)
MV2	12.5% (5)	10% (8)	14.6% (13)
VV1	2.5% (1)	1.3% (1)	4.5% (4)
VV2	15% (6)	13.8% (11)	12.4% (11)
MM1/2	2.5% (1)	6.3% (5)	1.1% (1)
MV1/2	0% (0)	1.3% (1)	4.5% (4)
VV1/2	0% (0)	2.5% (2)	2.2% (2)
Total tested	n = 40	n = 80	n = 89
Not tested	*125*	*153*	*172*

(actual numbers shown in brackets)

Fig 3.15

Parchi subtype in Definite sCJD by year of death: 1993-2004
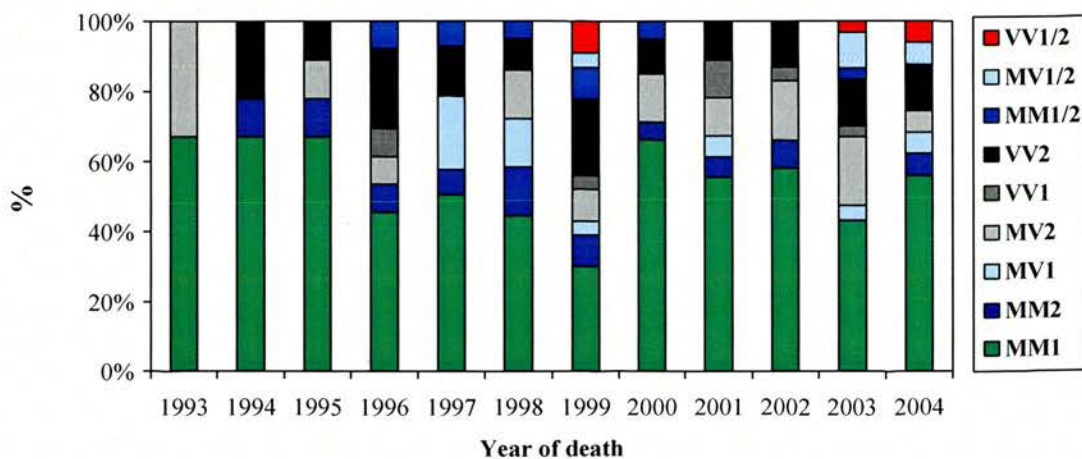
Summary of overview of 1993 – 2004 UK sCJD data

- There has been a significant overall increase in sCJD referrals to the NCJDSU between 1993 and 2004, but with an unexplained decrease in 2004.

- Mean age of sCJD onset, death and median disease duration have all remained constant with time.

- Each year the majority of Cases are referred prior to death by neurologists.

- Autopsy rates in suspected sCJD have shown a non significant decline with time.

- MM is the commonest *PRNP* genotype but has decreased non significantly with time.

- There has been no significant change in Parchi subtype or PrP isotype with time, with the exception of the recognition of mixed PrP types (1 / 2A) within individuals.

3B. Sporadic CJD in 2003-4 compared with 1993-4

3.1 Demographics

3.1.1 Number and classification of referrals

In 1993/4 there were 159 suspected sCJD referrals compared with 196 in 2003/4 [a]. In 1993/4 49.7% were seen in life, relatives were interviewed in a further 22.6% following the patient's death and 27.7% were not visited. In 2003/4 64.8% were seen in life, relatives were interviewed in 11.7% after the patient's death and no interview was performed in 23.5%.

Their final classifications are detailed in table 3.2. There were 95 classified as Cases in 1993/4 95 and 129 in 2003/4, where a Case is defined as meeting the WHO criteria for Definite or Probable sCJD. The percentage of cases compared to total referrals was similar for each time period (60% and 66%). However, the proportion of Definite and Probable classifications differed with time, with 86% of Cases being pathologically confirmed in 1993/4 compared to only 59% in 2003/4. This trend away from neuropathology is also demonstrated to a smaller extent with the Non Cases (defined as clinically or pathologically not sCJD corresponding to WHO criteria 4.2 and 4.3). 37% of the Non Cases were pathologically confirmed in 1993/4 compared to 29% in 2003/4. A smaller proportion of referrals were classified as Possible sCJD compared to 1993/4 (3.6% v 11.3%) but this may partly reflect a change in the classification system due to introduction of 14-3-3 testing (see section 4.3.1). Irrespective of the time period, only a minority of referrals to NCJDSU were confidently felt not to have sCJD.

a. In comparison there were 24 other (non sCJD suspect) CJD referrals to the NCJDSU in 1993/4 (classified by date of onset), including 13 familial / GSS, 9 iatrogenic and 1 variant CJD case and 1 patient initially suspected of vCJD that was not ultimately a case. In 2003/4 there were 73 other CJD referrals to the NCJDSU in total, including 22 familial / GSS, 9 iatrogenic and 37 variant CJD cases and 5 patients initially suspected of having vCJD that were ultimately not CJD cases.

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Table 3.2 Final classification of suspected sCJD referrals in 1993/4 and 2003/4 [b]

Year	Final Classification	Number of referrals	% for year
1993/4	Definite CJD	82	51.6 %
1993/4	Probable CJD	13	8.2 %
1993/4	Possible CJD	18	11.3 %
1993/4	Unclear diagnosis	8	5.0 %
1993/4	Clinically not CJD	24	15.1 %
1993/4	Pathologically not CJD	14	8.8 %
2003/4	Definite CJD	76	38.8 %
2003/4	Probable CJD	53	27.0 %
2003/4	Possible CJD	7	3.6 %
2003/4	Unclear diagnosis	25	12.8 %
2003/4	Clinically not CJD	25	12.8 %
2003/4	Pathologically not CJD	10	5.1 %

b. Following completion of data collection there have been a small number of revisions to 2003/4 patient classifications, as discussed in section 4.3.1. Two sCJD referrals have been reclassified, one from Probable sCJD to Unclear diagnosis, and the other from Unclear to Probable sCJD. Two suspected sCJD referrals were received late by death certificate, one subsequently classified as Possible sCJD and one as a Non Case. Finally one Probable sCJD case is highly likely to be a familial E200K mutation following the discovery of an estranged sibling with this mutation, but remains classified as Probable sCJD due to lack of genetic material for testing.

3.1.2 Gender

A slight excess of referrals were female for all suspected classifications. However, there was no significant gender difference between Cases and Non Cases, nor any change in gender distribution related to year of referral.

Table 3.3 Gender of sCJD Cases and Non Cases in 1993/4 and 2003/4

Classification / Year	% male : female
Case 1993/4	43 : 57
Possible / Unclear 1993/4	35 : 65
Non Case 1993/4	42 : 58
Case 2003/4	47 : 53
Possible / Unclear	44 : 56
Non Case 2003/4	37 : 63

3.1.3 Mean age of onset

Mean age of onset was 66 years, both for Cases referred in 1993/4 and in 2003/4. Mean onset age was also 66 years for Non Cases in both time periods (fig 3.16). Age at onset was normally distributed for Cases and Non Cases and for each time period. Mean onset age was higher at 72 years for Possible diagnoses in 2003/4 and Unclear diagnoses in 1993/4 but these were the two smallest groups with only 7 and 8 patients respectively. There were no statistically significant age differences between 1993/4 and 2003/4 referrals.

Fig 3.16

Mean age at disease onset by classification in 1993/4 and 2003/4
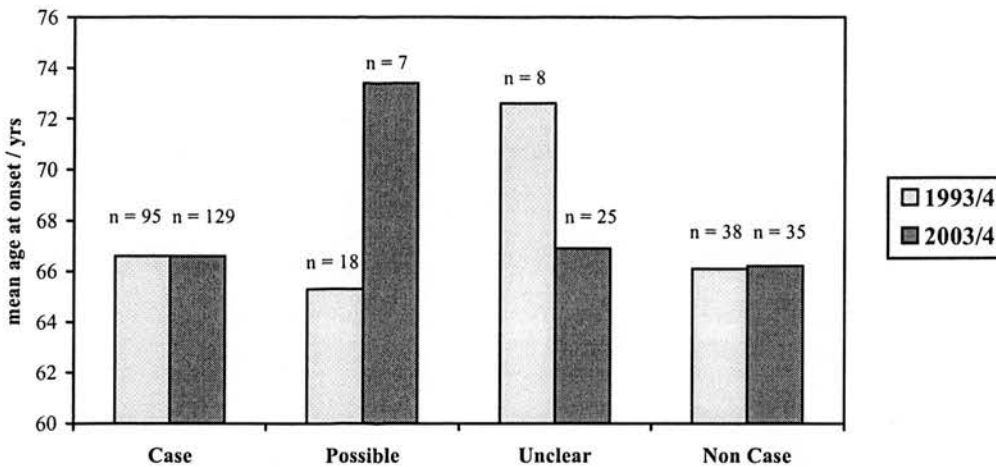
3.1.4 Disease duration

Median disease duration (from onset to death) was calculated for all suspected sCJD referrals in 1993/4 and 2003/4 (fig 3.17). Data was incomplete in 12 of the 1993/4 referrals and 39 of the 2003/4 referrals, due either to the patient still being alive (23, all from 2003/4), or because date of onset was not known (5 in 1993/4, 4 in 2003/4) or lack of information as to whether the patient had died and / or date of death (7 in 1993/4, 12 in 2003/4). For Definite sCJD median disease duration was 4.5 months for referrals in 1993/4 and 4.9 months for 2003/4 referrals. However, the range was wide with the longest pathologically confirmed patients in 1993/4 and 2003/4 surviving for 54 and 62 months respectively and the shortest for 1.5 and 1 month only. Non Cases had significantly longer illnesses than Cases (median 21.5 months for Non Cases versus 4.4 months for Cases, $p < 0.001$ Mann-Whitney test).

When median duration was compared between 1993/4 and 2003/4 referrals the only significant difference was for Non Cases, with longer duration in 1993/4 than in 2003/4 (36.5 months versus 8.5 months, $p = 0.007$). The average disease duration for all other classifications was similar between the two time periods.

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Fig 3.17

Median disease duration by CJD classification for all suspect sCJD referrals in 1993/4 and 2003/4
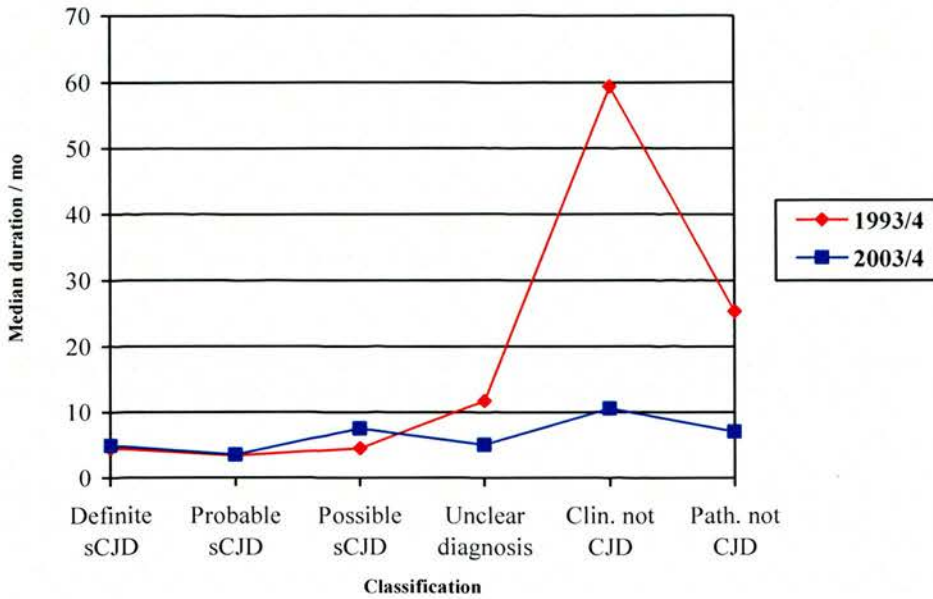
Summary of demographic findings in sCJD referrals in 1993/4 and 2003/4

- There were 196 suspected sCJD referrals to the NCJDSU in 2003/4 compared to 159 in 1993/4, but a higher proportion were pathologically confirmed or excluded in 1993/4.

- Approximately 60% of all suspected sCJD referrals in 1993/4 and 2003/4 were confirmed as sCJD Cases based on WHO diagnostic criteria (Definite and Probable)

- Approximately 20% of all suspected sCJD referrals were ultimately classified as having alternative diagnoses, with the figure being slightly higher in 1993/4 than in 2003/4

- Mean age of onset was stable at 66 years for Cases and Non Cases in 1993/4 and 2003/4

- Median disease duration was stable at 4 - 5 months for Cases in 1993/4 and 2003/4 but significantly longer in Non Cases, particularly in 1993/4 referrals

- There was no significant gender difference with time or classification

3.2 Referral process in 1993/4 and 2003/4

3.2.1 Referral Source

Referral source in 1993/4 and 2003/4

Source of referral was identified for all suspected sCJD patients in 1993/4 (n = 159) and 2003/4 (n= 196) and are summarised in figs 3.18 and 3.19. The majority of referrals were seen by neurology at some stage during their illness (83% in 1993/4 and 91% in 2003/4). The commonest referral source, irrespective of time period, was neurology or neurophysiology. This accounted for 56.6% of referrals in 1993/4 and 66.3% in 2003/4. There were fewer referrals by physicians and geriatricians in 1993/4 compared to a decade later (8.8% v 17.9%). The proportion of referrals made by psychiatry was small but remained fairly constant (5% and 6%). The most obvious difference with time was the dramatic reduction in referrals made by neuropathology and death certificate. In 1993/4 17.0% of suspect cases were notified to the NCJDSU by neuropathology and 9.4% by death certificate. This contrasts with 10 years later when only 5.6% were neuropathology referrals and just 0.5% were via death certificate (a single patient). In total in 1993/4 32% were notified after death whereas in 2003/4 this figure was 9.2%. This difference was significant (p< 0.0001 Mann Whitney) and cannot be accounted for by delays in receiving neuropathology and death certificate referrals at the time data collection stopped (see discussion 4.3.1).

A total of twelve referrals were made by 'other' sources. i.e. not neurologists, physicians, geriatricians, psychiatrists, neuropathologists or by death certificate. These comprised four referrals by microbiologists / virologists, two by EEG technicians, two by relatives and one each by a general practitioner, neurosurgeon, nurse and palliative care specialist. There was no significant difference in these 'other' referrals with time.

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Fig 3.18

Referral source for all patients in 1993/1994
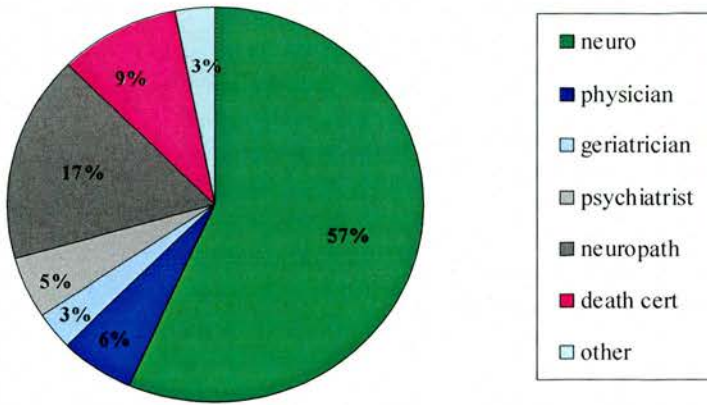
Fig 3.19

Referral source for all patients in 2003/2004
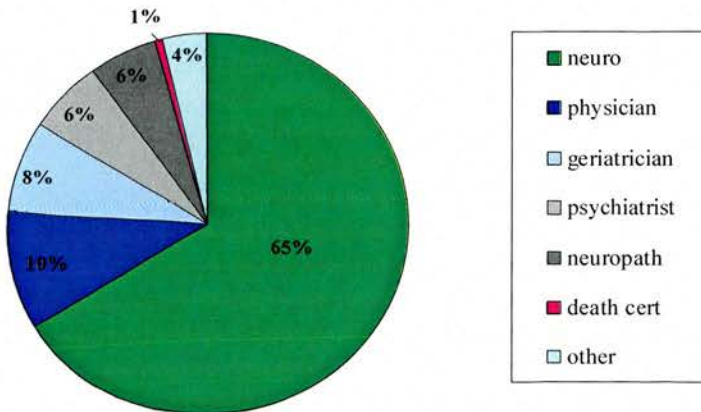
Referral source comparing Cases with Non Cases

Neurology / neurophysiology was the commonest referral source, both for Cases and Non Cases, at 64% and 51% respectively (figs 3.20 and 3.21). The most striking difference in referral patterns between Cases and Non Cases related to psychiatrists, with only 3% of Cases being referred by psychiatry compared to 12% of Non Cases. This was statistically significant ($p = 0.03$ χ^2). A higher proportion of Non Cases than Cases were referred by death certificate (with the death certificate diagnosis subsequently being reviewed once hospital notes were available and / or the registrar had visited relatives and corroborated the history) although this was not significant. As expected, more Cases were referred by neuropathology. A minority of Non Cases ($n = 3$) were referred to the NCJDSU by neuropathologists as suspected sCJD but on further pathological review they did not have sCJD and were reclassified. Their final diagnoses were Alzheimer's disease, cerebrovascular disease and dementia with no cause identified on post mortem (but no pathological features of sCJD).

Overall there was a significant difference in the distribution of referral sources for Cases compared to Non Cases ($p < 0.001$ χ^2).

Fig 3.20

Comparison of referral source for Cases and Non Cases

90
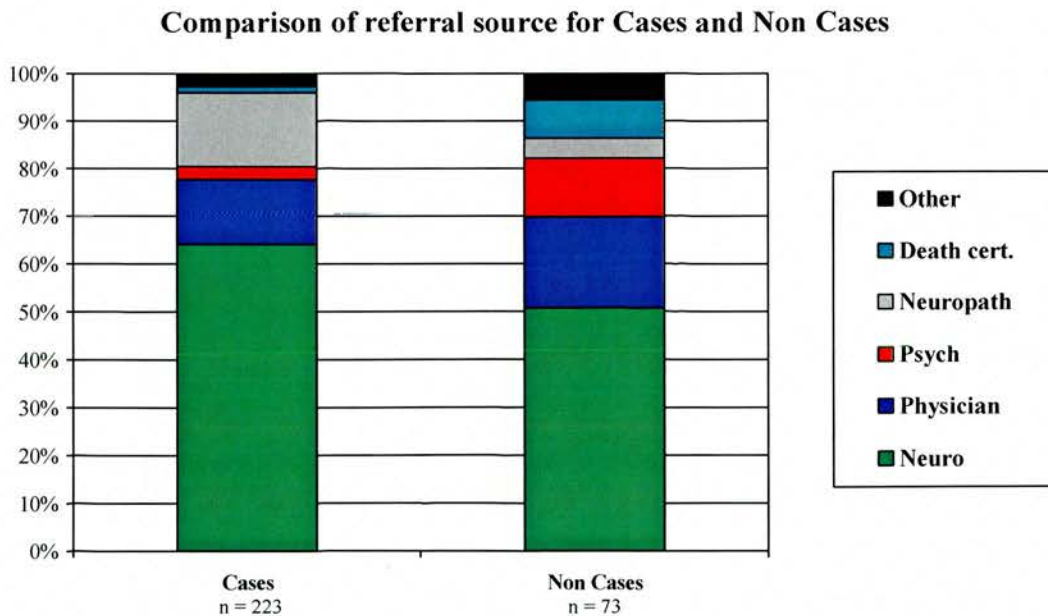
Fig 3.21

Referral source for sCJD Cases and Non Cases in 1993/4 and 2003/4
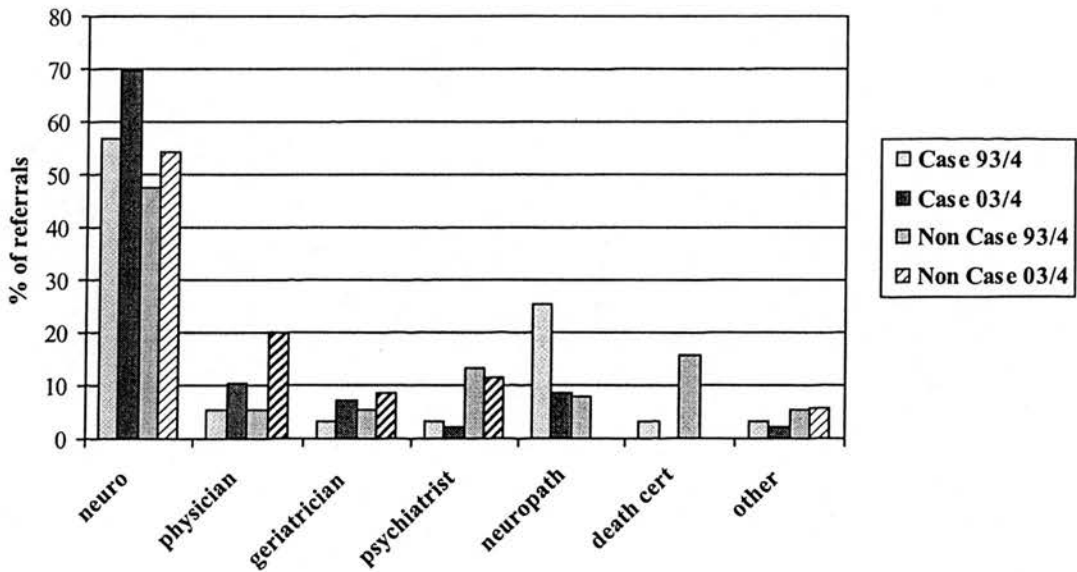
3.2.2 Who first suspected sCJD?

The data for who first suspected the diagnosis of sCJD is similar but not identical to data for source of referral and is summarised in fig. 3.22. The diagnosis was most commonly first suspected by a neurologist / neurophysiologist, in 67.1% of referrals in 1993/4 and 70.4% in 2003/4. These figures are slightly higher than neurology referral figures suggesting that sometimes the neurologist makes the diagnosis but does not refer. In 1993/4 many more sCJD referrals were made by pathology than were first suspected by them (24 versus 6) implying that some patients diagnosed in life were not being notified until autopsy. This was less prominent in 2003/4 referrals. Only a minority of Cases (6 in 1993/4, 3 in 2003/4) were first suspected by pathology; usually the diagnosis was suspected in life.

There was generally little difference as to who first suspected the diagnosis in 1993/4 compared with 2003/4.

There was insufficient information from the notes to determine who had first suggested the diagnosis in 9.4% (15 patients) in 1993/4 and 4.6% (9 patients) in 2003/4.

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Fig 3.22

Who first suspected diagnosis of sCJD in 1993/4 and 2003/4
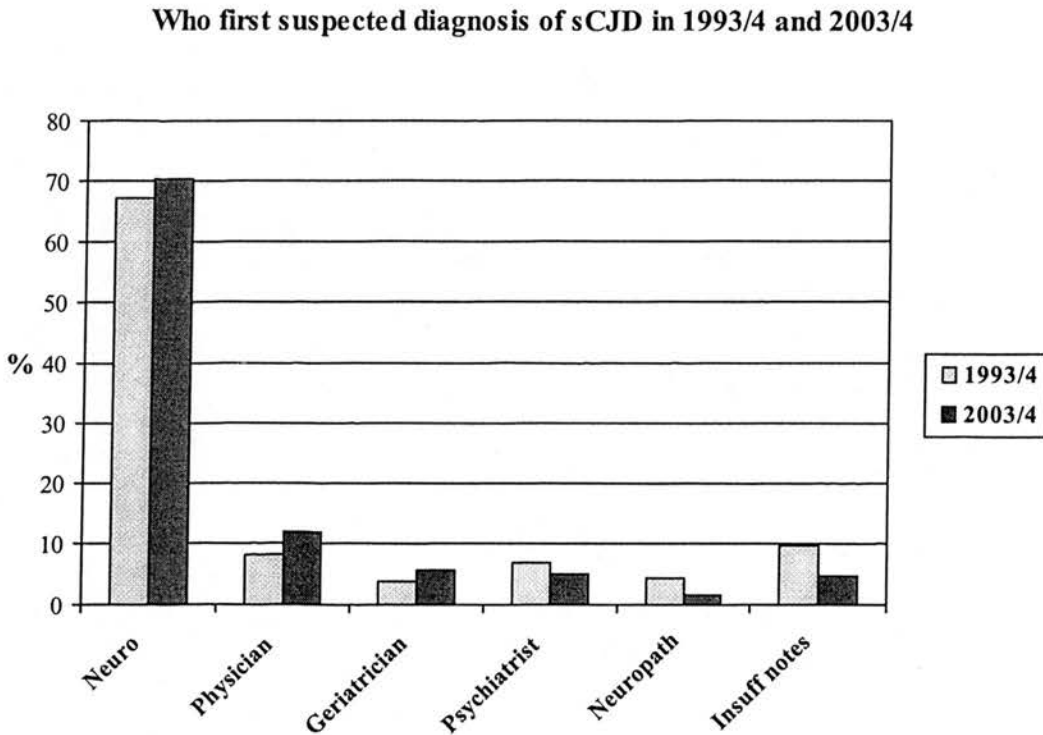
3.2.3 Time to suspect sCJD

The median time to suspect the diagnosis of sCJD in Cases was short at less than 3 months. Interestingly in 1993/4 the time was similar whether the final classification was sCJD Case, Possible sCJD or Unclear diagnosis, whereas in 2003/4 the times became progressively longer with increasing diagnostic uncertainty as reflected by the WHO criteria (i.e. Case < Possible < Unclear).

Time to suspect sCJD was significantly shorter for Non Cases in 2003/4 than in 1993/4. In 1993/4 individuals with a history extending back for up to seventeen years were being referred as suspected sCJD whereas the longest history for a Non Case in 2003/4 was less than four years and most were less than two years, possibly reflecting increasing understanding of the typical sCJD disease course.

Figs 3.23 and 3.24 graphically summarise the time to suspect sCJD for Cases and Non Cases in each time period. The majority of Cases were suspected of having sCJD within 8 months of illness onset, and most within 4 months. In contrast, although

sCJD was suggested (incorrectly) in some Non Cases within a few months of disease onset it was frequently not considered until much later, particularly in the case of 1993/4 referrals.

Table 3.4 Median time to suspect sCJD diagnosis in months (and range).

Classification	1993/4	2003/4	Significant diff. between 1993/4 and 2003/4?
Case	2.5 mo (0.5 - 22.9)	2.8 mo (0.5 - 61.9)	NS
Possible sCJD	2.6 mo (1.4 - 11.5)	4.5 mo (1.0 - 7.0)	NS
Unclear	2.6 mo (1.5 - 26.9)	5.0 mo (0.5 - 137.8)	NS
Non Case	9.5 mo (0.1 - 124.7)	3.5 mo (0.1 - 39)	p = 0.04

Fig 3.23

Time to suspect sCJD diagnosis for Cases and Non Cases in 1993/4 and 2003/4 (expressed as no. of referrals)

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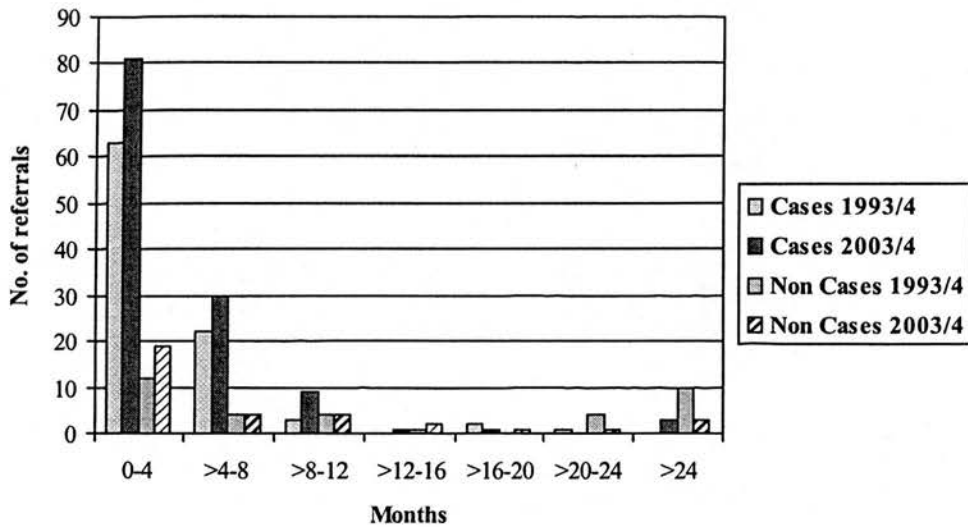
Fig 3.24

Time to suspect sCJD for Cases and Non Cases in 1993/4 and 2003/4 (expressed as %)
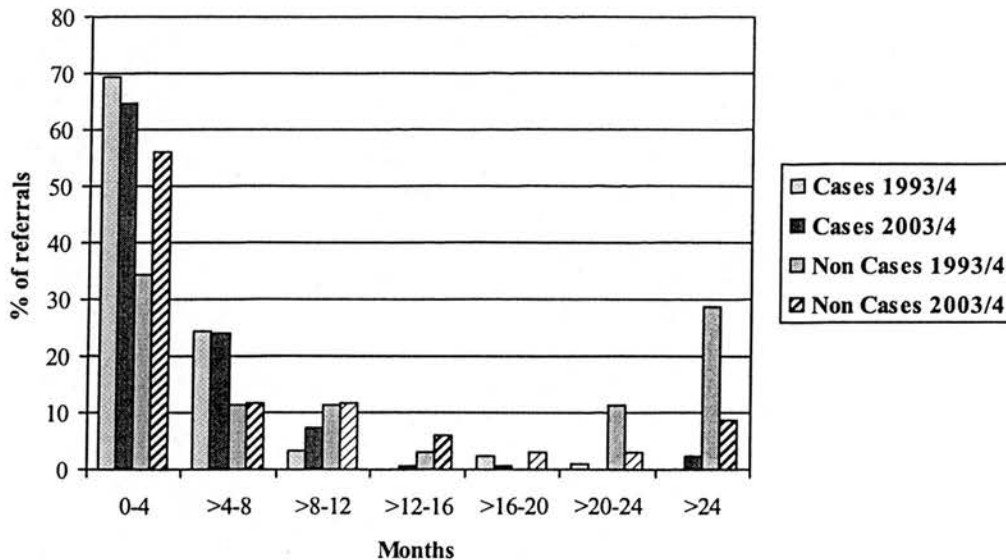
3.2.3 Time to referral

Median time to referral to NCJDSU for all suspected sCJD patients in 1993/4 was 4.0 months (interquartile range 2.4 - 8.7 mo) and in 2003/4 it was similar at 3.6 months (interquartile range 2.0 - 7.0 mo). However, if subdivided for sCJD classification it is apparent that time to referral for Non Cases was significantly shorter in 2003/4 than in 1993/4 (p = 0.006 Mann Whitney). There were no other significant differences comparing the two time periods.

Time to referral was significantly longer for Non Cases than Cases (p = 0.001 Mann Whitney). In 8 patients time to referral was not calculated because onset date was missing.

The median delay between suspecting the diagnosis of sCJD and referring to the NCJDSU was one month or less with no consistent differences between the two time periods or with different classifications. Median delay was used rather than mean as the values were not normally distributed. However, the range is also included to illustrate that although the median time delay was extremely short there was a minority of cases where referral was delayed by many months.

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Table 3.5 Median time to refer to NCJDSU in months and median delay in referral

Classificat-ion	Med. time to referral 1993/4	Med. time to referral 2003/4	Signif.	Med. delay to referral 1993/4	Med. delay to referral 2003/4	Signif.
Case	3.3 mo (1.0 - 23.4)	3.4 mo (0.9 - 61.9)	NS	0.1 mo (0 - 7.9)	0.5 mo (0 - 12.0)	NS
Possible sCJD	4.2 mo (1.5 - 20.4)	6.5 mo (1.0 - 11.0)	NS	0.6 mo (0 - 14.0)	1.0 mo (0 - 5.0)	NS
Unclear	4.6 mo (2.0 - 28.9)	6.0 mo (1.1 - 24.0)	NS	0 mo (o - 2.0)	0 mo (0 - 1.5)	NS
Non Cases	13.4 mo (0.1 - 124.7)	3.8 mo (0.1 - 38.9)	p = 0.006	0.5 mo (0 - 29.9)	0 mo (0 - 1.4)	NS

Summary of findings about the NCJDSU referral process in 1993/4 and 2003/4

- Sporadic CJD was suspected and the patient subsequently referred to the NCJDSU by a neurologist in the majority of instances in 1993/4 and 2003/4.

- In 2003/4 significantly more referrals were made when the patient was alive and correspondingly fewer referrals were made by neuropathologists or death certificate compared to 1993/4.

- A significantly higher proportion of Non Cases were referred by psychiatrists compared with Cases.

- In sCJD Cases median time to suspect diagnosis of was less than 3 months and median time to referral was less than 4 months in 1993/4 and 2003/4. The diagnosis of sCJD was suspected later and referral was delayed in Non Cases in 1993/4 whereas it was similar to Cases in 2003/4.

- Overall Cases were referred to the NCJDSU significantly earlier than Non Cases.

3.3 Clinical Phenotype: comparing suspected sCJD referrals in 1993/4 and 2003/4

The clinical phenotype in suspected sCJD referrals in 2003/4 was compared with referrals a decade earlier looking for any differences or evidence to support the emergence of a novel phenotype. Clinical features were divided into symptoms at onset, symptoms present at any stage in the illness, neurological signs at onset and at any stage. 1993/4 and 2003/4 referrals were compared, analysing Definite sCJD, Probable sCJD and Possible / Unclear diagnosis classifications separately.

3.3.1 Clinical presentation at onset

All suspected sCJD referrals were categorised by their mode of clinical presentation using the following categories: rapidly progressive dementia, slowly progressive dementia, Heidenhain's, pure psychiatric onset, pure cerebellar onset, extrapyramidal onset, stroke - like onset, sensory onset, other and incomplete data (see methods for precise definitions). The results for Cases and Possible / Unclear diagnosis classification are summarised in figs 3.25 and 3.26. There were no differences in clinical presentation of Cases in 1993/4 compared with 2003/4. Rapidly progressive dementia was overwhelmingly the most common presentation category (65% and 68% in 1993/4 and 2003/4 respectively), followed by pure cerebellar onset (12% and 8%). All other categories represented less than 10% of Cases. In particular only a single Case in 1993/4 and two Cases in 2003/4 had a pure psychiatric onset, and there were no sensory onsets in 1993/4 and two a decade later.

In the Possible / Unclear classification the numbers were small (26 in 1993/4, 32 in 2003/4) but again rapidly progressive dementia was most common followed by pure cerebellar onset. There were no sensory or psychiatric presentations in this group in either time period.

Fig 3.25

Clinical presentation in Definite and Probable sCJD Cases in 1993/4 and 2003/4

Legend: ☐ Cases 93/4 ■ Cases 03/4

X-axis categories: RPD, Heidenhain, Psychiatric, SPD, Cerebellar, Stroke like, Sensory, Other, Insuff data

X-axis label: Clinical Presentation
Y-axis label: %
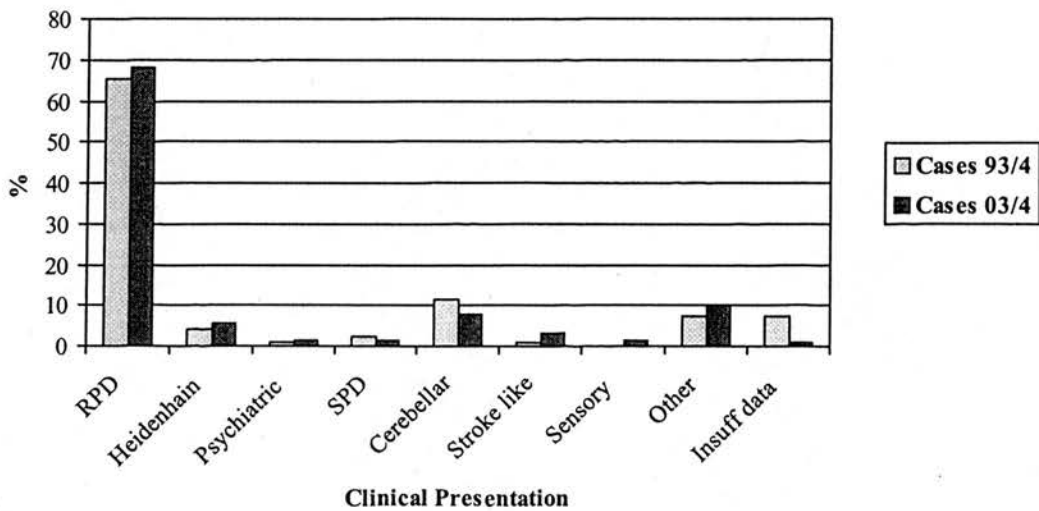
Fig 3.26

Clinical presentation in Possible and Unclear sCJD referrals in 1993/4 and 2003/4

Legend: ☐ Possible / unclear 93/4 ■ Possible / unclear 03/4

X-axis categories: RPD, Heidenhain, Psychiatric, SPD, Cerebellar, Extrapyramidal, Stroke like, Sensory, Other, Insuff data

X-axis label: Clinical Presentation
Y-axis label: %
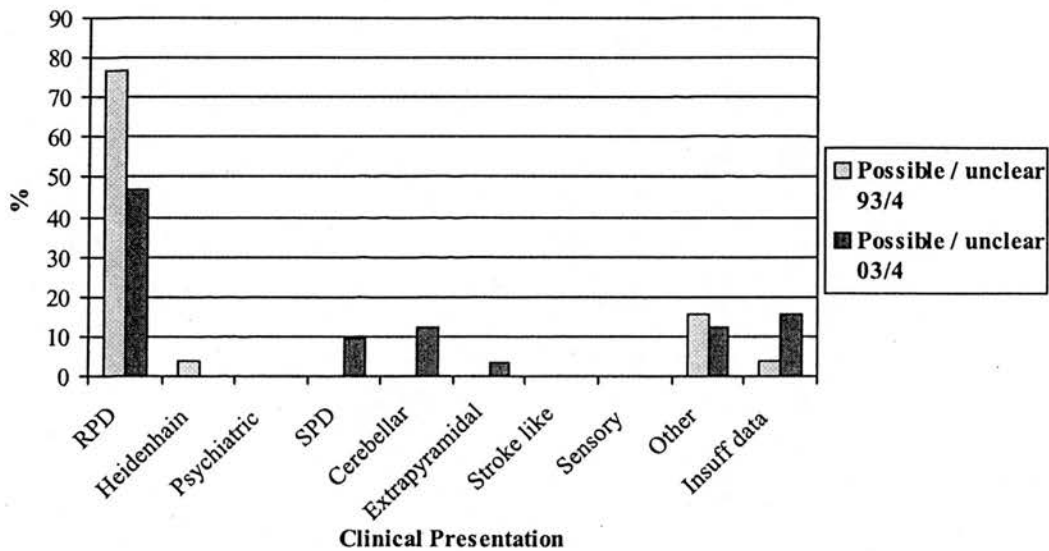
3.3.2 Clinical symptoms at onset

The frequency of the following onset symptoms were analysed: symptoms of impaired cognition ('forgetful'), symptoms suggesting cerebellar dysfunction ('unsteady'), focal weakness, visual disturbance, hallucinations, language disturbance ('speech'), headache, symptoms suggestive of a seizure, dizziness, disturbed sleep / fatigue, weight loss and sensory symptoms.

Symptoms of cognitive impairment were the commonest presenting feature irrespective of year group or final classification, being present at onset in 39 - 59%. Interestingly forgetfulness was at least as frequent in the Possible / Unclear diagnosis group as Definite and Probable classifications. Other common early symptoms included unsteadiness, fatigue / altered sleep pattern and visual disturbance. Rare onset features (present in less than 10%) were sensory disturbance, focal weakness, seizure activity and hallucinations. Figs 3.27, 3.28 and 3.29 graphically demonstrate the frequency of each onset symptom in Definite, Probable and Possible / Unclear diagnosis categories respectively.There were no significant differences between clinical symptoms at onset in 1993/4 and 2003/4 referrals of Definite and Probable cases. The only difference related to the possible sCJD / Unclear diagnosis group where dizziness was more commonly reported in 1993/4 (p = 0.04 χ^2 Fishers exact).

Fig 3.27

Clinical symptoms at onset in Definite sCJD cases in 1993/4 and 2003/4
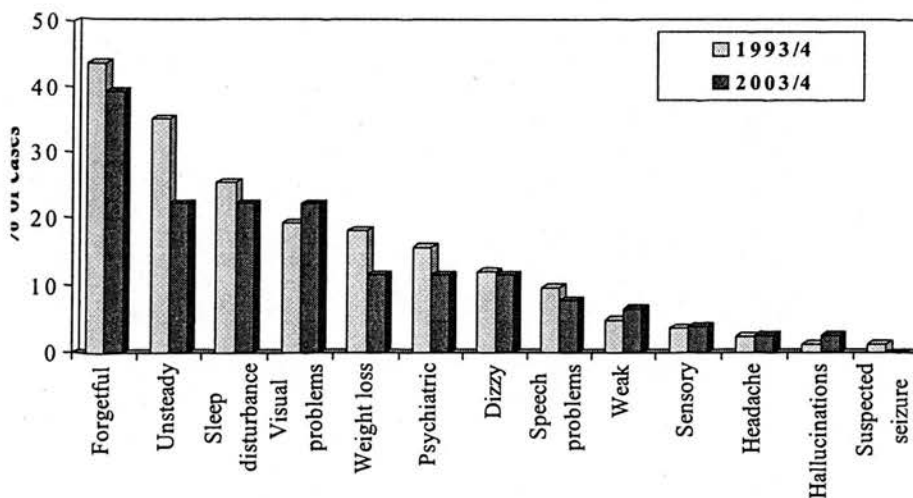
Fig 3.28

**Clinical symptoms at onset in Probable sCJD cases in
1993/4 and 2003/4**
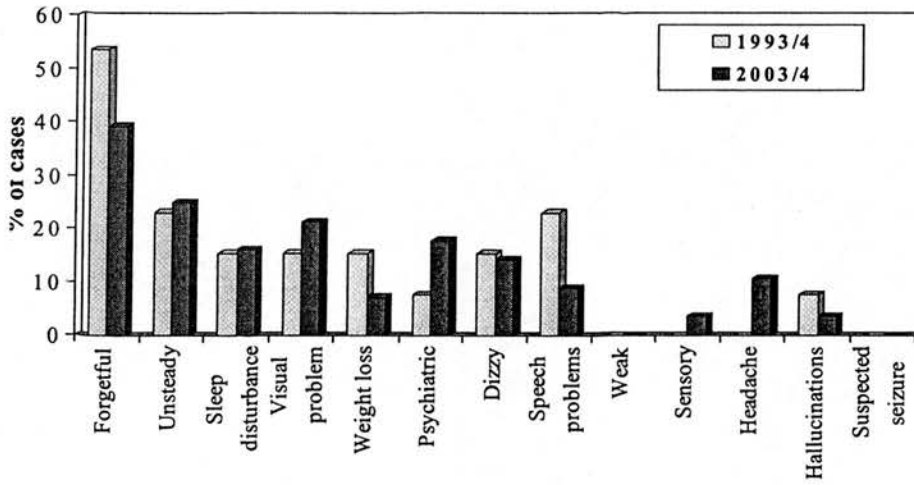
Fig 3.29

**Clinical symptoms at onset in Possible sCJD / Unclear
diagnosis in 1993/4 and 2003/4**
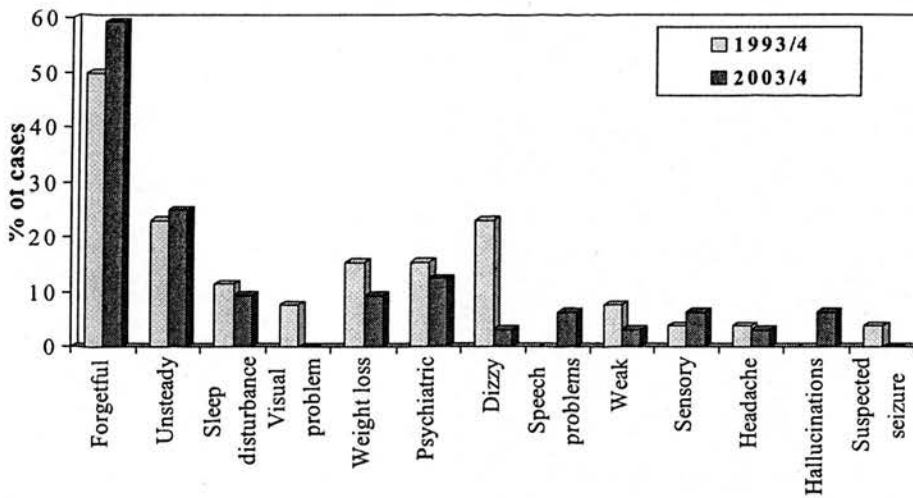
3.3.3 Clinical symptoms present at any stage

Clinical symptoms present at any stage of the illness were evaluated and are expressed graphically in figs 3.30, 3.31 and 3.32.

Forgetfulness / confusion was almost universal in all three classification groups, being confirmed in 92 - 100%. The second commonest symptom was unsteadiness, a feature of 89 - 98% of Definite and Probable cases and 65 - 85% of the Possible / Unclear diagnosis category. Speech and visual disturbances were also seen in the majority of patients but were less prevalent in the Possible / Unclear group.

Hallucinations were reported in half of 2003/4 referrals (for each of the three classification groups) but were less frequent in 1993/4, being recorded in approximately one third of referrals, although the difference with time was only significant for Possible / Unclear diagnosis patients. Psychiatric symptoms other than hallucinations were also relatively common and were present in around one third of patients, irrespective of year or final classification.

Sensory symptoms were less frequent and were identified in less than 20% of patients. Overall 1993/4 and 2003/4 referrals were generally similar with respect to symptomatology at any stage in the illness. In 1993/4 weight loss (Definite and Probable sCJD), fatigue / sleep disturbance (Definites) and focal weakness (Possible / Unclear diagnosis) were all recorded more frequently. In 2003/4 the only symptoms which were more prevalent than a decade earlier were sensory symptoms (Definite and Probable sCJD) and hallucinations (Possible / Unclear diagnosis). Other psychiatric symptoms had not increased in frequency. None of the observed differences were present in all three classifications (Definite, Probable and Possible / Unclear diagnosis).

Fig 3.30

Clinical symptoms at any stage in Definite sCJD cases in 1993/4 and 2003/4
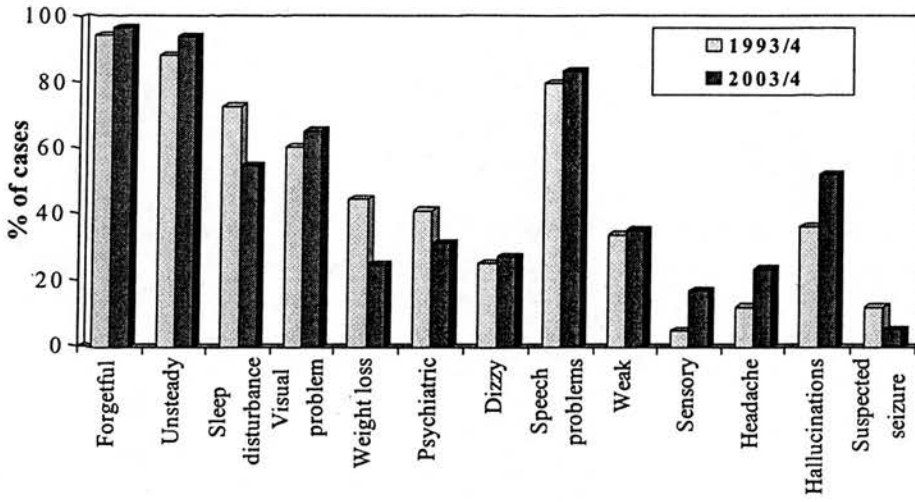
Fig 3.31

Clinical symptoms at any stage in Probable sCJD cases in 1993/4 and 2003/4
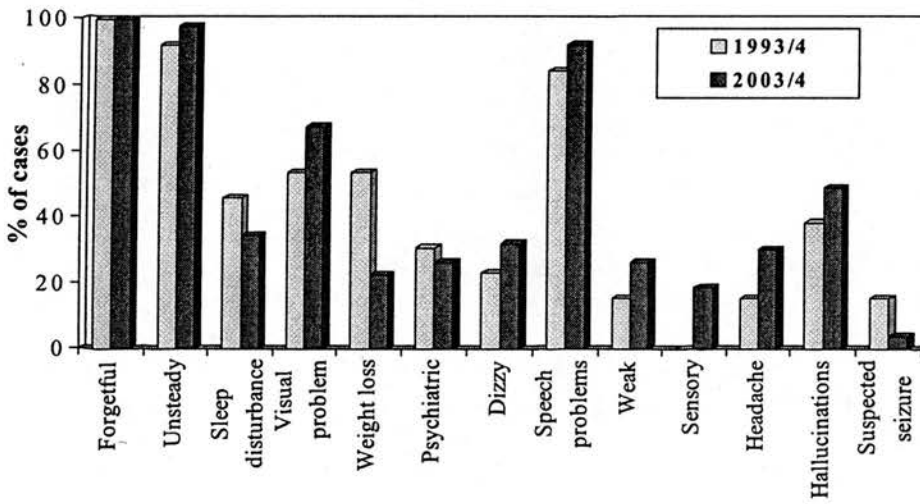
Fig 3.32

Clinical symptoms at any stage in Possible sCJD / Unclear diagnosis in 1993/4 and 2003/4
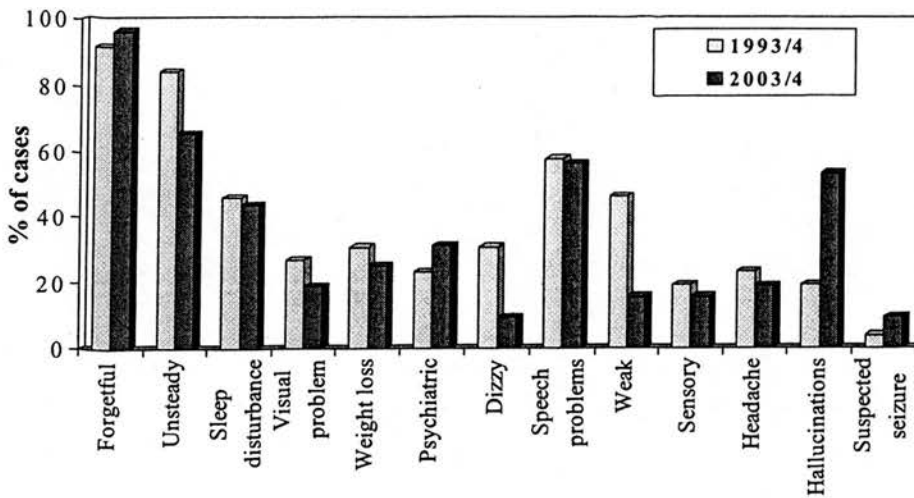
3.3.4 Signs present at first examination

Neurological signs present at the first documented examination were reviewed and the findings compared between 1993/4 and 2003/4. Dementia was the commonest finding but was by no means universal at this stage, being present in 50 - 65% of patients (with the exception of 1993/4 Probable sCJD patients where 92% had dementia, albeit with small numbers). Cerebellar signs were present in approximately half of patients at first assessment. Myoclonus was relatively infrequent at this stage being apparent in only 10 - 20%. Akinetic mutism was never present at first examination and cortical blindness, primitive reflexes, parkinsonism, movement disorders other than myoclonus and sensory signs were all rare at this stage (seen in less than 10%).

Overall there were no significant differences between signs at first examination in 1993/4 and 2003/4. Interpretation of these results is limited by the timing of the examination and also who performed it and how thorough it was. The vast majority of the examinations were performed by hospital neurologists or other physicians, either in the outpatient clinic or on admission to the ward. The experience level of the doctor ranged from junior house officer to consultant, and a small number were neurological assessments documented by the referring GP. There was considerable variation in

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timing of the first examination, ranging from within a week of disease onset to the terminal stages. However, examination timings for the different classifications in either 1993/4 or 2003/4 were actually relatively similar with a median of 1.5 - 3.5 months or 42 - 52% through the illness as a whole (table 3.6).

Table 3.6 Timing and clinical features at first examination, by sCJD classification, in 1993/4 and 2003/4

Year	Classifi-cation	Median time to 1st exam. In months (+ range)	Time to 1st exam. as median % through illness (+ range)	% with dementia	% with cerebellar signs	% with myoclonus
1993/4	Definite (n = 83)	2.0 months (0.5 - 21.9))	51 (5 - 100)	56	40	10
1993/4	Probable (n = 13)	1.5 months (0.5 - 2.5)	43 (12 - 94)	92	62	15
1993/4	Possible /Unclear (n = 26)	2.0 months (0.5 - 8.0)	45 (4 - 83)	65	46	19
2003/4	Definite (n = 76)	2.5 months (0.0 - 61.3)	52 (2 - 99)	63	49	20
2003/4	Probable (n = 53)	1.9 months (0.1 - 19.4)	50 (3 - 95)	62	56	19
2003/4	Possible /Unclear (n = 32)	3.5 months (0.0 - 14.5)	42 (0 - 88)	53	22	13

3.3.5   Signs present at any stage of the illness

Figs 3.33, 3.34 and 3.35 summarise the examination findings in Definite, Probable and Possible / Unclear diagnosis referrals in 1993/4 compared to 2003/4.

Dementia was the commonest clinical sign in all three classification groups in 1993/4 and 2003/4. It was identified on examination in 93 - 100% of patients. In the small minority where cognitive impairment was not confirmed this was due to difficulty with examination (e.g. patient mute by first assessment) or limited information rather than definite absence of dementia.

The second commonest sign in suspected sCJD was myoclonus (seen in 78 - 98%). Approximately two thirds of individuals had cerebellar signs on examination, although this value was slightly lower in the Possible / Unclear diagnosis group (at 47 - 61%). Around half of all patients had pyramidal signs and primitive reflexes at some stage throughout their illness. Parkinsonism, movement disorders other than myoclonus and sensory signs were all infrequent but well recognised findings. However, definite lower motor neurone abnormalities (as opposed to isolated mild wasting consistent with disuse) were rarely recognised (< 5%) and may have been coincidental rather than a feature of sCJD per se.

Akinetic mutism and cortical blindness were of particular interest as they were significantly less frequent in 2003/4 compared to a decade earlier. Approximately two thirds of Definite and Probable cases in 1993/4 were defined as akinetic and mute at some stage, compared to only one third in 2003/4. The same trend was apparent for Possible / Unclear diagnosis patients although the proportions were smaller (39% v 9%). Similarly cortical blindness was commoner in 1993/4 than 2003/4 with 24% of Definites, 54% of Probables and 12% of Possible / Unclear diagnosis patients being affected in 1993/4 compared to 9%, 23% and 0% respectively in 2003/4.

Variant CJD is associated with chorea and dystonia more frequently than sCJD but the incidence of movement disorders did not significantly increase in 2003/4 compared with 1993/4.

Fig 3.33

Clinical signs at any stage in Definite sCJD cases in 1993/4 and 2003/4
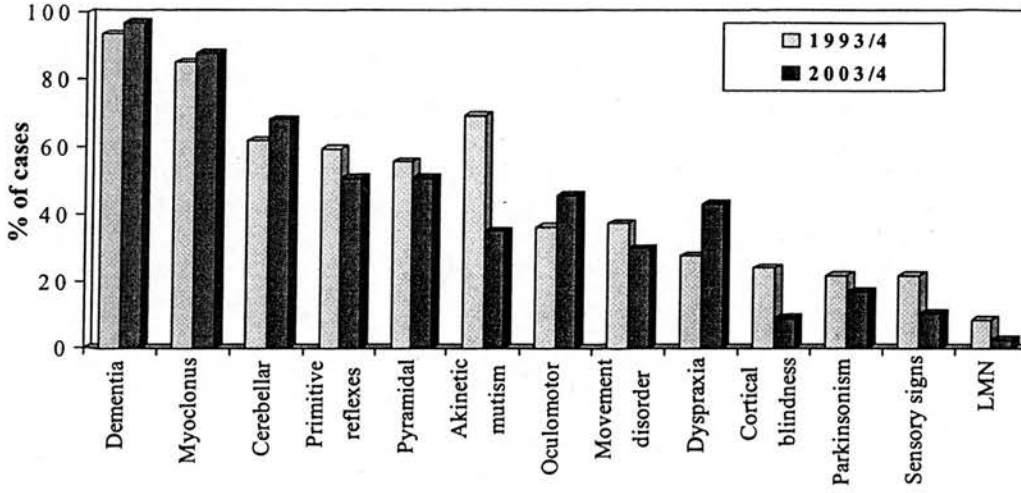
Fig 3.34

Clinical signs at any stage in Probable sCJD cases in 1993/4 and 2003/4
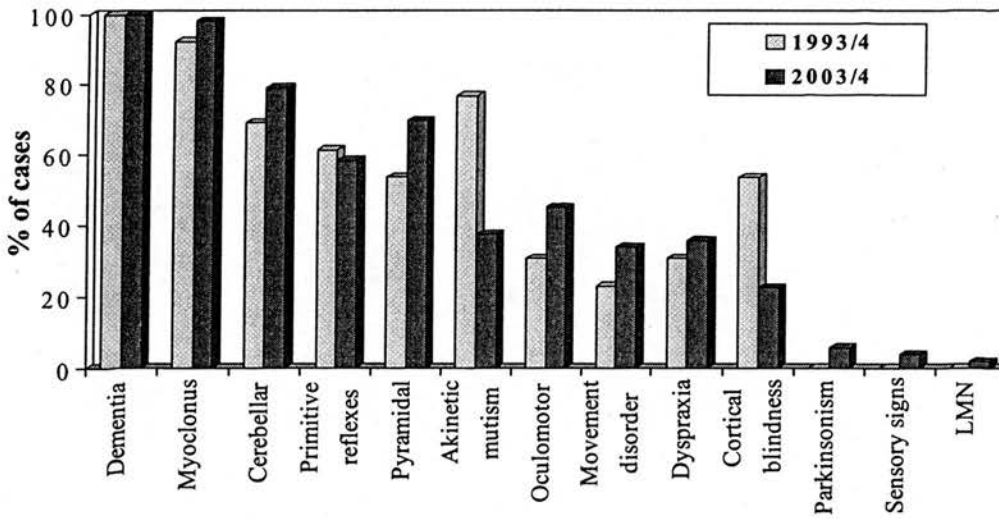
Fig 3.35

Clinical signs at any stage in Possible sCJD / Unclear diagnosis in 1993/4 and 2003/4
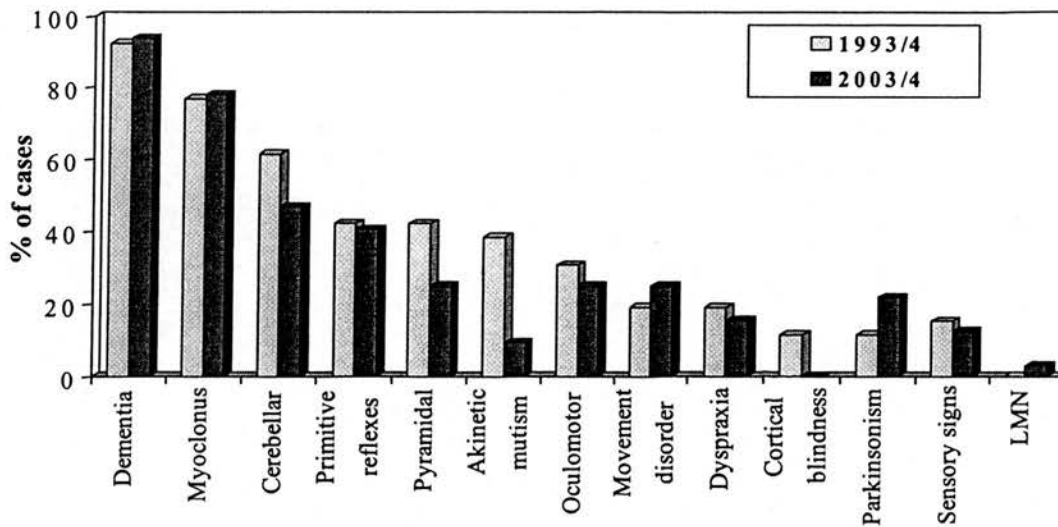
3.3.6 Summary of statistically significant differences in clinical phenotype between 1993/4 and 2003/4

Generally the clinical phenotypes seen in the two populations (1993/4 and 2003/4 referrals) were similar and table 3.7 summarises the statistically significant differences. Results in bold highlight features that were more common in 2003/4 compared to 1993/4.

Table 3.7 Summary of statistically significant differences in clinical phenotype Between 1993/4 and 2003/4

Clinical feature	Classification	Significance (χ^2)
Akinetic mutism	Definite	p < 0.001
Akinetic mutism	Probable	p = 0.01
Akinetic mutism	Possible / Unclear diag.	p = 0.01

Akinetic mutism	Cases	p < 0.0001
Cortical blindness	Definite	p = 0.02
Cortical blindness	Probable	p = 0.04
Cortical blindness	Cases	p = 0.02
Weight loss	Definite	p = 0.01
Weight loss	Probable	p = 0.04
Weight loss	Cases	p = 0.001
Sensory symptoms	**Definite**	**p = 0.02**
Sensory symptoms	**Cases**	**p = 0.003**
Fatigue / sleep disturbance	Definite	p = 0.02
Fatigue / sleep disturbance	Cases	p = 0.004
Hallucinations	**Possible / Unclear diag.**	**p = 0.01**
Hallucinations	**Cases**	**p = 0.04**
Dyspraxia	**Definite**	**p = 0.05***
Headache	**Cases**	**p = 0.01**
Dizziness at onset	Possible / Unclear diag.	p = 0.04
Weakness	Possible / Unclear diag.	p = 0.02
Suspected seizure	Cases	p = 0.05**

* p = 0.048   ** p = 0.045

Summary of results of clinical phenotype in 1993/4 and 2003/4

- Sporadic CJD Cases presented in a similar manner in 1993/4 and 2003/4.

- Rapidly progressive dementia was overwhelmingly the commonest mode of presentation and occurred in around two thirds of Cases. Approximately 10% had a cerebellar syndrome. All other types of presentation were rare.

- Cognitive impairment was the commonest single presenting symptom, irrespective of year or classification.

- There were no significant differences between sCJD onset symptoms in 1993/4 and 2003/4 Cases.

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- Clinical signs at first examination were similar in 1993/4 and 2003/4 but were heavily influenced by the timing and quality of the examination.

- The commonest symptoms present at any stage of the illness were forgetfulness, unsteadiness and speech disturbance and were reported in over 80% of sCJD Cases.

- The commonest signs present at any stage of the illness were dementia, myoclonus and cerebellar signs.

- Akinetic mutism, cortical blindness and weight loss were recorded significantly more frequently in 1993/4 Cases whereas sensory symptoms were more frequently reported in 2003/4 Cases.

- There was no difference between the proportion of Cases demonstrating psychiatric symptoms such as depression and anxiety in 1993/4 and 2003/4, but hallucinations were more commonly reported in 2003/4.

3.4 Investigation of suspected sCJD in 1993/4 and 2003/4

The standard investigations to support a clinical diagnosis of sCJD include EEG, CSF examination and neuroimaging, ideally MRI. Fig 3.36 summarises the use of these diagnostic tools in sCJD Cases referred in 1993/4 and 2003/4. EEG was used in at least 90% of patients, irrespective of the year. CSF examination was also performed in the vast majority of patients. The increased use in 2003/4 referrals compared to 1993/4 (88% v 73%) might be explained by the availability of the 14-3-3 protein assay from 1997. This provides a sensitive and relatively specific diagnostic test for sCJD whereas previously CSF analysis would primarily be performed to exclude other pathology such as infection. In 1993/4 there was increased reliance on CT as an imaging tool and correspondingly lower use of MRI whereas this was reversed in 2003/4. This is likely to reflect the increasing availability of MRI with time, plus the increasing awareness of the characteristic MRI changes associated with CJD. No sCJD patient referred in 1993/4 and only one in 2003/4 definitely did not have neuroimaging, and in this case it was planned but the individual died before scanning

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was performed. There was insufficient information about imaging in four patients (three in 1993/4, one in 2003/4).

Fig 3.36

Use of investigations in sCJD Cases referred in 1993/4 and 2003/4
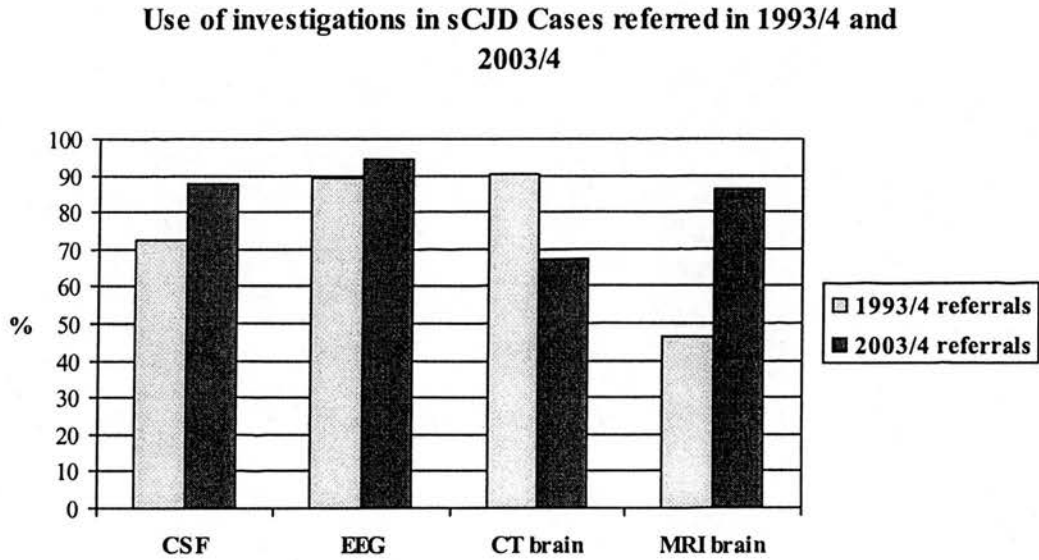
3.4.1 Cerebrospinal fluid

CSF protein and white cell count results

CSF examination was performed in 69 / 95 1993/4 Cases (73%) and 113 / 129 2003/4 Cases (88%). CSF protein results were available in all but 2 of the 1993/4 group but were missing in 23 patients in 2003/4, due either to insufficient details in the hospital notes or the laboratory refusing to perform the test due to concerns regarding CJD infectivity. Similarly the white cell count was missing in one instance in 1993/4 and in 10 2003/4 individuals.

Table 3.8 details the CSF protein results. There was no major difference with time. Approximately two thirds of Cases had a normal result, a third had mildly elevated protein and just 3% showed marked elevation defined as greater than 1g / L. On reviewing these individuals with protein in excess of 1g / L there were no obvious, consistent unusual features. All five had acellular CSF and four presented with rapidly progressive dementia and followed a characteristic sCJD course. Only one of these

individuals was unusual, with a psychiatric onset followed by an illness lasting twenty months with an unexplained raised creatinine kinase of 3600 U/L (normal < 180 U/L) in association with a CSF protein of 1.45 g / L.

3.8   Table 3.8 CSF protein levels in sCJD Cases in 1993/4 and 2003/4

CSF protein (g / L)	1993/4 Cases	2003/4 Cases
< 0.5	43 (64%)	59 (66%)
0.5 – 0.99	22 (33%)	28 (31%)
≥ 1	2 (3%)	3 (3%)

The vast majority of Cases had normal CSF white cell counts (96% in 1993/4, 100% in 2003/4). In 1993/4 four patients had 5 - 10 x 10^9 white cells / mm ^{3}. One of these could be explained by a traumatic tap with over 2000 x 10^9 red cells / mm ^{3}. The remaining three had only minimally elevated white cell counts at 5, 6 and 7 x 10^9 white cells / mm ^{3} and no alternative causes were identified for these findings. No Cases had a white cell count greater than 10 x 10^9 / mm^3.

CSF 14-3-3 and S100 results

In 1993/4 14-3-3 and S100 assays were not available as diagnostic tools for sCJD. 100 Cases in 2003/4 had 14-3-3 results and 92 had S100 results. The discrepancy of 8 is explained by CSF samples that were of insufficient volume or frozen too late to perform S100 testing or the S100 result was occasionally unavailable if the test was performed out with the NCJDSU (at the National Prion Clinic, London). 96% of the 14-3-3 results were positive. However, it must be remembered that to be classified as a Case a patient must meet either the Definite or Probable criteria and a positive 14-3-3 result is actually part of the Probable criteria. Considering pathologically proven patients alone 73% (40/ 55) of the 14-3-3 assays were positive.
S100 was normal (≤ 0.38) in 5% (5 / 92) of Cases, moderately elevated (between 0.39 and 0.99) in 38% (35 / 92) and markedly elevated (≥ 1) in 57% (52 / 92). None of the 4 patients with negative 14-3-3 results had normal S100s. Their S100 levels ranged between 0.75 and 2.0 with one unknown result.

14-3-3 negative pathologically confirmed sCJD patients

The 14-3-3 negative pathologically confirmed sCJD patients are an interesting population and to investigate them further the NCJDSU database was used to identify all such cases from the introduction of 14-3-3 testing in December 1996 up until December 2004. 26 individuals were identified but no clinical information was available on one, who was therefore excluded from further analysis. Two patients had repeat CSF testing with a subsequent positive 14-3-3 result but were still included. In the same time period 166 Definite sCJD patients had positive 14-3-3 assays giving a sensitivity of 87% in this population.

14-3-3 negative patients were then compared with 14-3-3 positive, pathologically confirmed sCJD cases from 2003/4 (n = 64) with respect to clinical phenotype and *PRNP* codon 129 / PrP isotype. Mean disease duration was significantly longer and mean age at referral lower in the 14-3-3 negative group compared to the 14-3-3 positive cohort although the age difference did not reach statistical significance (table 3.9).

Table 3.9 Mean age at referral and mean disease duration in 14-3-3 negative and positive sCJD

	-ve 14-3-3 sCJD	+ve 14-3-3 sCJD	Signif.
Mean age at referral / yrs	59.8 (SD 12.5)	64.9 (SD 9.2)	p = 0.12
Mean disease duration / months	15.4 (SD 8.9)	6.7 (SD 7.3)	p<0.0001

The clinical phenotype also appeared slightly different in 14-3-3 negative patients. Clinical onset more frequently included symptoms of cerebellar dysfunction in 14-3-3 negative sCJD than in 14-3-3 positive sCJD and visual disturbance was never seen as a presenting feature in 14-3-3 negative patients (p = 0.01 χ^2 Fishers exact test) (Fig 3.37). When clinical features were reviewed throughout the course of the illness visual disturbance and myoclonus were significantly rarer at any stage in the disease in 14-3-3 negative patients (p = 0.001 χ^2, p = 0.001 χ^2 Fisher's exact test respectively).

Fig 3.37

Presenting clinical features in 14-3-3 negative and positive sCJD

Fig 3.38

Comparison of clinical features in 14-3-3 negative and positive sporadic CJD

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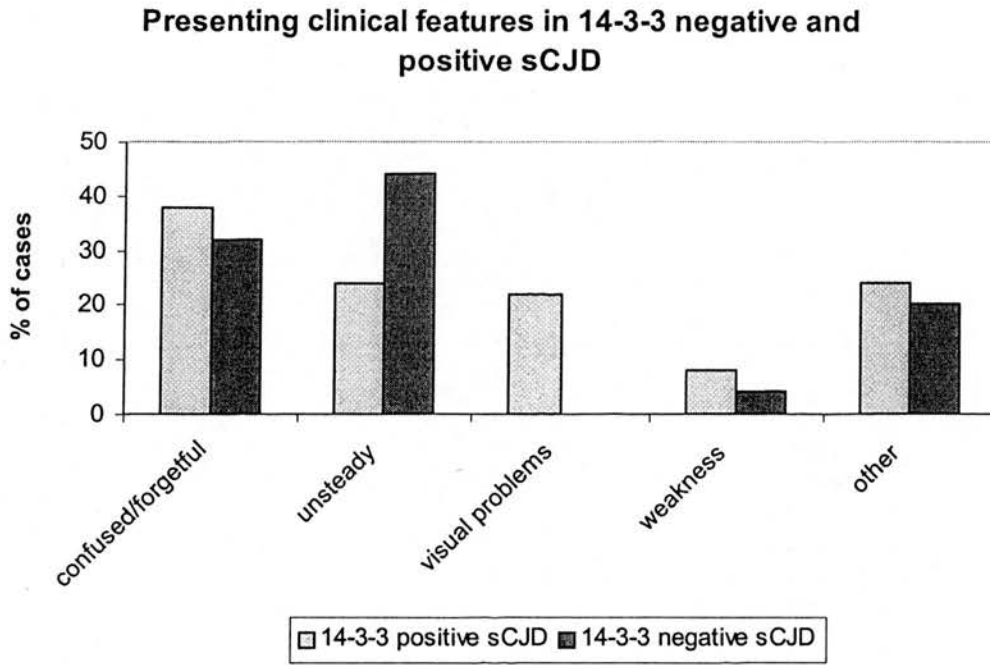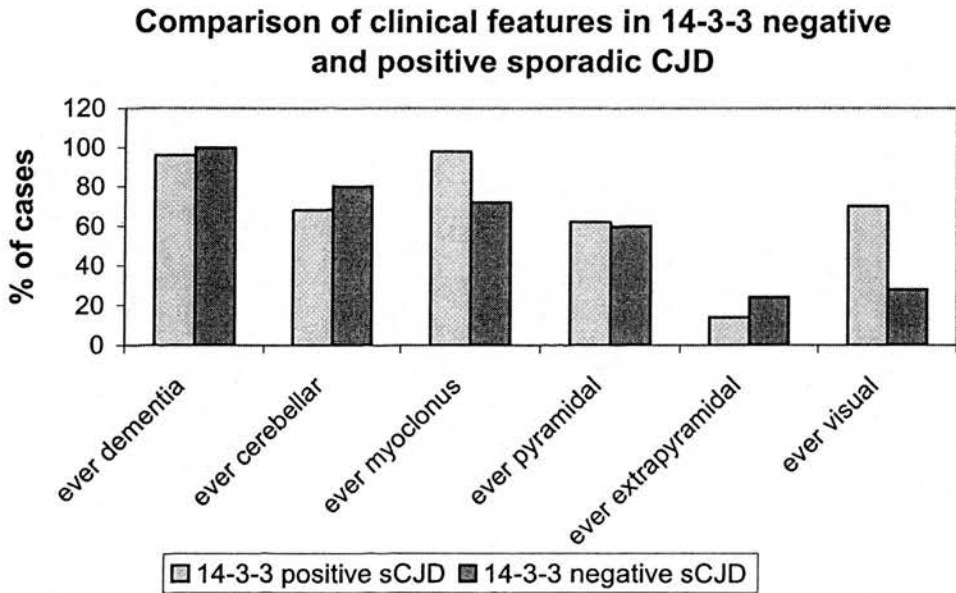
Only 4 / 25 (16%) of the 14-3-3 negative cases had an EEG typical for sCJD with periodic triphasic complexes. 7 / 22 (32%) had a characteristic sCJD MRI with basal ganglia high signal. Almost half (12 patients) had negative results for all 3 of EEG, MRI and 14-3-3.

In the 14-3-3 negative sCJD population PrP isotype / codon 129 genotype differed significantly from sCJD patients with positive 14-3-3 ($p < 0.001$ χ^2) (fig 24). MM1, which is associated with a typical sCJD presentation, was significantly less common in 14-3-3 negative patients ($p = 0.03$ χ^2).

Pathology was as expected for codon 129 / prion protein type with at least 9 of the cases having predominantly subcortical rather than cortical pathology.

Fig 3.39

Codon 129-PrP subtype distribution in 14-3-3 negative sCJD compared to 14-3-3 positive sCJD
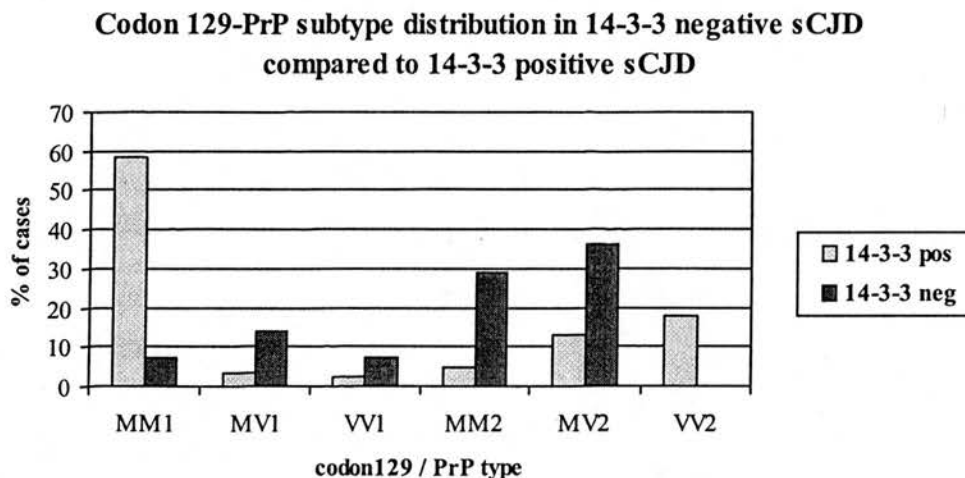
The timing of the CSF testing was calculated to assess if this was different between 14-3-3 negative and positive patients. In the 14-3-3 negative population the median time to take CSF was 6.0 months (range 2 - 36 months) and the mean proportion through the illness was 59% (SD 20.7). This compares with 14-3-3 positive patients where median time to take CSF was shorter at 3.0 months (range 0.5 - 41 months) but mean proportion through the illness was similar at 66% (SD 21.1), reflecting the longer disease duration in the 14-3-3 negative group.

3.4.2 MRI

In 1993/4 44 of the 95 Cases had MRI brain imaging (46%) compared to 111 / 129 (86%) in 2003/4. In one case in 1993/4 and five cases in 2003/4 the MRI was either not interpretable (due to poor quality scanning or excessive movement artefact) or the result was unknown. These scans were therefore excluded from further analysis.

Only 2 of the 1993/4 scans were available for review by the NCJDSU radiographers. Both were reported as having caudate / putamen hyperintensity and were therefore classified as positive scans. Two other 1993/4 MRIs were described as having basal ganglia high signal according to the local radiologists but were not available for review. Therefore 9% (4 / 44) of the scans were considered positive. 37/44 scans were reported as normal locally and were not reviewed, two had alternative abnormalities unrelated to sCJD (established and multiple infarcts compatible with underlying cerebrovascular disease in both cases) and one scan was not interpretable due to movement artefact. None of the scans were reported as having cortical hyperintensity.

In 2003/4 more MRI scans were both performed and reviewed by the NCJDSU. 34 scans were confirmed as positive on review. A further 14 were unconfirmed positive results resulting in a total positivity rate of 45% (n = 48). In addition cortical hyperintensity alone was noted on review of six scans and reported on another. In isolation cortical hyperintensity does not permit classification as a positive MRI. 20 scans were normal on review and 30 were normal by report. One MRI showed non CJD pathology, namely T2 high signal in the pons raising the possibility of central pontine myelinolysis but there was no history of hyponatremia and on balance it was felt to reflect ischaemic change. No scans showed the pulvinar sign that is characteristic of vCJD. There were significantly more MRIs with the characteristic changes of sCJD in 2003/4 compared to 1993/4 (p < 0.001 Mann Whitney test). Figs 3.40 and 3.41 summarises these MRI result

Fig 3.40

MRI results in sCJD Cases in 1993/4

5%
n = 2

9%
n = 4

86%
n = 37

- Normal
- Caudate / putamen hyperintensity
- Other
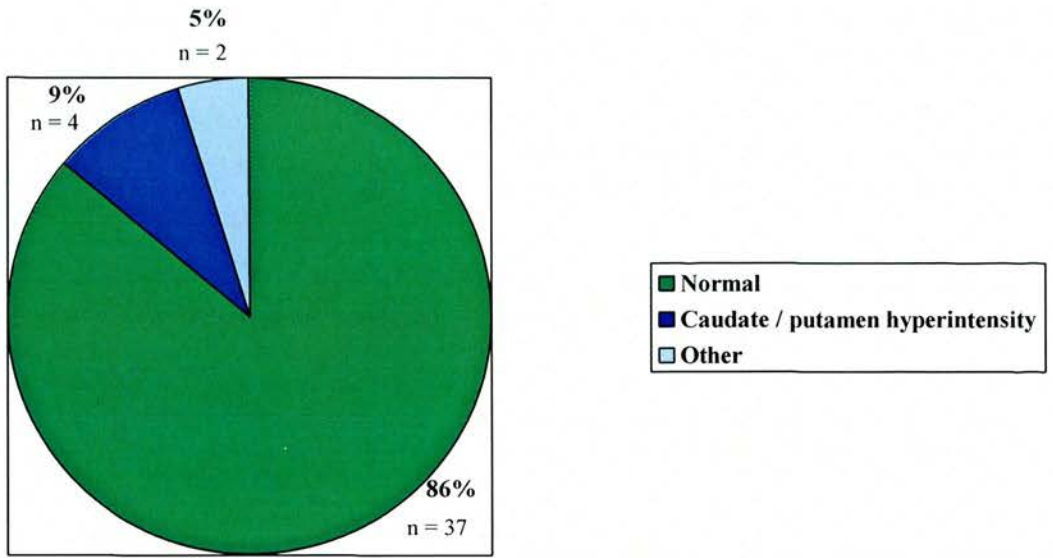
Fig 3.41

MRI results in sCJD Cases in 2003/4

7%
n = 7

1%
n = 1

47%
n = 50

45%
n = 48

- Normal
- Caudate / putamen hyperintensity
- Cortical high signal only
- Other
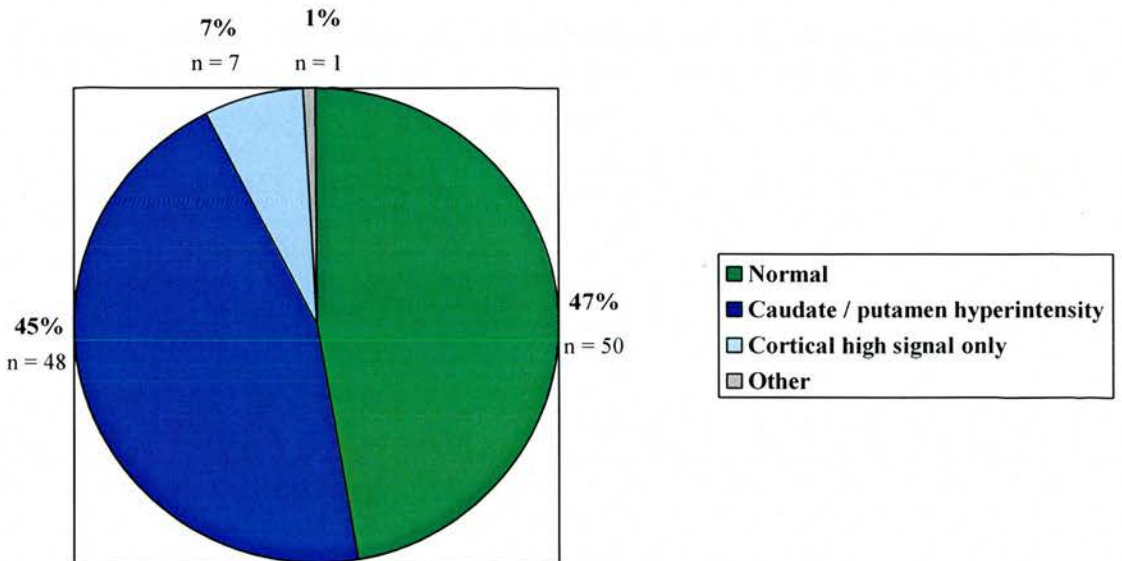
MRI results were also collated for the Possible and Unclear diagnosis classifications for each time period. In 1993/4 only 5 / 26 (19%) patients had an MRI and all were reported as normal although none were available for review. In 2003/4 a higher proportion had MRI performed (24 / 32, 75%) and 8 were positive (6 confirmed, 2 by report only) giving a positivity rate of 33% in this subgroup. Of these 8 individuals 3 were Possible sCJD and 5 Unclear diagnosis. The 5 Unclear diagnosis patients either had a disease duration greater than two years or insufficient clinical features to fulfil sCJD diagnostic criteria, but all had a characteristic EEG or positive 14-3-3 in addition to the typical MRI appearances. In all eight individuals the 'best guess' diagnosis was felt to be sCJD. 15 scans were normal (4 confirmed, 11 by report) and 1 scan showed alternative pathology with bilateral temporal lobe atrophy and hyperintensity felt to be radiologically suggestive of either mitochondrial disease or chronic herpes simplex encephalitis. However, clinically no diagnosis has been made and the individual remains classified Unclear diagnosis as sCJD remains a possibility. The timing of the MRI may potentially influence the result and therefore time to MRI was compared in Cases with a positive or negative MRI result. Timing was assessed in two ways; as the number of months between disease onset and MRI, and secondly MRI timing as a percentage of the total illness duration. The former measure was not normally distributed so medians were used whereas the percentages were normally distributed and therefore means were compared. Table 3.10 summarises the results. The MRI was performed significantly earlier in the Cases with a negative scan. However, when MRI timing was considered proportionate to the illness duration there was no significant difference between those with a positive and negative scan result.

Table 3.10 Timing of MRI in sCJD

	Positive MRI	**Negative MRI**	**Significance**
Median time to performing MRI	3.5 months	2.5 months	P = 0.01 (Mann Whitney test)
MRI timing as mean percentage through illness	65%	60%	NS (t test)

The relationship between basal ganglia high signal on MRI and *PRNP* codon 129 genotype and PrP isotype was also explored. When only the scans reviewed in the NCJDSU were considered 86% of VV cases had basal ganglia hyperintensity on MRI compared to 57% of MV patients and 54% of MM cases (fig 3.42). If unconfirmed scan reports were also included the proportion of positive scans decreased for all genotypes but the trend persisted (basal ganglia hyperintensity VV 57%, MV 37%, MM 31%). Despite this MM was the most common genotype in cases with a positive MRI, reflecting the predominance of MM in sCJD generally. If sCJD cases were stratified by MRI findings (using confirmed MRI results only) there was a higher frequency of valine homozygosity in the subgroup with MRI high signal (41% v 13%), whereas the reverse was true with methionine homozygosity (45% v 69%) and, to a lesser extent, heterozygotes (14% v 19%) (fig 3.43). These results were not statistically significant (χ^2 p = 0.47 analysing confirmed MRI scans only or p = 0.08 analysing all MRIs)

Fig 3.42

MRI and codon 129 genotype
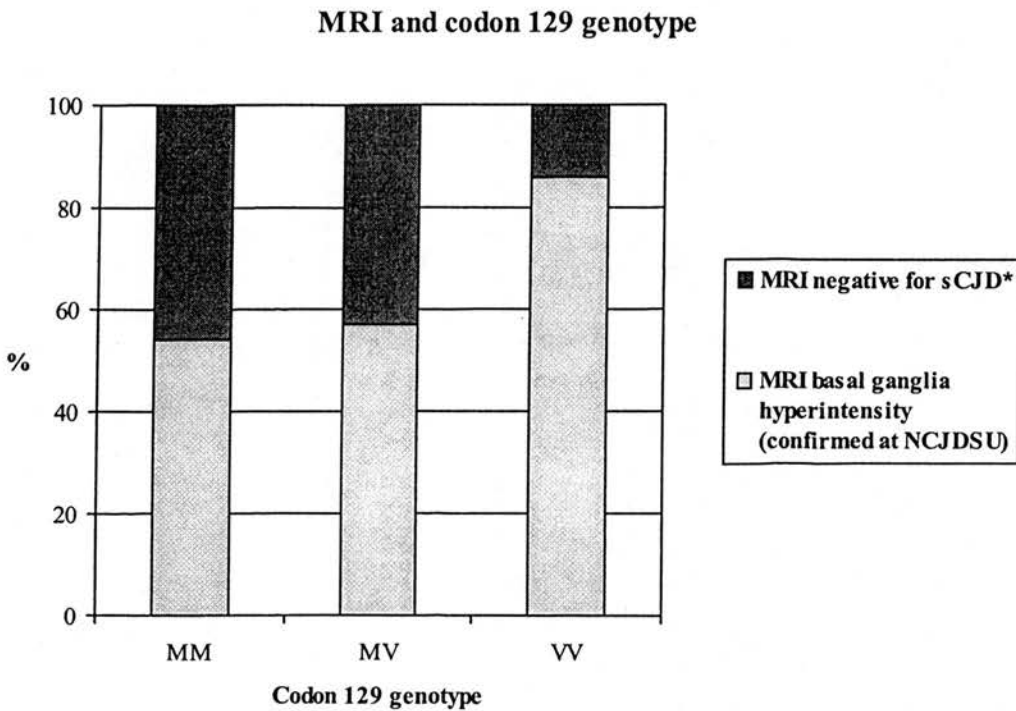
* MRI negative = no basal ganglia hyperintensity

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Fig 3.43

MRI basal ganglia high signal and codon 129 genotype
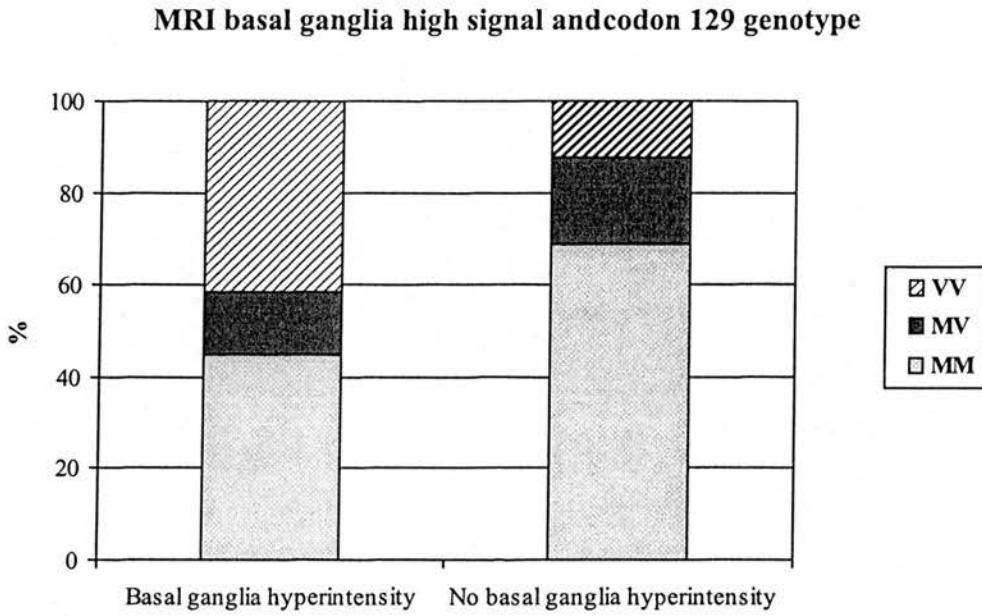
There were only a small number of cases where PrP type was known and MRI imaging had been reviewed at the NCJDSU. Of these 36.4% (4/11) of PrP 1 cases had characteristic caudate / putamen changes on MRI compared to 77.8% (7/9) of PrP 2 cases. If unconfirmed scans were included 38.5% (5/18) were positive in PrP 1 cases versus 50% (9/18) in PrP 2 patients. This was not statistically significant (χ^2 p = 0.06 using confirmed MRIs or p = 0.13 using all MRIs).

Table 3.11 summarises the MRI findings in the different Parchi subtypes. Unfortunately the numbers are too small for any meaningful interpretation but MRI proved a useful diagnostic tool in three out four of the VV2 patients where images were reviewed and two out of three MV2 cases.

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Table 3.11 MRI results by Parchi subtype

Parchi subtype	MM1	MM2	MV1	MV2	VV1	VV2
No. of cases with confirmed basal ganglia hyperintensity on MRI (unconfirmed MRI results)	4 (5)	1 (1)	0 (0)	2 (2)	0 (0)	3 (5)
No. of cases with confirmed absence of basal ganglia hyperintensity (unconfirmed MRI results)	6 (11)	0 (0)	0 (1)	1 (4)	0 (0)	1 (4)

MRI and extrapyramidal features

A positive association between extrapyramidal features and basal ganglia hyperintensity on MRI has been postulated in sCJD. However, in this study there was no such positive correlation. 13.5% of sCJD Cases with caudate / putamen high signal on MRI had extrapyramidal signs, compared to 13.3% of Cases with a negative MRI (not significant).

3.4.3 EEG

The vast majority of sCJD Cases were investigated with EEG. In 1993/4 89.5% of the Cases (85 / 95) had EEGs. In 2003/4 the percentage was marginally higher at 94.6% (122 / 129). The mean number of EEGs per individual Case was similar at 1.65 in 1993/4 and 1.56 in 2003/4 with a range of 0 - 5 EEGs for both time periods. However, fewer EEGs were available for review at the NCJDSU in 1993/4 Cases compared to 2003/4 Cases (52 versus 104).

Timing of the EEG was similar in 1993/4 and 2003/4 with median time to EEG of 2.7 months (range 0.6 - 18.9) and 2.6 months (range 0.5 - 41.3) respectively. EEG date was missing in one Case in 1993/4 and three in 2003/4 so these were excluded from the analysis. When time to EEG was expressed as a proportion of the total illness duration the median values were similar in 1993/4 and 2003/4 at 77.1% (range 6.6 - 100%) and 72.0% (range 13.7 - 100%).

Overall just over half of 1993/4 Cases and one third of 2003/4 Cases had EEGs that were characteristic of sCJD and were sufficient to classify the individual as a Probable Case if clinical features allowed (fig 3.44). This difference between the time periods was significant ($p = 0.02$ Mann Whitney). If the percentage of characteristic EEGs is calculated based only on the traces that were reviewed in the NCJDSU the difference is even more marked with 73.1% of reviewed EEGs being classifiable in 1993/4 compared to 38.5% in 2003/4. Generally EEGs were only classified as characteristic if they were reviewed by one of two individuals in the NCJDSU (RGW, RK). However, there were six exceptions, all in 1993/4, whereby EEGs were examined by the visiting registrar or NCJDSU consultant and termed characteristic but were then missing by the time this study was performed so could not be reviewed and reclassified.

Figs 3.45 and 3.46 summarises the breakdown of EEG classifications for each time period. 27% ($n = 23$) of EEGs in 1993/4 were entirely typical for sCJD compared to 17% ($n = 21$) in 2003/4 whereas the proportion of highly suggestive traces was similar at 20% and 17% respectively ($n = 17$ and 20). 38% of EEGs were unavailable for review in 1993/4 compared to 13% in 2003/4.

Fig 3.44

Proportion of characteristic EEGs in Cases in 1993/4 and 2003/4

120
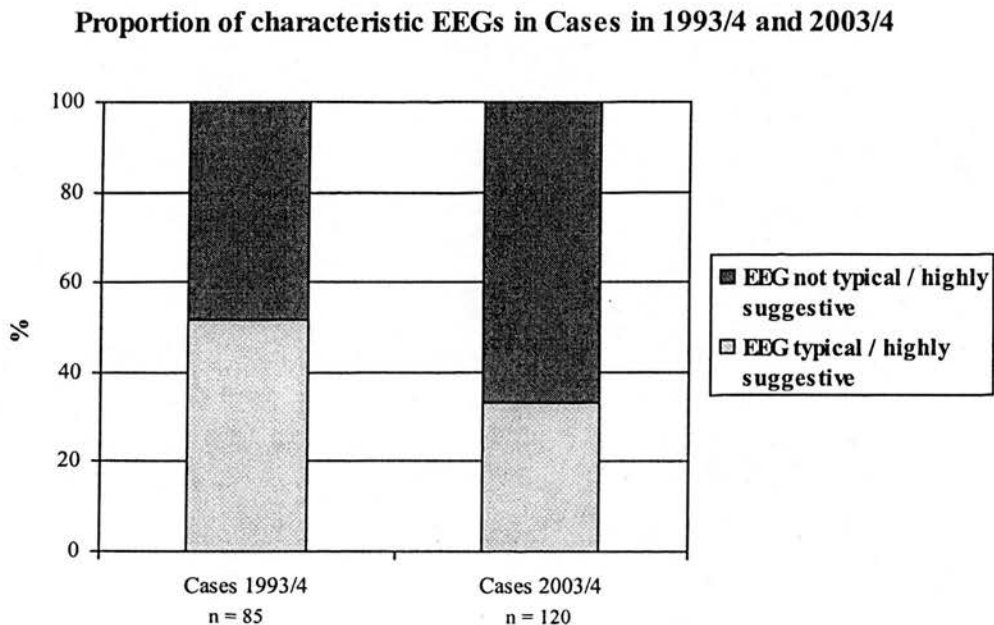
Fig 3.45

EEG results for 1993/4 Cases

24%
n = 20

27%
n = 23

15%
n = 13

7%
n = 6

7%
n = 6

20%
n = 17

- Typical
- Highly suggestive
- Suggestive
- Non-specific
- No trace, report suggestive
- No trace, report non-specific
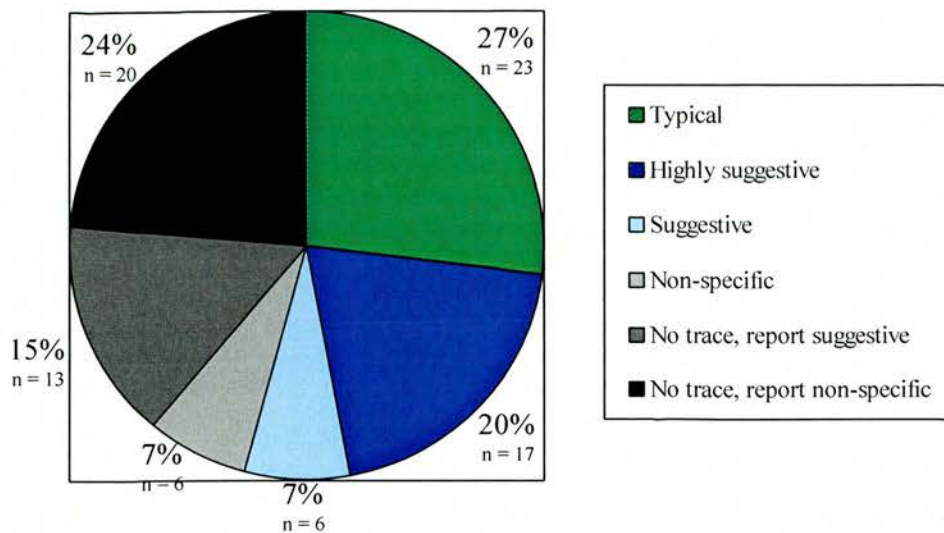
Fig 3.46

EEG results for 2003/4 Cases

8%
n = 10

5%
n = 6

2%
n = 2

17%
n = 21

27%
n = 32

17%
n = 20

24%
n = 29

- Typical
- Highly suggestive
- Suggestive
- Non-specific
- Normal
- No trace, report suggestive
- No trace, report non-specific
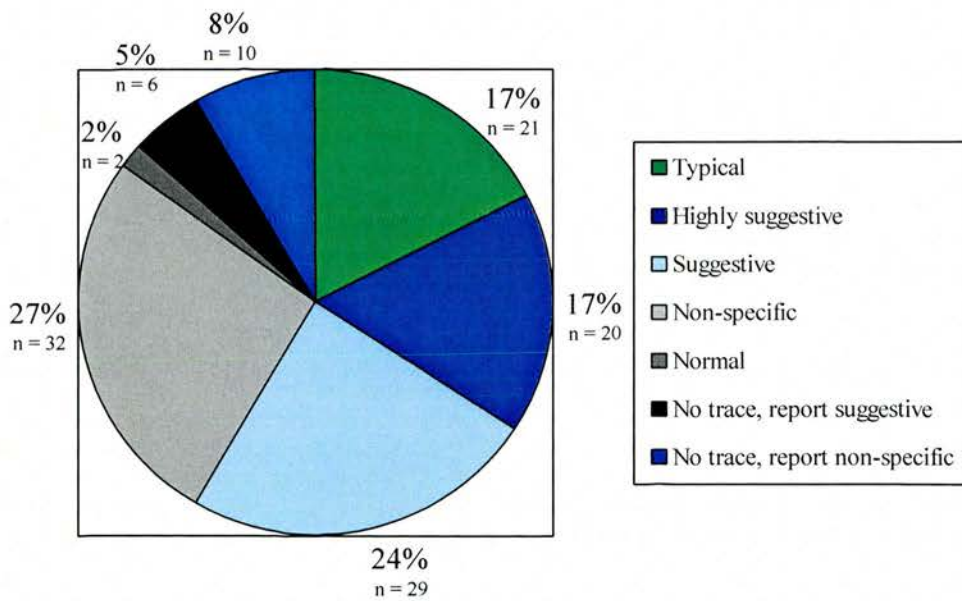
The EEG findings were also analysed for suspect sCJD referrals that were ultimately classified as only Possible sCJD or Unclear diagnosis (figs 3.47 and 3.48). Unfortunately the numbers were small and over half of the traces were unavailable for review (58% in 1993/4, 51% in 2003/4). In both 1993/4 and 2003/4 referrals 14% were considered characteristic of sCJD. In 1993/4 all 14% were classified as highly suggestive (n = 3) whereas in 2003/4 7% (n = 2) were highly suggestive and 7% (n = 2) typical.

Figs 3.47 and 3.48

EEG results in Possible sCJD / Unclear diagnosis referrals in 1993/4
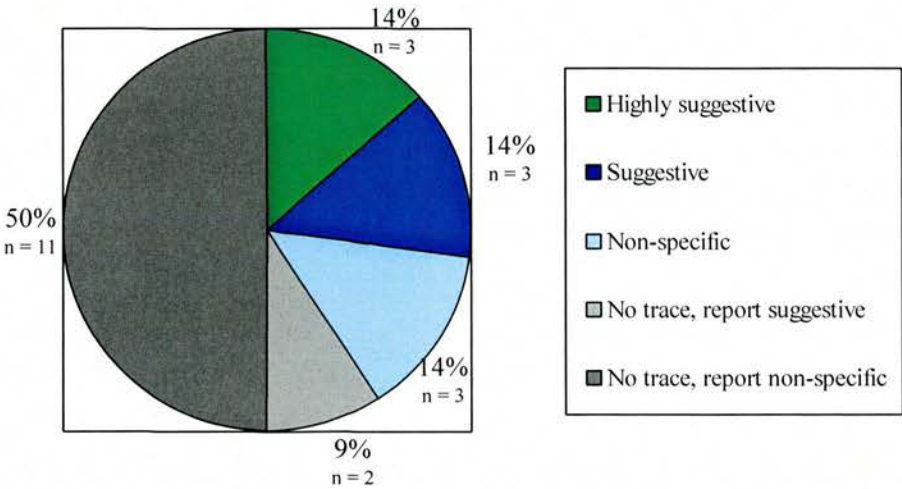
EEG results in Possible sCJD / Unclear diagnosis referrals in 2003/4

122
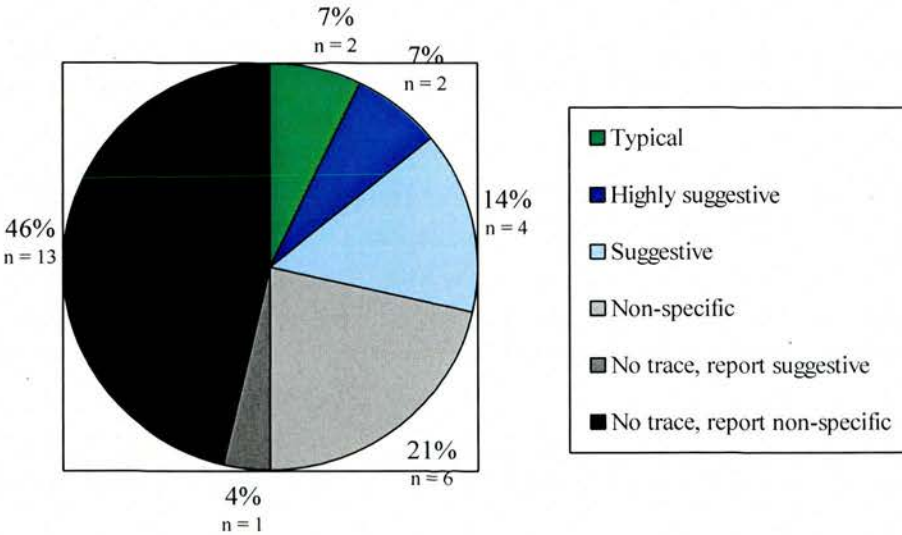
The relationship between *PRNP* codon 129 genotype and the EEG was explored (fig 3.49). When 1993/4 and 2003/4 referrals were analysed together MM genotype was significantly more common amongst patients with an EEG characteristic for sCJD (p < 0.001 χ^2). This statement remains valid if 1993/4 and 2003/4 referrals are analysed separately (p < 0.001 Fisher's exact χ^2 for 1993/4 and for 2003/4).

93.5% (n = 58) of Cases with typical / highly suggestive EEGs were methionine homozygous and only 3.2% (n = 2) were valine homozygous and 3.2% (n = 2) methionine valine heterozygous. In contrast in those Cases where there was no characteristic EEG (either because no EEG was available or because it was reviewed and felt to be non specific or suggestive at best) *PRNP* genotype was more evenly distributed (MM 36.9%, n = 31; MV 23.8%, n = 20; VV 39.8%, n = 33). This difference was slightly more pronounced if only EEGs that were reviewed in the NCJDSU and deemed not characteristic were included although the numbers were smaller (MM 33.3%, n = 15; MV 28.9%, n = 13; VV 37.85%, n = 17).

Fig 3.49

Relationship between characteristic sCJD EEG and codon 129 genotype
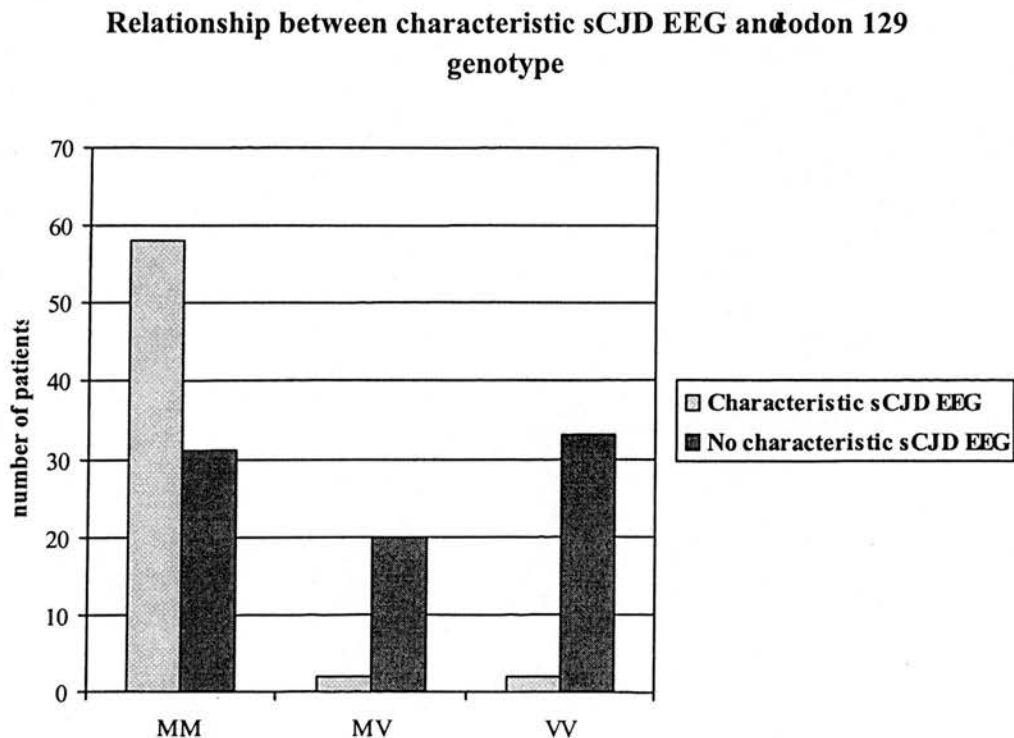
Assessment of the impact of PrP isotype on the EEG was limited because of small sample sizes. Despite this there appears to be an excess of PrP type 1 in Cases with typical / highly suggestive EEGs and this was statistically significant (p = 0.001 Fisher's exact χ^2). Table 3.12 summarises the findings when 1993/4 and 2003/4 Cases are combined.

Table 3.12 EEG results by PrP isotype

PrP isotype	Characteristic sCJD EEG	No characteristic sCJD EEG
1	11 (100%)	17 (45.9%)
2A	0 (0%)	20 (54.1%)

EEGs in Non Cases

Three individuals were referred as suspected sCJD and had characteristic EEG appearances but ultimately proved pathologically to have alternative diagnoses. Two fulfilled criteria for Probable sCJD in life, whereas in the third case the dementia was considered slowly progressive and therefore unlikely to be due to sCJD. Interestingly one of these patients was referred on the basis of clinical features prior to the EEG being performed. They are of particular clinical interest and are described in more detail below:

(i) In 2003/4 a previously well female presented at the age of eighty with mild unsteadiness of gait. This remained relatively static for eighteen months until subtle cognitive impairment was noted and the patient began falling. There onwards the illness progressed relentlessly with increasing memory problems, poor balance and urinary urgency and frequency.

CT brain imaging at eighteen months revealed ventriculomegaly, initially attributed to cerebrovascular related atrophy. At three years a lumbar puncture was done with normal opening pressure and marked improvement in mobility and cognition, supporting the clinical impression of normal pressure hydrocephalus. This was followed by lumbar drainage with a good but transient response lasting two weeks. Ventriculostomy was then performed but was complicated by sepsis and hyponatremia and the patient never recovered to her immediate pre-operative level of function, despite a further attempt at ventriculoperitoneal shunting.

She continued to deteriorate and when reviewed by the NCJDSU registrar 39 months into her illness she was bed bound with confused speech, spontaneous multifocal myoclonus, generally brisk reflexes and a positive pout. She died 2 months later.

5 months prior to death an EEG showed periodic complexes, 14-3-3 CSF protein was positive and MRI showed small vessel ischaemic changes only. Post mortem demonstrated marked enlargement of the third and lateral ventricles and minimal cerebrovascular disease and occasional Alzheimer type neurofibrillary tangles (both felt unlikely to be of clinical significance). The appearances were felt to be consistent with normal pressure hydrocephalus. There was no pathological evidence of a spongiform encephalopathy.

(ii) In 1993/4 a seventy year old lady presented with dementia progressed rapidly over nine months with the emergence of pyramidal and extrapyramidal features, akinetic mutism but no myoclonus. During this period she also underwent cataract surgery. She died with a total disease duration of ten months.

EEG just prior to death showed periodic complexes at a frequency of 1 - 2 Hertz, and was reported by the local neurophysiologist and the NCJDSU as being highly suggestive of sCJD (fig 3.50). MRI showed only generalised cerebral atrophy.

Pathology demonstrated Lewy bodies within the cortex, thalamus and brainstem consistent with diffuse dementia with Lewy bodies. There was no evidence of spongiform encephalopathy.

Fig 3.50
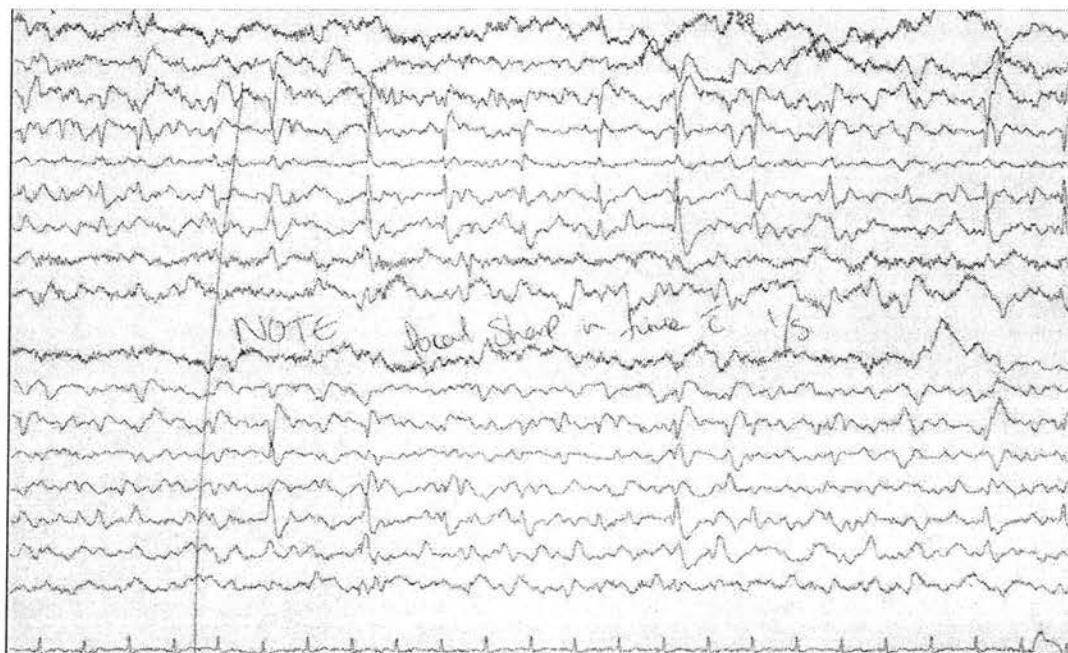
(iii) The third individual, also female, developed mild memory problems aged 56 resulting in early retirement from her job as a secretary. She was treated for depression without any benefit. The cognitive problems progressed slowly over several years with the eventual development of dysphasia, startle myoclonus, infrequent generalized seizures and visual hallucinations. Examination confirmed myoclonus, global dementia, pyramidal signs and primitive reflexes. She died aged 65, 9 years after the onset of her cognitive impairment.

CT brain imaging demonstrated mild generalised atrophy with disproportionate left temporal lobe atrophy and marked periventricular white matter changes. SPECT scan showed severe perfusion deficits throughout the cortex but was not typical of any particular dementia. CSF and bloods were normal. Three EEGs performed in the last year of the illness were felt to be typical for sCJD, both by the reporting neurophysiologist and the NCJDSU (fig 3.51). Prion gene analysis showed that she was homozygous for methionine at codon 129 and no mutations were present.

At autopsy there was no evidence of CJD. However, there were widespread senile plaques and neurofibrillary tangles consistent with Alzheimer's disease (CERAD definite) plus moderate arteriosclerosis.

Fig 3.51
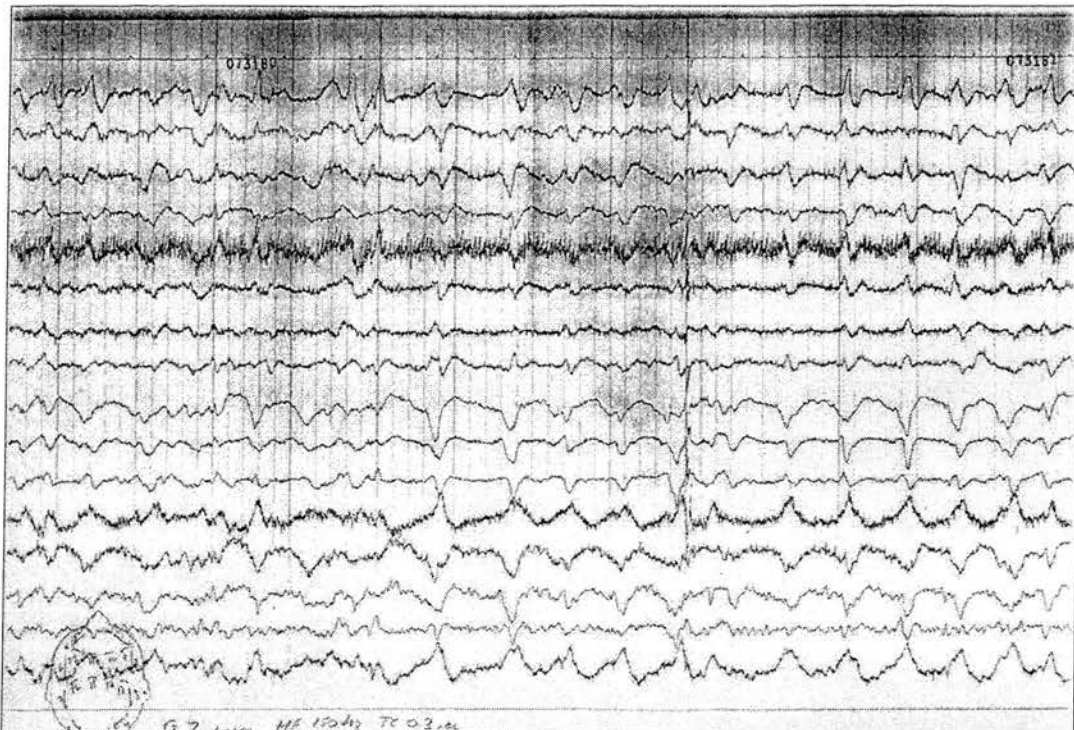
Interestingly two of these unusual cases underwent surgery during their final illnesses (one neurosurgical, one opthalmic). Therefore the EEG findings taken in conjunction with the clinical features stimulated major public health concerns regarding the possibility of CJD and subsequent transmission. In fact in both cases the instruments were quarantined until the autopsy results were available.

A further nine Non Cases had EEGs which were reviewed in the NCJDSU and designated 'suggestive' of sCJD although not sufficient to use in classification. The final diagnoses in these patients is summarised in table 3.13.

Table 3.13: Diagnoses in Non Cases with EEG appearances characteristic or suggestive of sCJD

Final diagnosis	Pathologically or clinically defined Non Case and year	EEG classification
Alzheimer's disease	Pathological 1993/4	Typical
Dementia with Lewy Bodies	Pathological 1993/4	Highly suggestive
Normal pressure hydrocephalus	Pathological 2003/4	Highly suggestive
Metastatic small cell cancer	Pathological 1993/4	Suggestive
Alzheimer's disease	Clinical 1993/4	Suggestive
Epilepsy	Clinical 1993/4	Suggestive
Parkinson's disease with dementia	Clinical 1993/4	Suggestive
Parkinson's disease with dementia	Clinical 1993/4	Suggestive
Viral encephalitis	Pathological 2003/4	Suggestive
Encephalitis ? cause	Pathological 2003/4	Suggestive
Central pontine myelinolysis	Clinical 2003/4	Suggestive
No diagnosis but clinically not compatible with sCJD	Clinical 2003/4	Suggestive

Six Non Cases had EEG traces that were reported by the local neurophysiologist as suggesting sCJD but were unavailable for review. Interestingly one of these patients presented with rapidly progressive dementia and EEG was reported locally as characteristic of sCJD with periodic complexes at 1-2 second intervals on a slow background. However, CJD was then discounted because she made a dramatic spontaneous recovery although no alternative diagnosis was ever made.

3.4.4 Brain biopsy

Brain biopsy is not part of the routine work up of a suspected sCJD patient. It was done infrequently in both referral periods with five patients in 1993/4 and five patients in 2003/4 undergoing brain biopsy (representing 5.3% and 3.9% of Cases respectively). All ten individuals had brain biopsy results supporting a diagnosis of sCJD although in one case this was felt to be inconclusive. Half ultimately proceeded to autopsy with the diagnosis being confirmed in all patients. No brain biopsies were performed on referrals that subsequently turned out not to have sCJD (although this partly reflects the study design as a suspected sCJD patient with a subsequent brain biopsy proven alternative diagnosis will obviously not be referred to the NCJDSU at this stage). Interestingly eight of the ten brain biopsies were performed in a single centre (including all five 2003/4 patients), raising the possibility that different hospitals have different practices and thresholds for performing biopsies. It is important to note that brain biopsy is a rare investigation for sCJD and the figures have not increased since the emergence of vCJD.

This cohort of sCJD patients that underwent brain biopsy were studied in more detail to determine if they differed from usual sCJD cases, or if the biopsy could have been avoided on the grounds of a secure diagnosis based on clinical features and other, less invasive investigations (table 3.14). The five cases from 1993/4 and the five from 2003/4 were combined for these analyses and compared with the total pathologically proven sCJD cohort (1993/4 and 2003/4 excluding the brain biopsy cases).

Table 3.14 Comparison of demographics, clinical features and investigation results in biopsy and non – biopsy Definite sCJD

	Brain biopsy patients (n = 10)	Pathologically proven sCJD without brain biopsy (n = 148)	Significance
Age (years)	54.3 (SD 15.8)	67.3 (SD 9.8)	**p = 0.005**
Mean duration (months)	16.5 (SD 15.4)	6.7 (SD 7.9)	**p = 0.003**
Clinical presentation	RPD* 50% (5) Cerebellar 20% (2) Other 30% (3)	RPD* 63.5% (94) Cerebellar 10.1% (15) Heidenhain 4.1% (6) Stroke-like 2.7% (4) SPD** 2.0% (3) Psychiatric 1.4% (2) Sensory 0.7% (1) Other 10.1% (15) Insufficient data 5.4% (8)	
CSF 14-3-3	+ve 75% (3) -ve 25% (1) (Not done 6)	+ve 94.1% (48) -ve 5.9% (3) (Not done 97)	NS
EEG	Typical 10% (1) Not typical 90% (9)	Typical 37.4% (49) Not typical 62.6% (82) (Not done / known 17)	NS
MRI brain	Caudate / putamen high signal 40% (4) Cortical high signal alone 10% (1) Negative 50% (5)	Caudate / putamen high signal 30.3% (27) Cortical high signal alone 3.4% (3) Negative 66.3% (59) (Not done 59)	NS
Codon 129 genotype	MM 25% (2) MV 37.5% (3) VV 37.5% (3) (Not known 2)	MM 64.4% (65) MV 13.9% (14) VV 21.8% (22) (Not known 47)	NS

* RPD = rapidly progressive dementia   ** SPD = slowly progressive dementia

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It is difficult to draw firm conclusions due to the small number of patients who underwent brain biopsy but in general they appear to be significantly younger than non brain biopsy sCJD patients (p = 0.005 Mann Whitney), with a significantly longer mean illness duration (p = 0.003 Mann Whitney). The clinical presentation in 70% of the brain biopsy patients was fairly typical for sCJD with either rapidly progressive dementia or cerebellar onset. However, the three other onsets were more unusual with one individual presenting with abdominal pain and weight loss raising the possibility of a neoplastic or paraneoplastic disorder, one presenting with chorea and one with personality change and irritability. Codon 129 genotype was only known in eight of the brain biopsy patients and the results were not typical of codon 129 distribution in sCJD generally. Only 25% of the biopsy cases were methionine homozygous whereas 64% of the other pathologically proven cases were methionine homozygous. In contrast MV and VV genotypes appeared more frequently than one would expect although the numbers are small. These differences in *PRNP* codon 129 distribution between biopsy and non-biopsy patients were not quite significant, probably reflecting the small numbers (p = 0.07 χ^2).

Half of the biopsy cohort had an MRI scan which supported the diagnosis of sCJD (compared to one third of non biopsy cases). All the positive MRIs were performed prior to the biopsy so one can question whether brain biopsy was still required. Similarly CSF 14-3-3 protein was positive in the majority of the brain biopsy patients who had this investigation, whereas EEG only provided positive support for the diagnosis of sCJD in one individual (and in this case the EEG was performed prior to biopsy). There were no statistically significant differences between brain biopsy and non biopsy sCJD patients with respect to EEG, 14-33 and MRI results.

Without pathology four of the brain biopsy cases fulfilled criteria for Probable sCJD, four would have been classified as Possible sCJD and two were Unclear diagnosis, in both instances due to their prolonged disease duration of over two years. sCJD was suspected clinically in all ten cases before the brain biopsy was done.

3.4.5 Pathology and codon 129 genotype

PRNP 129 genotype distribution was compared between 1993/4 and 2003/4 sCJD referrals. The findings are summarised in figs 3.52, 3.53, 3.54 and 3.55 looking at Definite and Probable patients separately and either including or excluding those where genotype was unknown. In both time periods the genotype was not available in a significant proportion of sCJD patients, either because the relatives did not consent

to genetic testing or because the individual was referred after life and genotyping was not possible on the available autopsy tissue. When these 'unknown' results were excluded there was no statistically significant difference between codon 129 genotypes with time, either in pathologically proven sCJD ($p = 0.84 \chi^2$), Probable sCJD ($p = 0.5$ Fisher's exact χ^2) or in Definite and Probable Cases combined ($p = 0.49 \chi^2$). However, there was a non significant trend for a higher proportion of VV genotypes in 2003/4 compared to 1993/4, with correspondingly fewer MM genotypes in 2003/4 (Definite sCJD 20.8% VV in 1993/4 v 29.4% VV in 2003/4, Probable sCJD 19.3% VV in 1993/4 v 27.0% VV in 2003/4).

Fig 3.52

Codon 129 genotype in pathologically proven sCJD in 1993/4 and 2003/4
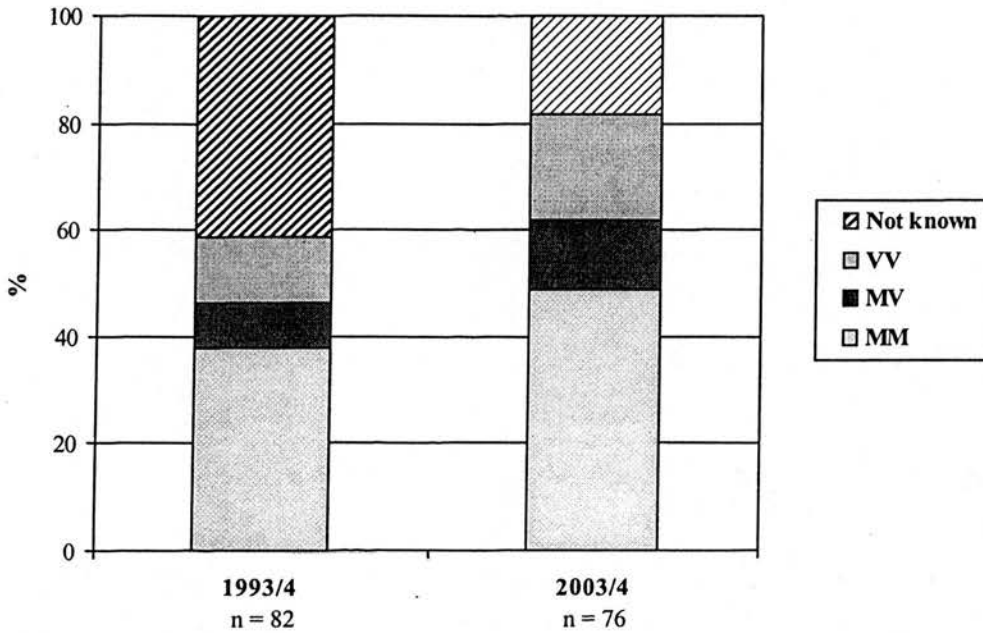
Fig 3.53

Codon 129 distribution in pathologically proven sCJD in 1993/4 and 2003/4 (excluding patients where genotype unknown)
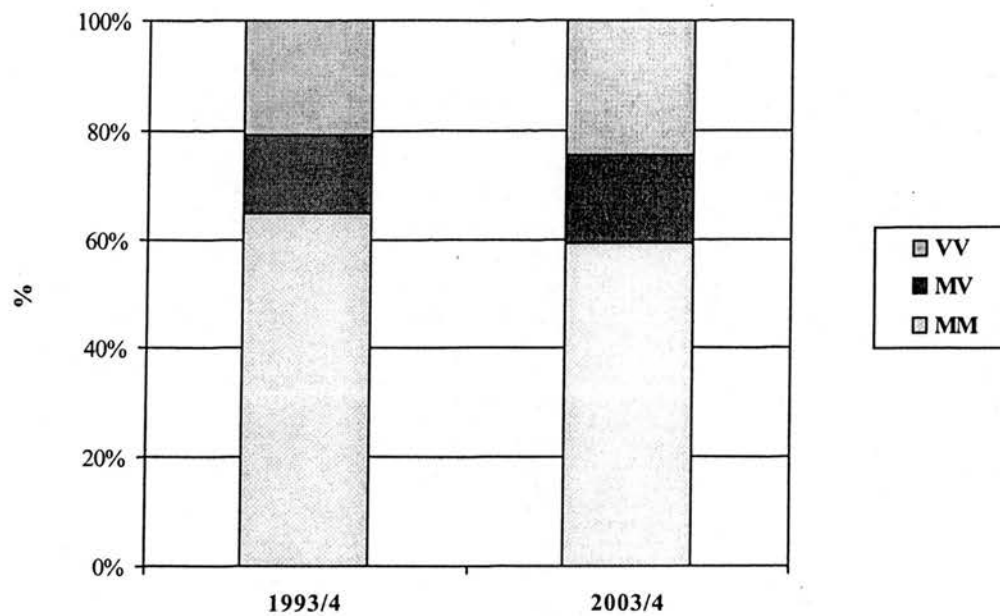
Fig 3.54

Codon 129 genotype in Probable sCJD in 1993/4 and 2003/4
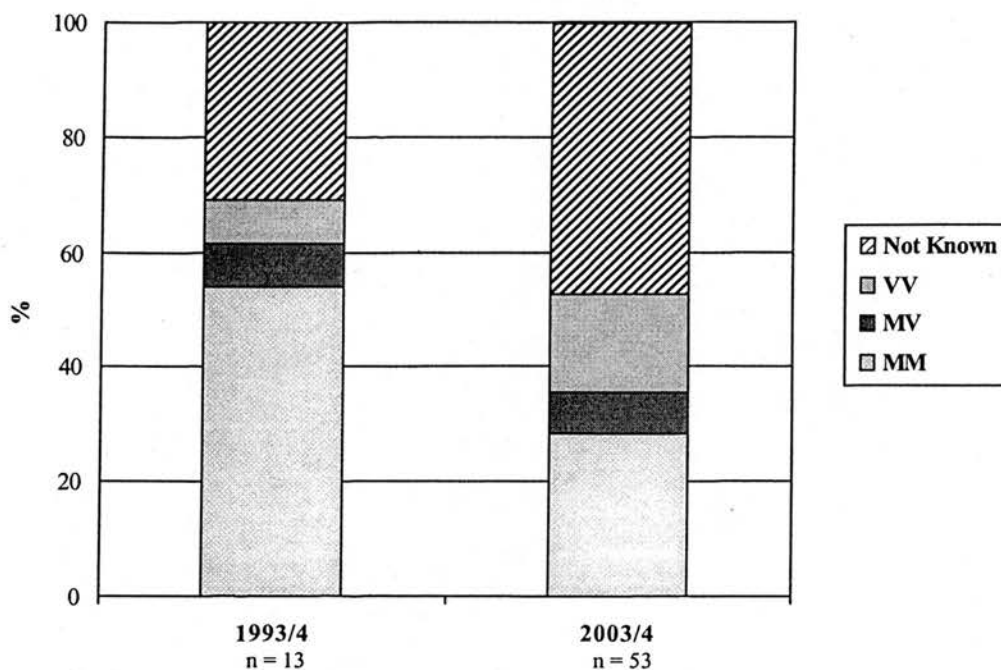
Fig 3.55

Codon 129 distribution in Probable sCJD patients in 1993/4 and 2003/4 (excluding those where genotype unknown)
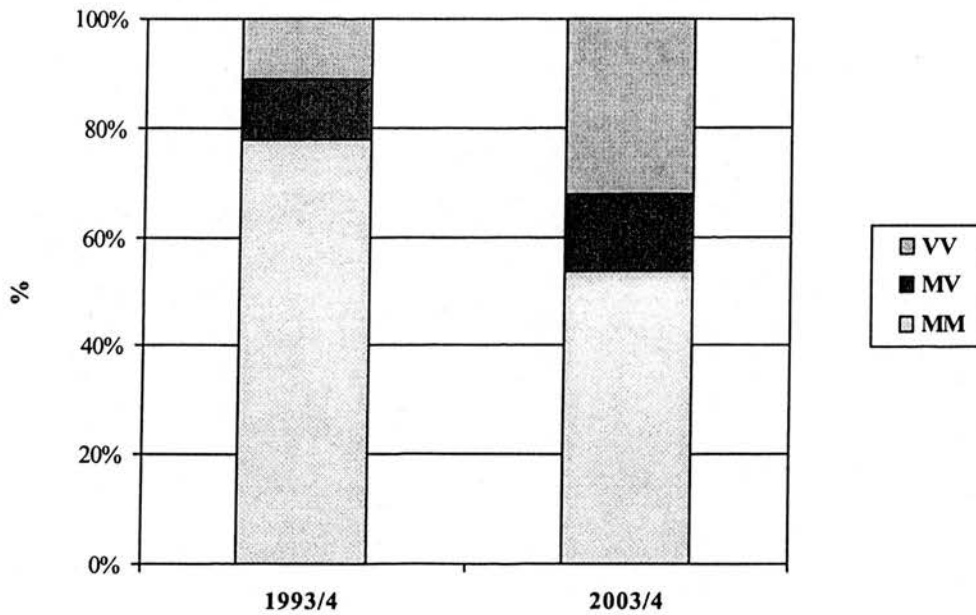
The possible impact of *PRNP* genotype on sCJD duration and age of onset was explored. Onset age was similar, irrespective of codon 129 type (no significant differences with Mann Whitney tests comparing MM with MV, MM with VV and MV with VV). Disease duration was significantly longer in MV compared to MM cases ($p < 0.001$ Mann Whitney) and VV compared to MM cases ($p < 0.001$ Mann Whitney). The proportion of each genotype undergoing autopsy was also reviewed but there were no significant differences ($p = 0.87$ χ^2). Table 3.15 summarises the findings.

Table 3.15 sCJD onset age, duration and PM rate by *PRNP* type

PRNP type	Mean age at onset / yrs	Median disease duration / mo	% pathologically confirmed
MM	67.4	3.0	75.3
MV	64.6	8.6	77.3
VV	65.0	5.5	71.4

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PrP isotype was rarely known for 1993/4 referrals as isotyping was not routinely carried out at this time. Therefore only two such individuals have PrP results, one being PrP type 1 and the other type 2A. In contrast PrP type was analysed in 67% of 2003/4 Definite sCJD patients and table 3.16 summarises the findings. Because of the disparity in numbers it is not possible to make comparisons between the two time periods. A single case was found to have both PrP 1 and PrP 2A. No individual was positive for PrP 2B, the isotype characteristic of vCJD.

Table 3.16 PrP type in Definite sCJD in 1993/4 and 2003/4

	Definite sCJD 1993/4 (n = 82)	Definite sCJD 2003/4 (n = 76)
PrP 1	1	30 (58.8%)
PrP 2A	1	20 (39.2%)
PrP 1 + 2A	0	1 (2.0%)
Not known	80	25

No sCJD referrals in either time period had the florid plaques characteristic of vCJD. However, a minority of pathologically proven cases had kuru type amyloid plaques on histopathology. These were significantly more common in 2003/4 than in 1993/4 referrals (n = 11, 14.5% in 2003/4 compared to n = 3, 3.7% in 1993/4; p = 0.02 Mann Whitney). Kuru plaques are typically associated with the MV2 Parchi subtype and 7 of the 14 patients with kuru plaques had full *PRNP* / PrP isotype analysis. 6 of the 7 were MV2 with 1 individual being MM1, and the neuropathologist commented that this Parchi subtype was unusual given the pathological appearances. Unfortunately it is not possible to compare the proportion of MV2 sCJD patients for each time period due to the lack of PrP testing in 1993/4. However, the proportion of Definite cases heterozygous for methionine valine was similar for both time periods (15% in 1993/4 and 16% in 2003/4 of those tested).

Summary of results regarding sCJD investigations in 1993/4 and 2003/4

- Sporadic CJD is associated with a normal CSF white cell count.

- In pathologically proven sCJD CSF 14-3-3 analysis had a sensitivity of 73%.

- 14-3-3 negative sCJD patients are uncommon and clinically and pathologically atypical, probably in keeping with the underlying codon 129 / prion protein type.

- A negative CSF 14-3-3 result does not exclude the diagnosis of sCJD, particularly in young patients with unusual clinical presentations and prolonged disease course.

- 45% of 2003/4 sCJD Cases undergoing MRI were recognised to have basal ganglia hyperintensity compared to only 9% in 1993/4.

- Typical sCJD appearances of basal ganglia high signal on MRI were more frequently recognised in *PRNP* codon 129 valine homozygotes and in association with PrP 2A isotype but these findings were not statistically significant.

- There were significantly fewer EEGs characteristic of sCJD in 2003/4 Cases compared to 1993/4 Cases.

- Typical EEGs were associated with methionine homozygosity at PRNP codon 129 and with PrP 1 isotype.

- Three pathologically proven Non Cases had EEG appearances that were characteristic of sCJD, implying that such periodic sharp wave complexes are not specific to sCJD.

- Brain biopsy was rarely performed in the work-up for sCJD and biopsy Cases tended to be younger and with longer disease duration than Cases without cerebral biopsy.

- There was no significant difference in *PRNP* codon 129 distribution between sCJD Cases in 1993/4 and 2003/4 although there was a trend towards more valine homozygotes and fewer methionine homozygotes in 2003/4.

- *PRNP* MM Cases had significantly shorter disease durations than either MV or VV sCJD cases.

- Kuru plaques were rare but significantly more common in 2003/4 referrals than in 1993/4, and were usually associated with the MV2 Parchi subtype. No individual had florid plaques on neuropathological examination.

3.5 The differential diagnosis of sCJD

Fig 3.56 summarises the number of Non Cases that were referred to the NCJDSU as suspected sCJD each year between 1993 and 2004. The number of Non Cases increased gradually between 1993 and 2000 but there was a marked drop in 2002 which has persisted. The proportion of pathologically confirmed Non Cases was between 40% and 57% between 1994 and 1999 but more recently it has decreased with a low of 28% in 2004.

Fig 3.56

Number of Non Cases referred annually between 1993 and 2004

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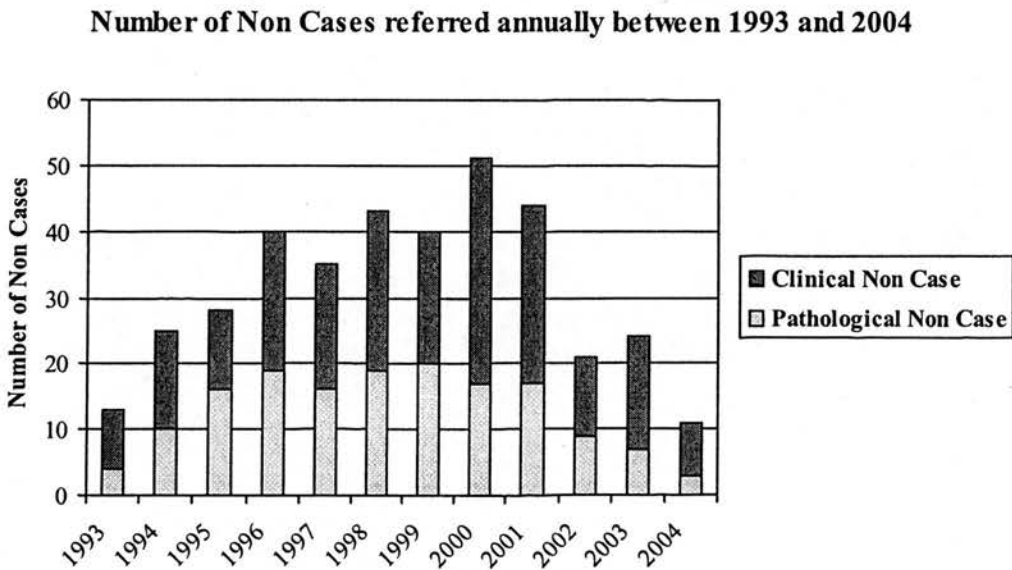
Non Cases referred in 1993, 1994, 2003 and 2004 were analysed in more depth. There were 38 Non Cases in 1993/4, of which 14 (37%) had pathologically proven alternative diagnoses and 24 (63%) were clinical diagnoses. In 2003/4 there were 35 Non Cases, 10 of which were pathologically confirmed (29%) and 25 clinical diagnoses (71%).

3.5.1 Diagnosis in pathologically proven Non Cases

Table 3.17 summarises the final pathological diagnoses in suspected sCJD referrals in 1993/4 and 2003/4 that were ultimately Non Cases. Other forms of CJD (genetic, iatrogenic, variant) were excluded. There was a wide range of alternative diagnoses, all but one of which were primary neurological disorders (the exception being generalised sepsis and renal failure). The commonest pathologically proven alternative was Alzheimer's disease seen in 8 / 24 patients (33%). Dementia with Lewy bodies accounted for 3 / 24 (13 %), as did encephalitis of unknown cause. Two individuals had dual pathology with both Alzheimer's disease and Lewy body dementia pathologically.

There were two malignancy - associated cases, one with cerebral and meningeal metastases from a presumed small cell lung primary, and one with cerebral non Hodgkins lymphoma. There were no definite paraneoplastic cases. Interestingly the precise cause of death in three individuals remained unclear despite post mortem; one being reported as subacute encephalitis, one as cerebellar encephalitis and one as chronic limbic encephalitis, all of unknown aetiology. In all three instances the pathologist commented that the appearances would be consistent with a paraneoplastic process although there was no positive evidence to support this such as identification of a tumour or positive paraneoplastic antibodies in blood or tissue.

Table 3.17 Final diagnosis after autopsy in Non Cases referred in 1993/4 and 2003/4

Final diagnosis after autopsy	Frequency
Alzheimer's disease	8*
Dementia with Lewy Bodies (DLB)**	3*
Encephalopathy / encephalitis cause unknown	3
Cerebrovascular disease	2
Parkinson's disease with dementia (PDD)**	2
Malignancy associated	2
Dementia - type unknown	2
Normal pressure hydrocephalus	1
Multifocal calcifying leucoencephalopathy	1
Viral encephalitis	1
Sepsis / Acute renal failure	1
Total no. of pathological Non Cases	**24**

* 2 patients had dual pathology with both Alzheimer's disease and Lewy body dementia on autopsy

** DLB defined as dementia within a year of onset of Parkinsonism , whereas PDD defined as cognitive problems coming on more than a year after Parkinsonian features

3.5.2 Diagnosis in clinical Non Cases

Table 3.18 summarises the diagnoses in those patients who were felt not to have CJD but where the alternative diagnosis was made on clinical rather than pathological grounds. Again Alzheimer's disease was the commonest diagnosis (20%, 10 / 49) and a further five had dementia which was not classifiable clinically.

Two patients were diagnosed with CNS vasculitis; one had a positive vasculitic blood screen and the second responded to steroids but deteriorated and died some six months later with a death certificate diagnosis of CNS vasculitis. The single malignancy associated case had positive anti - Yo antibodies suggesting paraneoplastic aetiology. Two patients were ultimately diagnosed with motor neurone disease (MND). One presented with fasiculations and had a family history of MND but sCJD was suggested as a diagnosis because of mild cognitive impairment, cerebellar signs and a positive 14-3-3 CSF protein although the subsequent disease

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course favoured MND. In the second individual a clinical diagnosis of MND was supported by evidence of anterior horn cell dysfunction on EMG, but he was initially referred as a possible sCJD case due to associated mild cognitive impairment and a history suggestive of complex partial seizures. Five patients had no diagnosis or improvement but their clinical course was felt incompatible with sCJD.

There is likely to be some overlap between the diagnoses. E.g. Four patients improved without a clinical diagnosis (two spontaneously and two with steroids) and some of these may have had vasculitis or encephalitis.

Table 3.18 Final clinical diagnosis in Non Cases referred in 1993/4 and 2003/4

Final clinical diagnosis	Frequency
Alzheimer's disease	10
Dementia - type unknown (not CJD)	5
No diagnosis but clinically not CJD	5
Dementia with Lewy Bodies (DLB)	4
Cerebrovascular disease	3
Parkinson's disease with dementia (PDD)	3
Epilepsy	3
Motor neurone disease +/- frontotemporal dementia	2
CNS vasculitis	2
Improved with steroids without diagnosis	2
Improved spontaneously without diagnosis	2
Malignancy associated	1
Hypoxic encephalopathy	1
Normal pressure hydrocephalus	1
Central pontine myelinolysis	1
Viral encephalitis	1
Encephalopathy / encephalitis - cause unknown	1
Acute confusion with shingles	1
Learning disabilities	1
Total no. of clinical Non Cases	**49**

3.5.3 Why was sCJD suspected in Non Cases?

8 of the 73 Non Cases fulfilled the WHO criteria for Probable sCJD based on clinical features and either a characteristic EEG or positive 14-3-3 result. Seven were 2003/4 referrals and one was referred in 1993/4 prior to the introduction of 14-3-3. Their final diagnoses and the reasons they were classified as Probable are summarised in table 3.19. A further 20 Non Cases could have been classified as Possible sCJD based on clinical features alone. Therefore 45 Non Cases fulfilled neither the Probable or Possible sCJD diagnostic criteria, yet were still referred to the NCJDSU as suspected sCJD, presumably based on the clinical suspicion of the referring consultant in most instances.

Table 3.19 Final diagnosis in Non Cases that fulfilled Probable sCJD criteria

Final diagnosis	Pathological / Clinical Diagnosis	Reason Probable criteria fulfilled
Alzheimer's disease	Pathological	+ ve 14-3-3
Alzheimer's disease	Pathological	+ ve 14-3-3
Normal pressure hydrocephalus / cerebrovascular disease	Pathological	+ ve 14-3-3 and typical EEG
Dementia with Lewy Bodies*	Pathological	Typical EEG
Dementia with Lewy Bodies	Clinical	+ ve 14-3-3
CNS vasculitis	Clinical	+ ve 14--3-3
Central pontine myelinolysis	Clinical	+ ve 14-3-3
No diagnosis but not sCJD**	Clinical	+ ve 14-3-3

* 1993/4 Non Case

** No clinical diagnosis reached but still alive at 2 years and felt not to be CJD at final review by National Prion Clinic.

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3.5.4 The clinical phenotype of Non Cases

Figs 3.57, 3.58 and 3.59 summarise the symptoms and signs in Non Cases compared to sCJD Cases. There were numerous significant differences between Cases and Non Cases with respect to onset symptoms and symptoms and signs present at any stage during the illness (table 3.20). As one might predict almost all the clinical features were recorded more frequently in sCJD Cases rather than Non Cases. The exceptions were extrapyramidal signs, symptoms suggesting a seizure at any stage and interestingly sensory symptoms at onset, all of which were noted more frequently in Non Cases. One needs to interpret this data with caution as there tended to be less clinical information available on Non Cases, which may have biased the results. These analyses regarded absence of a symptom / sign and insufficient information as a single category, but even if the analyses were recalculated using only definite presence or absence of a clinical feature then the significant results were not markedly different.

Fig 3.57

Clinical symptoms at onset in Non Cases compared to sCJD Cases
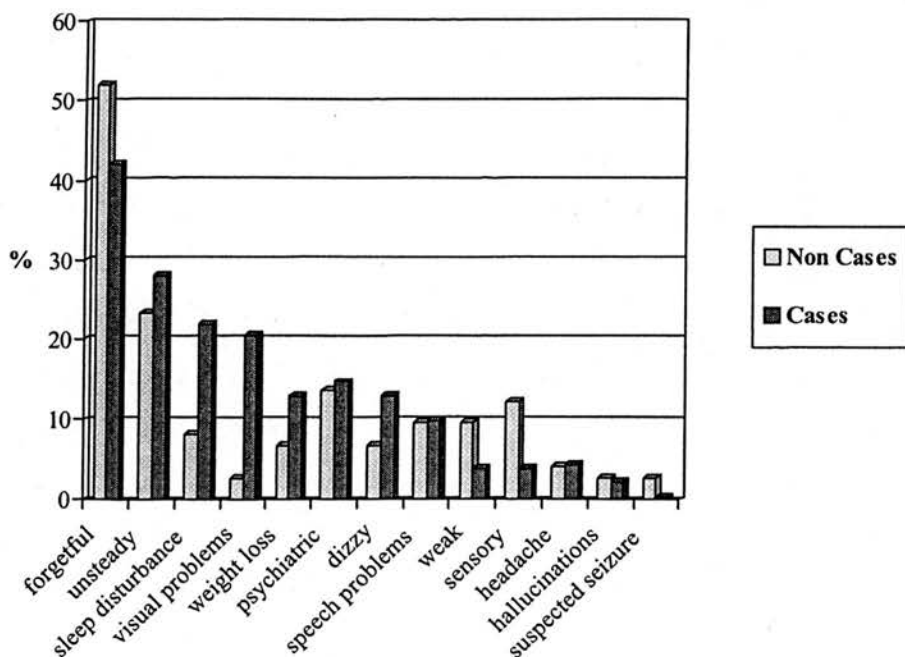
Fig 3.58

Clinical symptoms at any stage in Non Cases compared to sCJD Cases
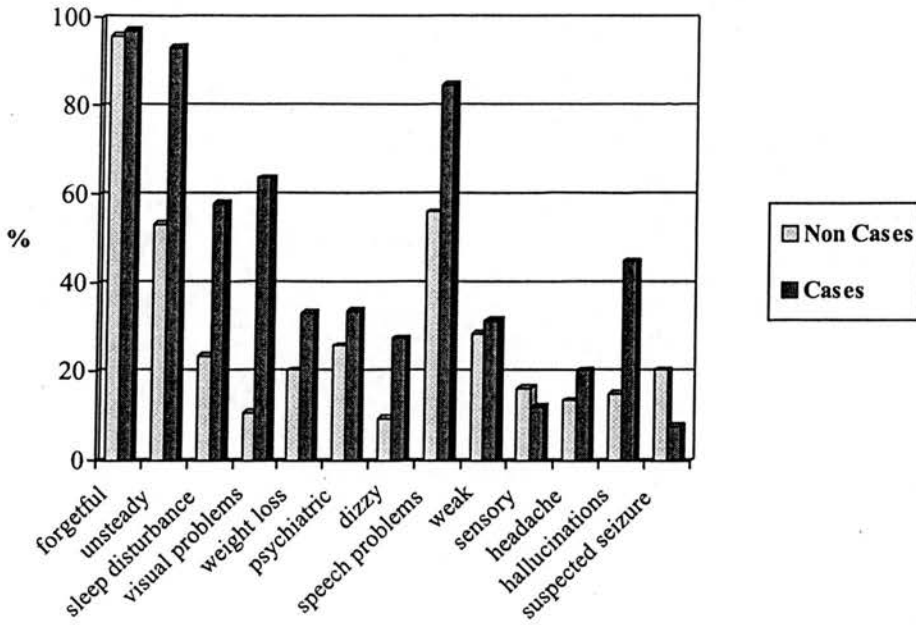
Fig 3.59

Clinical signs at any stage in Non Cases compared to sCJD Cases
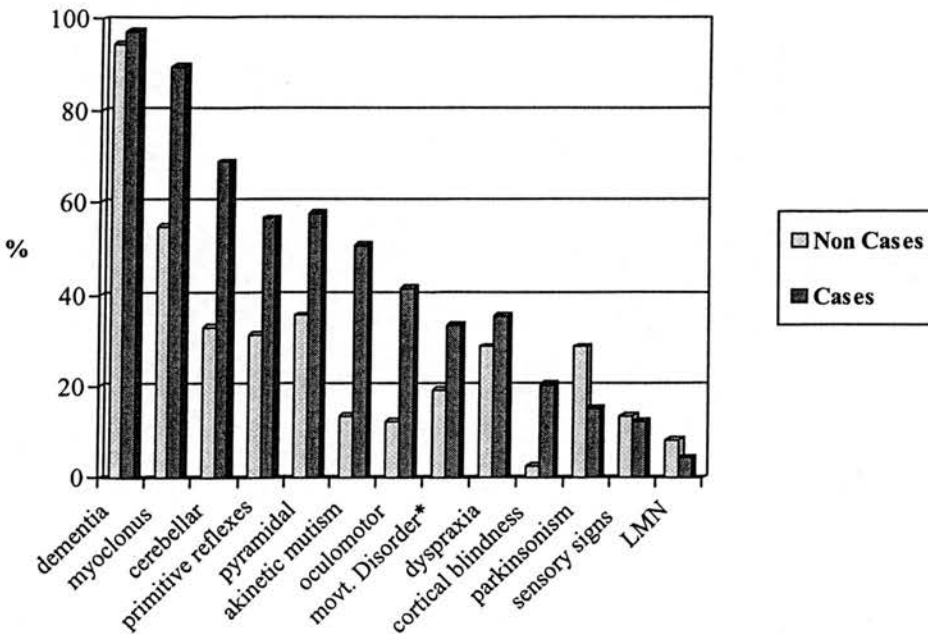
Table 3.20 Statistically significant differences in clinical features between Cases and Non Cases

	Clinical feature	Significance (χ^2)
Symptoms at onset	Visual disturbance	p < 0.001
	Sleep disturbance	p = 0.009
	Sensory symptoms*	p = 0.01
Symptoms at any stage	Unsteadiness	p < 0.001
	Visual disturbance	p < 0.001
	Sleep disturbance	p < 0.001
	Hallucinations	p < 0.001
	Speech disturbance	p < 0.001
	Dizziness	p = 0.002
	Weight loss	p = 0.04
	Seizure*	p = 0.005
Signs at any stage	Cerebellar	p < 0.001
	Myoclonus	p < 0.001
	Cortical blindness	p < 0.001
	Akinetic mutism	p < 0.001
	Oculomotor	p < 0.001
	Primitive reflexes	p < 0.001
	Pyramidal	p = 0.001
	Movement disorder	p = 0.003
	Parkinsonism *	p = 0.01

* more common in Non Cases than Cases

3.5.5 Diagnosis in Possible sCJD / 'Unclear diagnosis' classifications

Amongst 1993/4 referrals there were 18 individuals finally classified as Possible sCJD and in 2003/4 there were 7 Possible sCJD referrals. In 1993/4 they were of a similar onset age to the sCJD Cases (mean 65 years) whereas in 2003/4 they were a little older (mean 73 years). Median disease duration was similar to Definite and Probable

sCJD Cases (4.5 months in 1993/4 and 7.5 months in 2003/4). The majority were referred whilst alive (12 in 1993/4, 5 in 2003/4) and a neurologist reviewed all but one patient. The NCJDSU visited the patient and / or family in 10 of the 18 1993/4 patients and 5 of the 7 2003/4 referrals. None of the 1993/4 Possibles had the characteristic MRI changes associated with sCJD, although only 5 had an MRI performed and none of these were reviewed at the NCJDSU. In contrast in 2003/4 Possibles 3 underwent MRI scanning and all 3 had basal ganglia hyperintensity (2 confirmed by NCJDSU, 1 by report). Obviously no individual classified as Possible sCJD had either a brain biopsy or post mortem to our knowledge. *PRNP* type was known in only 10 of the 25 Possibles and of these 4 were methionine homozygous, 2 valine homozygous and 4 were heterozygotes. Sporadic CJD was considered the most likely diagnosis for all the individuals ultimately classified as Possible sCJD, but there are a number of provisos to this statement that are addressed in the discussion (section 4.6).

In the 'Unclear diagnosis' group there was a range of 'best guess' diagnoses but in a substantial minority it was not possible to provide any diagnosis (27%). One third (11 / 33) were felt to represent sCJD cases that simply failed to meet the diagnostic criteria. In a further five (15 %) sCJD remained a distinct possibility. The remaining referrals (52%) were suspected not to have sCJD and the provisional diagnoses included Alzheimer's disease (1), dementia with Lewy bodies (3), cerebrovascular disease (4) and paraneoplastic syndromes (2). However, the clinical picture was not sufficient to confidently exclude sCJD and hence they remain classified in the 4.1s 'Unclear diagnosis' category rather than 4.2 'Clinically not sCJD' category.

Investigations were of some diagnostic value in this Unclear diagnosis group who failed to fulfil sCJD criteria clinically. Twenty five 4.1s patients were referred in 2003/4 and of these ten had a positive 14-3-3 result, three had a typical EEG and five had an MRI showing basal ganglia hyperintensity (confirmed by NCJDSU in 4/5 instances). All these Unclear diagnosis patients with a typical EEG and / or positive MRI had a 'best guess' diagnosis of sCJD. Seven of the 4.1s patients with a positive 14-3-3 were ultimately thought to have sCJD, with the remaining three having 'best guess' diagnoses of Alzheimer's disease, dementia with Lewy bodies and no diagnosis but unlikely sCJD.

None of the eight Unclear diagnosis patients referred in 1993/4 had supportive EEG or MRI results (and 14-3-3 was not available at this time).

Summary of differential diagnosis of sCJD results

- The differential diagnosis of sCJD is wide and includes isolated cases of numerous neurological conditions.

- Alzheimer's disease was the commonest pathologically confirmed alternative to sCJD, followed by dementia with Lewy bodies / Parkinson's disease with dementia.

- Alzheimer's disease was the commonest clinically identified alternative to sCJD.

- No diagnosis was made in a significant proportion of patients, sometimes despite autopsy.

- A minority of non CJD patients fulfil WHO diagnostic criteria for sCJD, usually on the basis of a positive 14-3-3 result in conjunction with clinical features.

- Sensory symptoms at onset, symptoms suggesting a seizure and signs of parkinsonism were more common in Non Cases than in sCJD Cases.

3.6 The diagnostic criteria

The current WHO diagnostic criteria date from January 1998 (Rotterdam) when the previous Rome criteria from 1993 were revised with the addition of CSF 14-3-3 analysis. A positive 14-3-3 result now permits a clinically Possible patient to be reclassified as Probable (as does a typical EEG). To review the sensitivity, specificity and predictive value of the criteria they were retrospectively applied to all pathologically confirmed sCJD cases in 2003/4 and all Non Cases (clinically or pathologically defined) in the same time period (table 3.21). There was insufficient data to classify one Non Case which was excluded from the analysis.

The same process was applied with 1993/4 referrals of pathologically proven cases and clinical and pathological Non Cases in order to validate the previous diagnostic criteria for comparison (table 3.22). Three cases and two Non Cases were excluded due to insufficient information.

Table 3.21 sCJD Cases and Non Cases fulfilling diagnostic criteria for Probable and Possible sCJD in 2003/4

2003/4 referrals	Pathologically confirmed sCJD	Non Cases
No. meeting probable criteria	55	7
No. meeting possible criteria	12	11
No. not meeting criteria	9	16
Total	76	34

Table 3.22 sCJD Cases and Non Cases fulfilling diagnostic criteria for Probable and Possible sCJD in 1993/4

1993/4 referrals	Pathologically confirmed sCJD	Non Cases
No. meeting probable criteria	33	1
No. meeting possible criteria	41	9
No. not meeting criteria	5	26
Total	79	36

3.6.1 Sensitivity, specificity and predictive value of diagnostic criteria

Sensitivity, specificity, positive predictive value and negative predictive value were calculated for Probable classification in 2003/4 using the current Rotterdam criteria (1998) and similarly for Probable classification in 1993/4 where classification was based on the Rome criteria (1993). Findings are summarised in table 3.23.

Table 3.23 Validity of current and previous sCJD diagnostic criteria

	Current diagnostic criteria (Rotterdam 1998, including 14-3-3)	Previous diagnostic criteria (Rome 1993, pre 14-3-3)
Sensitivity	72.4 %	41.8 %
Specificity	79.4%	97.2 %
Positive predictive value	88.7 %	97.1 %
Negative predictive value	56.3 %	43.2 %

The inclusion of the 14-3-3 result in the newer criteria has resulted in improved sensitivity at the expense of lower specificity and lower positive predictive value. Therefore more sCJD patients will fulfil the criteria for a Probable case but equally a larger number of non CJD patients are also likely to be classified as Probable. Today the probability of a suspected case that meets the Probable criteria actually being a case of sCJD is just under 90%, whereas using the old criteria the probability was over 97%. The negative predictive value remains relatively low at 56%; consequently even if a patient is not classified as a Probable there is still a significant chance they have sCJD.

3.6.2 Effect of including MRI in the diagnostic criteria

At present MRI findings are not included in the diagnostic classification system for sCJD (although they are part of the vCJD criteria). However, basal ganglia hyperintensity is well recognised as a characteristic MRI appearance in sCJD, with cortical hyperintensity being recognised less frequently, and there has been considerable debate as to whether MRI results should be incorporated in the same way as a positive 14-3-3 result was. i.e. A 'positive' MRI permitting a Possible case to become Probable with 'positive' being defined as caudate / putamen hyperintensity. Therefore, the current criteria were also reviewed with the addition of MRI to assess the impact on diagnosis.

In 2003/4 twenty individuals with pathologically proven sCJD had MRI basal ganglia hyperintensity confirmed by the NCJDSU. A further seven had basal ganglia hyperintensity reported locally but scans were unavailable for confirmation. However, of these twenty seven patients twenty three already fulfilled Probable criteria in life,

based on their clinical phenotype and positive 14-3-3 protein or typical EEG. The remaining four patients previously only met Possible criteria so would be upgraded to Probable by the introduction of MRI. This would increase the sensitivity only slightly to 77.6 % (compared to 72.4 % without use of MRI). Three Non Cases referred in 2003/4 had caudate / putamen high signal on MRI (confirmed by NCJDSU in two of the three) but their final classification would not change because one was already a Probable and the other two did not have sufficient clinical features. Therefore test specificity remains unchanged despite addition of MRI. The effect of MRI on positive predictive value is also minor, with an improvement from 87 % to 89 %.

If a 'positive' MRI is more loosely defined including cortical hyperintensity as well as caudate and putamen changes then this would still have a relatively minor impact. In 2003/4 four pathologically proven sCJD cases had cortical hyperintensity alone on MRI but one already fulfilled Probable criteria and one did not have sufficient clinical features to be classified as Possible or Probable, so final classification would only be affected in two cases. No Non Cases had cortical hyperintensity. Therefore specificity remains unchanged at 79.4 % but sensitivity increases to 80.3 % and positive predictive value is essentially unchanged at 89.7 %. Table 3.24 summarises the effect of incorporating MRI results on the current diagnostic criteria.

MRI results do not have a significant impact on 1993/4 referrals as few scans from this time had either basal ganglia or cortical hyperintensity. This probably reflects the smaller number of MRIs performed, the minority reviewed in the NCJDSU and the lack of general awareness of characteristic sCJD appearances on MRI as opposed to any real change in MRI appearances in sCJD over a decade.

Table 3.24 Sensitivity, specificity and predictive value of sCJD diagnostic criteria with and without MRI

	Current diagnostic criteria 1998 (without MRI)	Diagnostic criteria incorporating MRI caudate / putamen hyperintensity	Diagnostic criteria incorporating MRI caudate / putamen + / or cortical hyperintensity
Sensitivity	72.4%	77.6%	80.3%
Specificity	79.4%	79.4%	79.4%
+ve predictive value	88.7%	89.4%	89.7%
-ve predictive value	56.3%	61.4%	64.3%

3.6.3 Sensitivity, specificity and predictive value of individual clinical features

The clinical features incorporated in the diagnostic criteria were also analysed individually for pathologically proven cases in 1993/4 and 2003/4 and for Non Cases for each referral period (table 3.25).

Unsurprisingly dementia was almost universal in both Definite sCJD patients and Non Cases for both time periods (and no individual was actually documented not to have dementia, simply that information confirming cognitive problems was lacking in a minority of referrals). Myoclonus was the second most sensitive clinical sign for Definite cases, being present in 85 - 90%. Cerebellar and visual problems were next most common being present in approx. 65% of sCJD patients, followed by pyramidal signs with a sensitivity of around 55%. Paarkinsonism was rarer being present in less than a quarter of definite cases. The only feature which showed a significantly different sensitivity in cases between 1993/4 and 2003/4 was akinetic mutism, being much less frequently reported in 2003/4 (36% versus 70%).

After dementia, myoclonus was the most prevalent clinical feature in Non Cases but was less common than in cases. Visual symptoms, cerebellar and pyramidal signs and akinetic mutism were all less prevalent in Non Cases compared to Definite cases. In contrast parkinsonism was more common in Non Cases than cases in 1993/4 and similar in 2003/4.

Table 3.25 Prevalence of individual clinical features in Definite sCJD and Non Cases

	Definite Case	Definite Case	Non Case	Non Case
	1993/4	2003/4	1993/4	2003/4
Dementia	95%	97%	94%	94%
Myoclonus	85%	88%	50%	60%
Cerebellar signs	62%	68%	18%	49%
Visual problems	61%	66%	8%	14%
Pyramidal signs	56%	52%	34%	37%
Parkinsonism	22%	17%	37%	20%
Akinetic mute	70%	36%	18%	9%

As the values from 1993/4 and 2003/4 were generally similar the data were combined to calculate sensitivity, specificity, positive and negative predictive values for each clinical feature used in the diagnostic criteria. They are summarised in table 3.26.

Table 3.26 Sensitivity, specificity and predictive value of individual clinical features in sCJD

Clinical feature	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Dementia	96%	10%	69%	40%
Myoclonus	87%	45%	77%	61%
Cerebellar signs	65%	67%	81%	47%
Visual problems	63%	89%	93%	53%
Pyramidal signs	54%	64%	77%	39%
Parkinsonism	20%	71%	60%	29%
Akinetic Mutism	53%	86%	89%	46%

Dementia was the most sensitive sign for sCJD but had extremely low specificity at 10%, reflecting the fact that almost all referred Definite Cases and Non Cases had dementia. Therefore it was not a valuable discriminating sign in the context of suspected sCJD referrals. The most specific clinical feature was visual disturbance (89%) whereas myoclonus had a low specificity at 45% despite high sensitivity. This low specificity might be explained by the observation that myoclonus is a well known and characteristic feature of sCJD and its very presence can trigger CJD to be considered, sometimes even if the rest of the clinical picture is atypical.

Positive predictive value was highest for visual problems and akinetic mutism at approx. 90% and was greater than 75% for every feature except dementia and parkinsonism. Negative predictive values were consistently low implying that the absence of any one clinical feature does not reliably predict against the diagnosis of sCJD.

Summary of results on sCJD diagnostic criteria

- Current sCJD diagnostic criteria have a sensitivity of 72%, specificity of 79% and positive predictive value of 89%.

- Incorporation of CSF 14-3-3 into the diagnostic criteria has significantly improved sensitivity at the expense of a reduction in specificity and positive predictive value.

- Incorporating MRI into the diagnostic criteria would improve sensitivity and positive predictive value only slightly without any major impact on specificity (based on available data).

- In the context of the NCJDSU, dementia and myoclonus were highly sensitive but poorly specific features, whereas visual problems and akinetic mutism were more useful at discriminating sCJD from non CJD disease.

3C. Young sCJD patients

3.7   Demographics

Variant CJD tends to affect young adults whereas sCJD is extremely rare in the under thirties and uncommon under the age of fifty (fig 3.60). Therefore young sCJD patients are of great interest, particularly comparing cases before and after the onset of vCJD to see if there has been any change in their clinical phenotype. The number of young sCJD referrals (definite and probable) annually between 1993 and 2004 is shown in fig 3.61, where 'young' is defined as onset at or below the age of fifty.

Fig 3.60

Number of Sporadic and Variant CJD cases by 10 year age group: 1993-2004
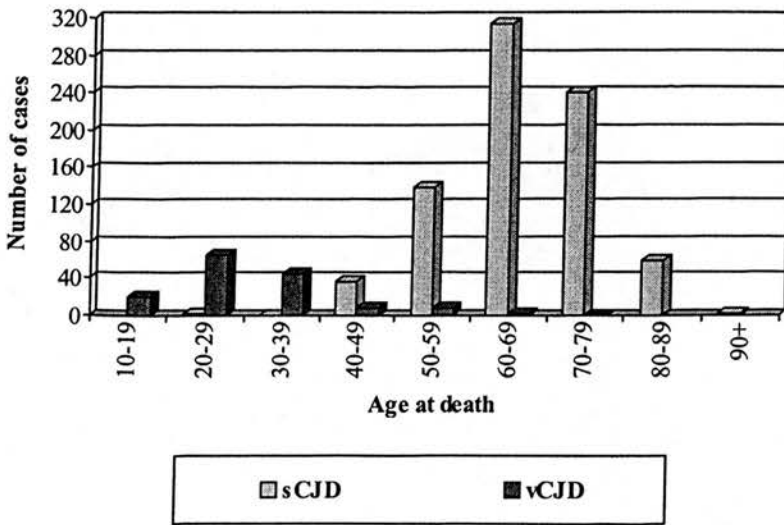
Fig 3.61

Number of young sporadic CJD cases referred annually in the UK
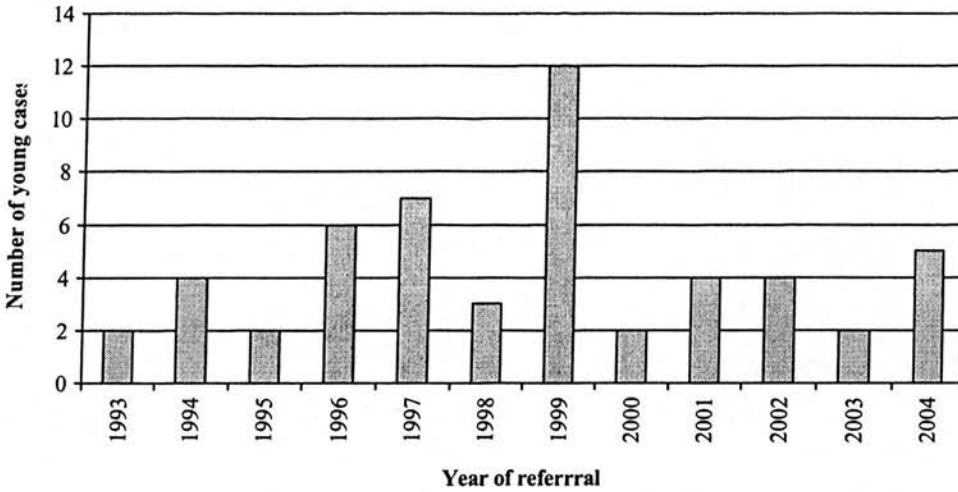
All sCJD cases aged fifty or under at onsets that were referred between 1993 and 2004 were reviewed. They were compared with a group of older sCJD patients, comprising Probable and Definite cases aged over fifty at onset referred in 1993/4 and 2003/4 (n = 210). There were 54 young patients, 46 (85%) of whom were ultimately classified as Definite and 8 (15%) remained Probable. The NCJDSU visited 40 (74%) cases while they were alive and the relatives were interviewed after death in a further 10 cases (19%). Only 4 patients (7%) had no visit at all.

Sporadic CJD was suspected in life in all but one instance. However, the possibility of vCJD was raised in many patients and was actually suspected by the visiting NCJDSU registrar in seven patients. Table 3.27 summarises the classifications made at the time of NCJDSU visit, or at referral if no visit occurred. The bold type denotes those where vCJD was considered to be the possible diagnosis. None of the young cases fulfilled the diagnostic criteria for probable variant CJD at any stage as no one had either a positive tonsil biopsy or the pulvinar sign on MRI. However, 19 (35%) met the criteria for Possible variant CJD based on their clinical features and illness duration greater than 6 months.

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Table 3.27 Classification of young and older onset sCJD at time of NCDSU visit

Classification at visit	No. of young sCJD Cases (%)	No. of older sCJD Cases (%)
Definite sCJD	14 (26%)	42 (20%)
Probable sCJD	11 (20%)	89 (42%)
Probable sCJD / Possible vCJD	**1 (2%)**	0 (0%)
Possible sCJD	13 (24%)	60 (29%)
Possible sCJD / vCJD	**3 (6%)**	0 (0%)
Unclear diagnosis ?sCJD	9 (17%)	18 (9%)
Unclear diagnosis ?sCJD / ?vCJD	**2 (4%)**	0 (0%)
Unclear diagnosis ?vCJD	**1 (2%)**	0 (0%)
Clinically not CJD	0 (0%)	1 (0.5%)
Total	54	210

In the majority of young sporadics the diagnosis was first suspected by a neurologist, similar to sCJD patients as a whole. Likewise referral was most frequently by neurology (table 3.28). 'Other' included one case where the diagnosis was first suspected by neuropsychology and another first suspected by a consultant in learning disabilities. One referral was made by a nurse.

Table 3.28 Who first suspected sCJD in young onset cases

	Individual first suspecting sCJD	Referrer to NCJDSU
Neurologist	45	40
Physician	3	4
Psychiatrist	1	0
Neuropathologist	2	7
Death Certificate	n/a	1
Other	2	1

Psychiatry only first suspected sCJD in one individual and did not refer any of the young cases. However, 44% (24) of the young sCJD patients were seen by psychiatrists at some point in their illness, most frequently in the early stages prior to diagnosing CJD because of concerns regarding depression and anxiety.

Mean and median disease durations were significantly longer in the younger patients using the Mann Whitney test (as duration was not normally distributed) (table 3.29).

Table 3.29 Disease duration in young compared to older onset sCJD

	Young sCJD	sCJD onset > 50 yrs	Significance
Mean disease duration	14.7 months	6.4 months	$p < 0.001$
Median disease duration	10.5 months	4.0 months	$p < 0.001$

3.8 Clinical features in young sporadic CJD patients

Fig 3.62 shows the clinical presentation of all the young sCJD patients compared to clinical presentation of the control group of older sCJD patients. The commonest clinical presentation in both young and older sCJD patients was with rapidly progressive dementia. The young cohort more frequently had a psychiatric or sensory onset (5.6% each) but this was still rare and not significantly different to the older sCJD cases. Presentation with 'other' symptoms not meeting any of the defined categories was also commoner in the young cohort. This included three patients with personality change (without clear cognitive impairment, one associated with painful cramps, two associated with fatigue), two presenting with reduced exercise tolerance and fatigue, two patients with visual disturbance (insufficient to meet a diagnosis of Heidenhain presentation) and one each of onset with headache, chorea and fatigue, progressive left sided weakness and numbness and episodic dysphasia and altered awareness. There were no statistically significant differences in clinical presentation with age.

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Fig 3.62

Clinical presentation in young patients with sCJD compared to patients >50 years at onset
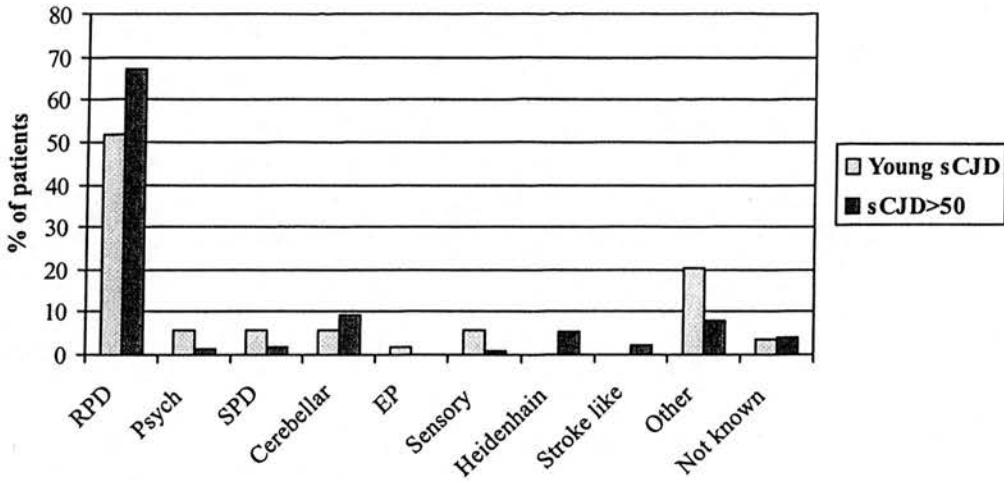
(RPD = rapidly progressive dementia, SPD = slowly progressive dementia, EP = extrapyramidal)

Fig 3.63 summarises the clinical features that were present at any stage of illness in the young sCJD cohort compared to sCJD cases with onset age greater than 50 years. Generally the two groups were clinically similar with dementia and myoclonus being almost universally present irrespective of age. Sensory and psychiatric features were of particular interest as these are more characteristic and common in vCJD than sCJD. In vCJD sensory symptoms need to be persistent and painful in order to fulfil the criteria. The only significant difference between the young and older sporadic cohorts related to sensory symptoms, which were more frequently reported in the young cases (35% v 11%, $p < 0.0001$ χ^2). These sensory symptoms were persistent and painful* in 19% (10 cases). Psychiatric features (depression, anxiety, psychosis) were present in slightly more young sCJD patients than older ones (44% v 33%) but this was not significant.

*Using the same definitions as vCJD criteria. i.e. frank pain and / or dysaesthesia. 'Persistent' is not clearly defined in the vCJD diagnostic criteria so this study used sensory symptoms reported on two or more separate occasions, or described as longstanding, persistent or present over weeks to months

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Fig 3.63

**Clinical features present at any stage in young sCJD compared
with sCJD cases aged > 50 yrs at onset**
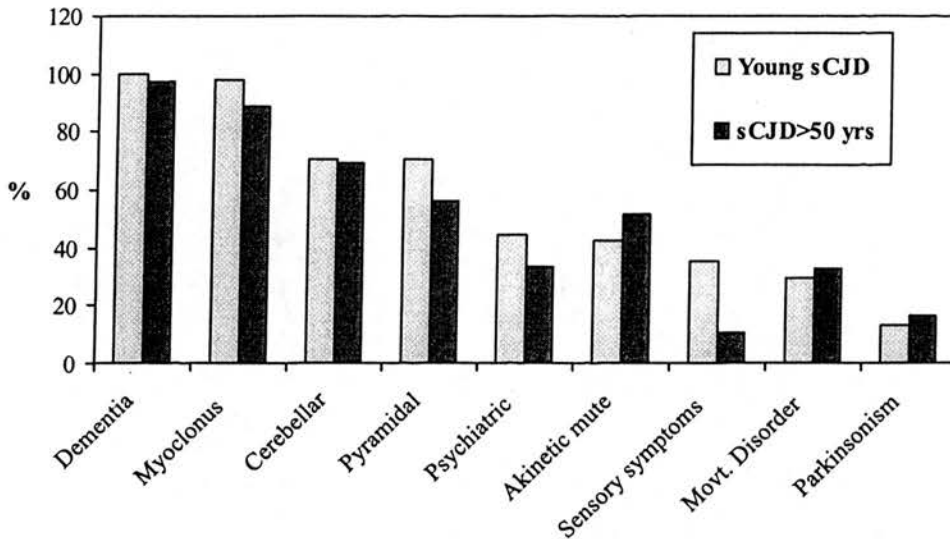
* Movt. disorder = movement disorder other than myoclonus

3.9 Investigations in young sporadic CJD patients

The young sCJD patients were investigated in a similar manner to older sCJD cases but, as might be anticipated, they were more thoroughly investigated. 98% had one or more EEG (compared to 92% of sCJD cases aged greater than fifty years at onset from 1993/4 and 2003/4 referrals), 91% had CSF analysis (compared to 81% of older Cases) and 87% had an MRI (compared to 69% of older Cases). The investigation results in young sporadic patients compared to older cases are summarised in table 3.30. Statistically significant results are in bold type. EEG was less likely to be typical in young sporadics compared to the older control group ($p < 0.001$ χ^2). CSF 14-3-3 result was more frequently negative in the young sCJD cohort compared to the older patients ($p = 0.005$ χ^2). In young sporadics fewer MRIs demonstrated caudate and putamen high signal and a slightly higher proportion had cortical hyperintensity than in the older onset cases but these findings did not reach statistical significance.

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Table 3.30 Comparison of investigation results in sCJD with onset less or greater than 50 years

Investigation	Young sCJD		Older sCJD control group	
EEG	Typical	**20%** (n = 10)	Typical	**39%** (n = 78)
CSF	**14-3-3 +ve**	**70%** (n = 21)	**14-3-3 +ve**	**98%** (n = 92)
	S100 < 0.38	8% (n = 2)	S100 < 0.38	5% (n = 4)
	0.38 - 1.0	36% (n = 9)	0.38 - 1.0	37% (n = 32)
	> 1.0	56% (n = 14)	> 1.0	58% (n = 50)
	wcc < 5	100% (n = 49)	wcc < $5x10^9$	98% (n = 173)
			5 - 10 x10^9	2% (n = 4)
	protein < 0.5	77% (n = 36)	protein < 0.5	63% (n = 92)
	(g/L) 0.5 - 1.0	21% (n = 10)	(g/L) 0.5 - 1.0	33% (n = 48)
	> 1.0	2% (n = 1)	> 1.0	3% (n = 5)
MRI	Caudate / putamen hyperintensity 22% (n = 10)* Cortical hyperintensity alone 9% (n = 4)		Caudate / putamen hyperintensity 36 % (n = 49)** Cortical hyperintensity alone 4% (n = 5)	

* 7 confirmed at NCJDSU   ** 34 confirmed at NCJDSU

A limitation of evaluating investigation results in Probable and Definite patients combined is that classification as Probable relies on either a positive EEG or 14-3-3. However, if the Probable young sCJD patients were excluded the results were not markedly different. 16% (7) of the Definite cases had a positive EEG and 73% (16) had a positive 14-3-3.

13% (7 / 54) of the young patients had a brain biopsy compared to 4% (8 / 210) of older sCJD patients. 11% (6 / 54) of the young sporadics underwent tonsil biopsy and all were negative. Of these 6 only 2 met the clinical criteria for Possible vCJD. None of the older sCJD cohort was known to have had a tonsil biopsy. 76% of the young sporadic cases had an autopsy compared with 55% of the older sCJD cases.

Codon 129 genotype was determined in 80% of the young sCJD patients. Of those tested just over half were methionine homozygous and one third were valine homozygous. This compares with older sCJD patients where 61% of those tested were methionine homozygous and 23% were valine homozygous, but no results were available in a higher proportion of the older cohort limiting comparisons (fig 3.64). The differences in codon 129 distribution in young and older sCJD cases were not significant, either when codon 129 type was analysed as a whole (p = 0.47 χ^2) or when individual genotypes (MM, MV and VV) were compared (χ^2 p = 0.82, 0.82 and 0.23 respectively).

PrP type was only available in 13 of the young cases and approximately half were PrP type 1 and half PrP type 2A (n = 6 and 7 respectively). Kuru plaques were present in 4 young cases, absent in 38 and in 12 either no post mortem was performed or there was insufficient information to determine if plaques were present.

Fig 3.64

Codon 129 genotypes in young sCJD patients and sCJD patients greater than 50 yrs at onset
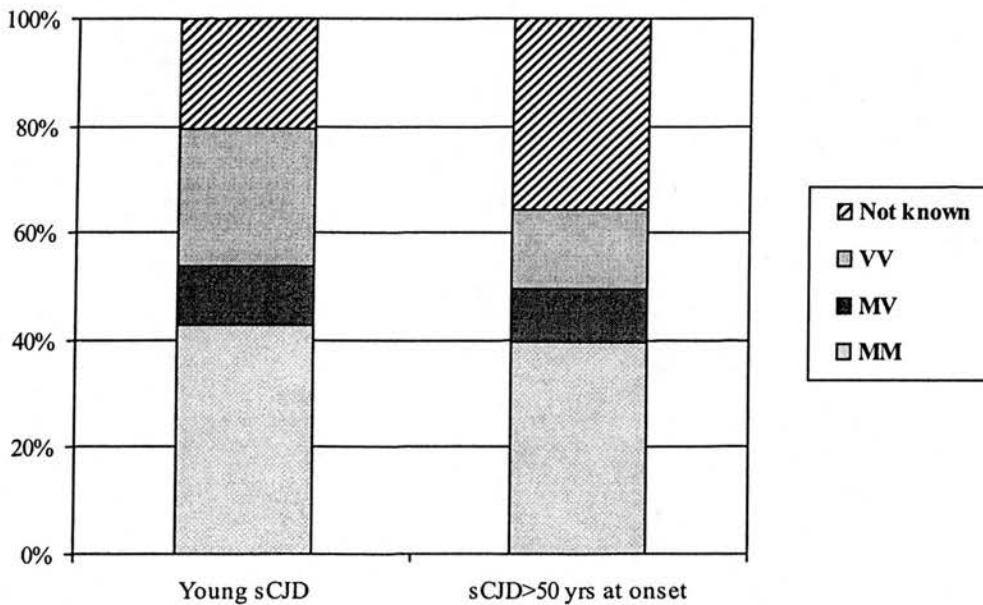
Summary of findings in young onset sCJD

- Sporadic CJD presenting at or below age fifty ('young sporadic') is rare but well recognised

- Young sporadic patients had a more prolonged disease course than older sCJD patients

- Clinical features did not significantly differ between young and older sCJD patients, with the exception of sensory symptoms, which were more frequently reported in young cases.

- Rapidly progressive dementia was the commonest presentation, irrespective of age.

- EEG was less often characteristic and CSF 14-3-3 less frequently positive in young sporadic patients.

- Young sporadic cases were more likely to undergo invasive investigation with brain and tonsil biopsies.

- Variant CJD was frequently suspected in young onset sporadic CJD patients, possibly by virtue of their age and disease duration.

3D. Sporadic CJD in the UK compared with EuroCJD nations

UK data was compared with results from the EuroCJD database for 1993 to 2004. French data was evaluated separately as France has had significantly more cases of vCJD than any country other than the UK, suggesting a higher level of exposure to BSE than the rest of mainland Europe. 'Other countries' includes Austria, Australia, Canada, Germany, Italy, Netherlands, Slovakia, Spain and Switzerland for the purposes of this analysis.

Mean age of onset of sCJD was similar in UK, France and 'other' countries (fig 3.65). Mean onset age was 65.9 years in the UK and 'other', and slightly (but not significantly) higher in France at 67.2 years. Similarly age at death was essentially the same in UK, France and 'other' sCJD cases (mean 66.6, 68.2 and 66.8 years in UK, France and 'other' respectively. Fig 3.66). Median disease duration remained stable at 4 to 6 months, irrespective of country of origin (fig 3.67).

Fig 3.65
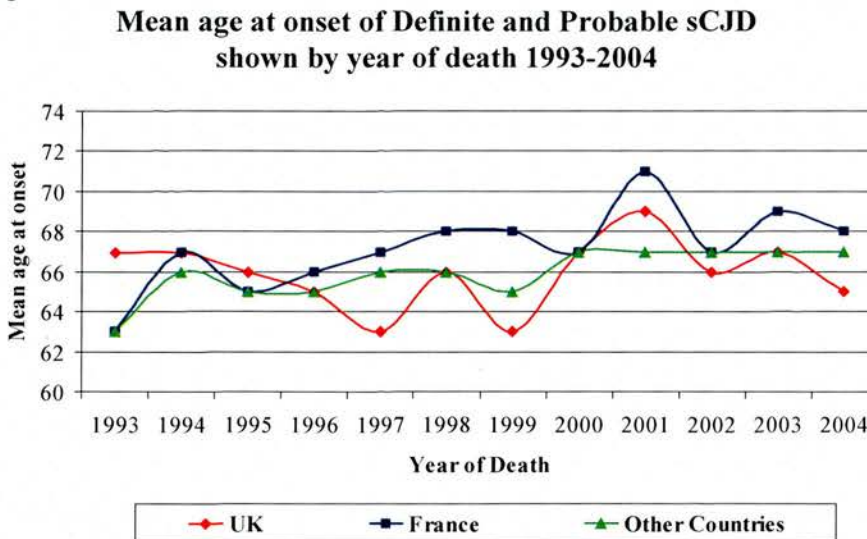
Mean age at onset of Definite and Probable sCJD shown by year of death 1993-2004

Other countries: Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

Fig 3.66

Mean age at death of Definite and Probable sCJD shown by year of death 1993-2004

Other countries: Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

Fig 3.67

Median duration of illness of Definite and Probable sCJD shown by year of death 1993-2004
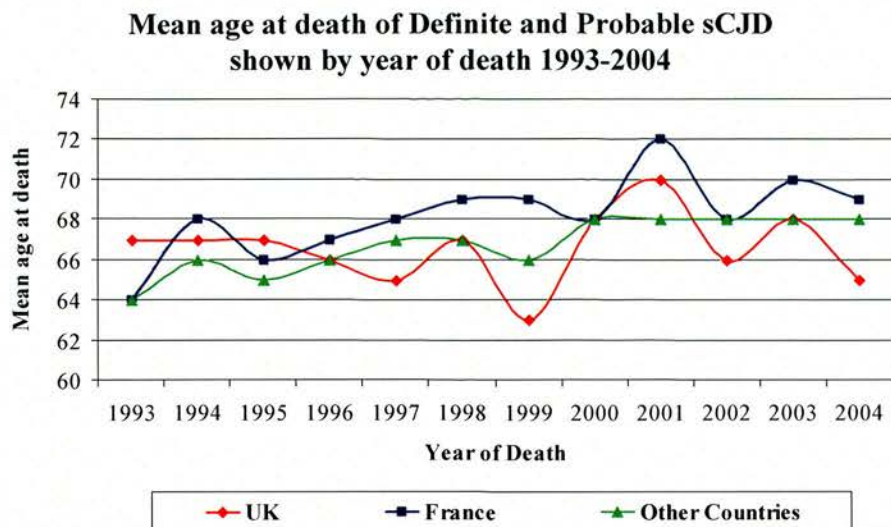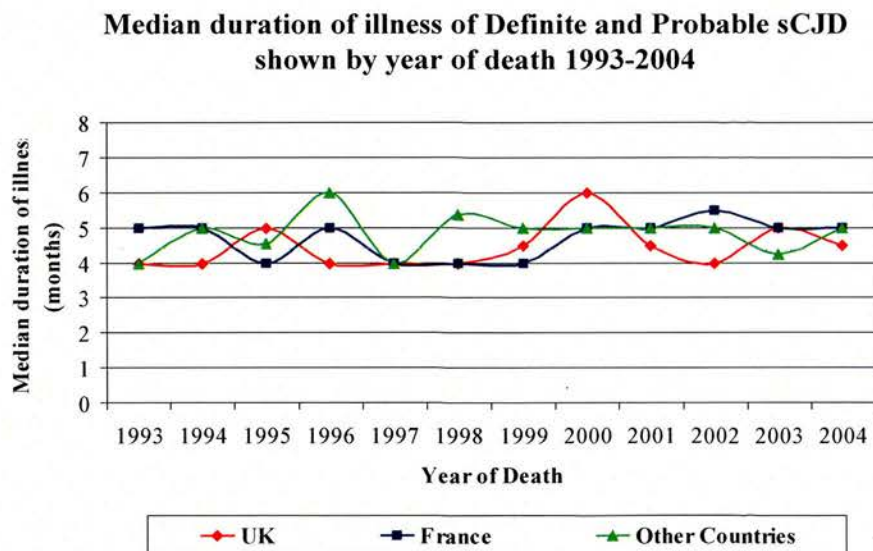
Other countries = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

Codon 129 distribution was compared in UK, France and 'other' sCJD populations. Overall France had a slightly higher proportion of cases where genotyping had been performed (76%) compared to the UK (66%) or other EuroCJD countries (63%).

There were no significant differences between the three geographical areas when the period 1993 to 2004 was assessed as a whole (figs 3.68 and 3.69). Considering sCJD cases where the *PRNP* genotype was known, the majority were methionine homozygous (61 - 67%), with the remaining 33 – 39% being divided fairly equally between methionine valine heterozygotes and valine homozygotes, irrespective of country of origin (fig 3.68).

When codon 129 distribution was examined by individual year the results were slightly different. The majority of cases were still methionine homozygous (MM), but in the UK and France there was a trend towards a smaller proportion of MM individuals with time (figs 3.70 and 3.71). Using logistic regression this was statistically significant (p = 0.004 for UK, p = 0.001 for France). However, the pattern of declining MM frequency was different in the two countries. In France the percentage of methionine homozygotes was stable between 1993 and 1998 and then dropped to a relatively stable, lower level between 1999 and 2004. In contrast in the UK there was a more general decrease in MM frequency which was most marked in 2003 and 2004. No significant decline in the proportion of methionine homozygous sCJD was observed in the other EuroCJD nations (fig 3.72).

When the same data was examined as actual numbers rather than percentages additional information becomes available (figs 3.73, 3.74 and 3.75). In France the number of Cases undergoing genotyping increased steadily year on year with the exception of 2004, but the actual number of MM patients was relatively static each year whereas numbers of MV and VV Cases increased. In contrast, in other EuroCJD countries the absolute number genotyped gradually increased with time up until 2003, but the numbers of MM, MV and VV all increased resulting in the percentages remaining fairly constant. In the UK the figures were more variable between years with less distinct patterns. However, overall they resemble the French findings, with a trend towards more Cases being genotyped, more MV and VV patients and relatively stable numbers of MM sCJD Cases with time.

Fig 3.68
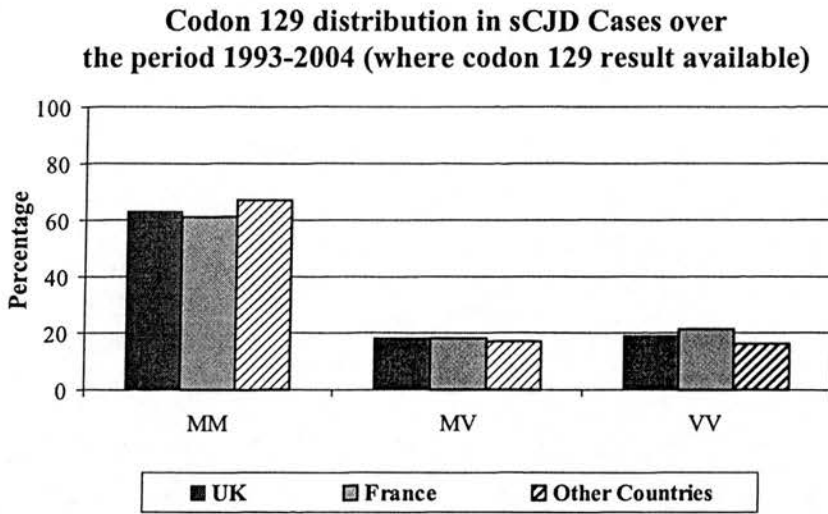
**Codon 129 distribution in sCJD Cases over
the period 1993-2004 (where codon 129 result available)**

Other countries = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia,
Spain, Switzerland

Fig 3.69

Codon 129 distribution over the period 1993-2004: all sCJD cases

Other countries = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia,
Spain, Switzerland

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Fig 3.70

Codon 129 distribution in sCJD cases in UK (where codon 129 result is available[1]) over the period 1993-2004

[1]codon 129 result is available for 76% of the French sporadic cases.

Fig 3.71

Codon 129 distribution in sCJD cases in France (where codon 129 result is available[1]) over the period 1993-2004

[1]codon 129 result is available for 76% of the French sporadic cases.

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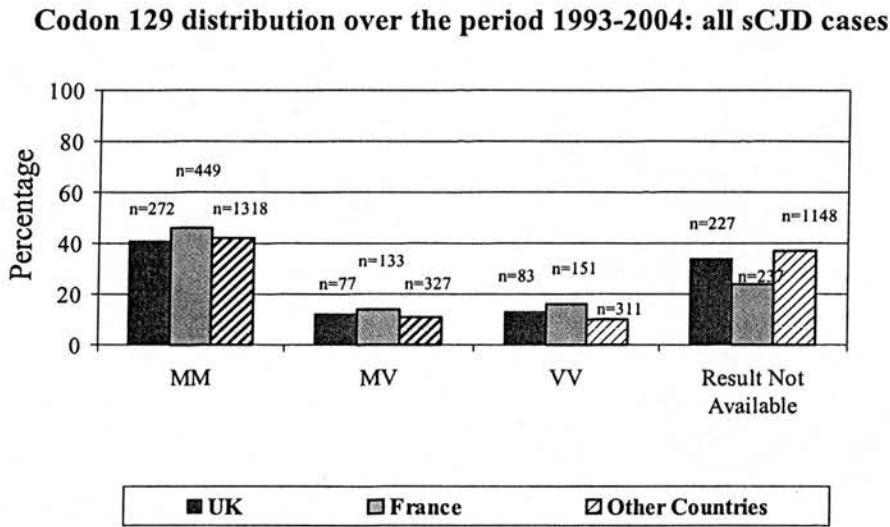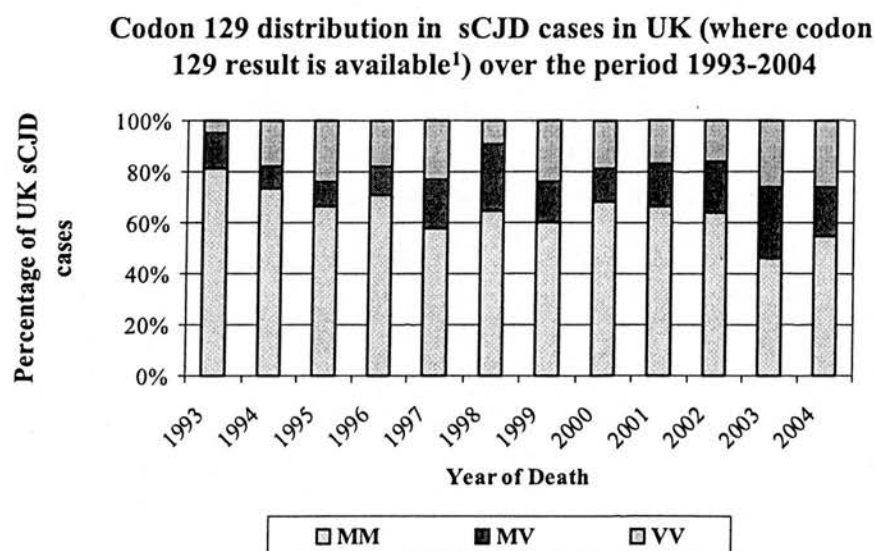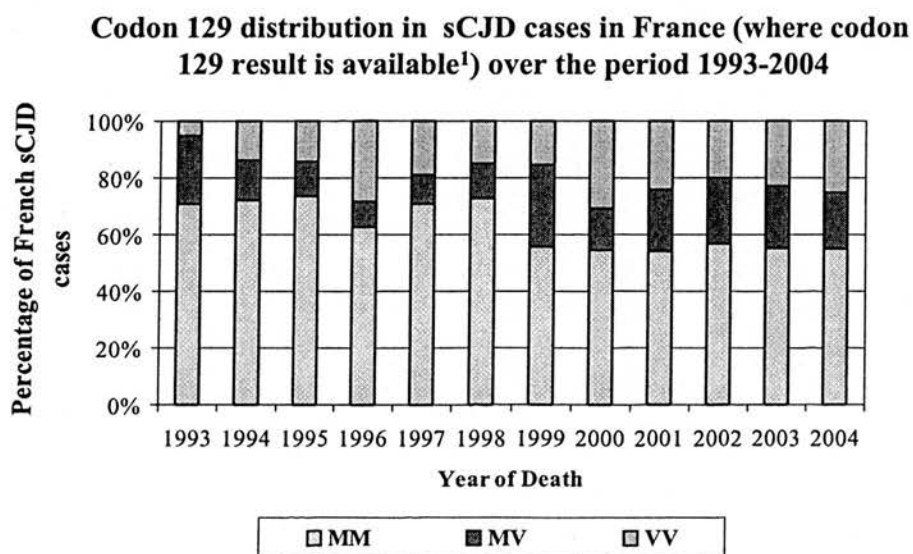
Fig 3.72

Codon 129 distribution in sCJD Cases in 'other countries' (where codon 129 result is available[1]) over the period 1993-2004
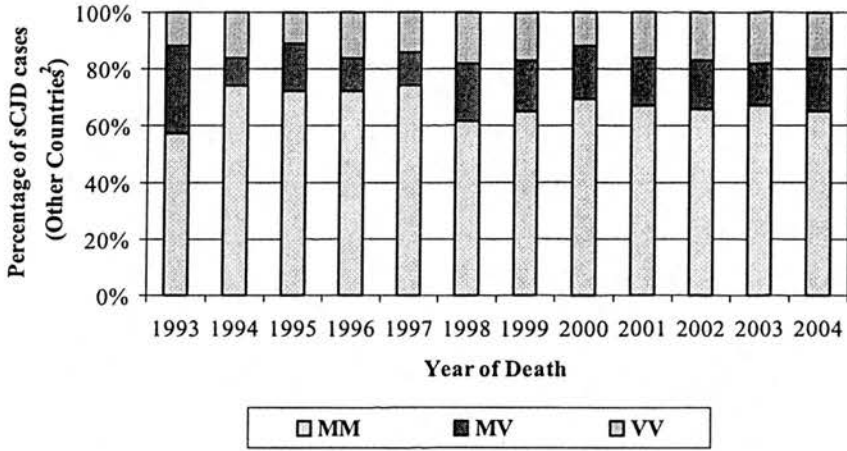
[1]codon 129 is available for 63% of sCJD cases.
[2]Other countries = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

Fig 3.73

Codon 129 distribution in UK by year and number of sCJD Cases

Fig 3.74

Codon 129 distribution in France by year and number of sCJD Cases

Fig 3.75

Codon 129 distribution in other EuroCJD countries by year and number of sCJD Cases
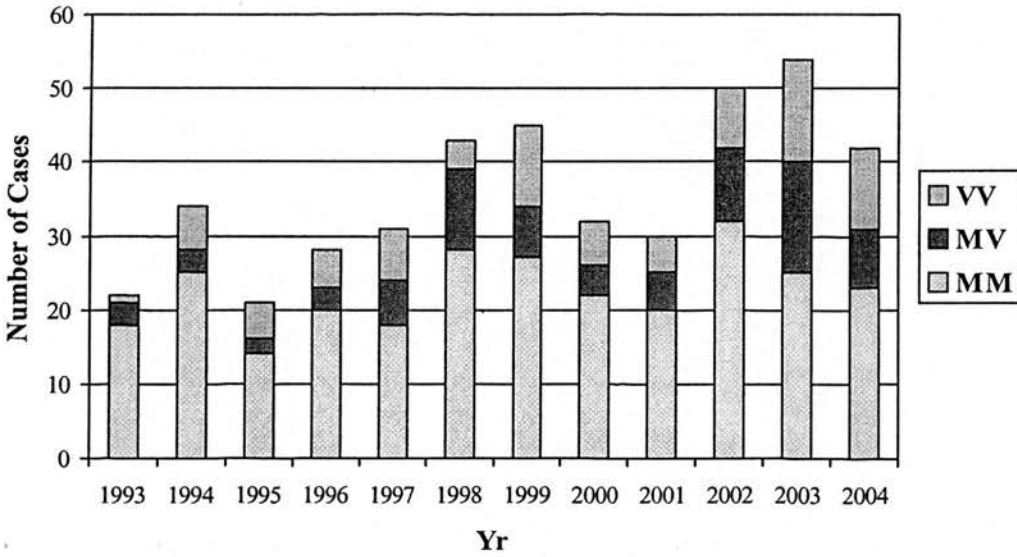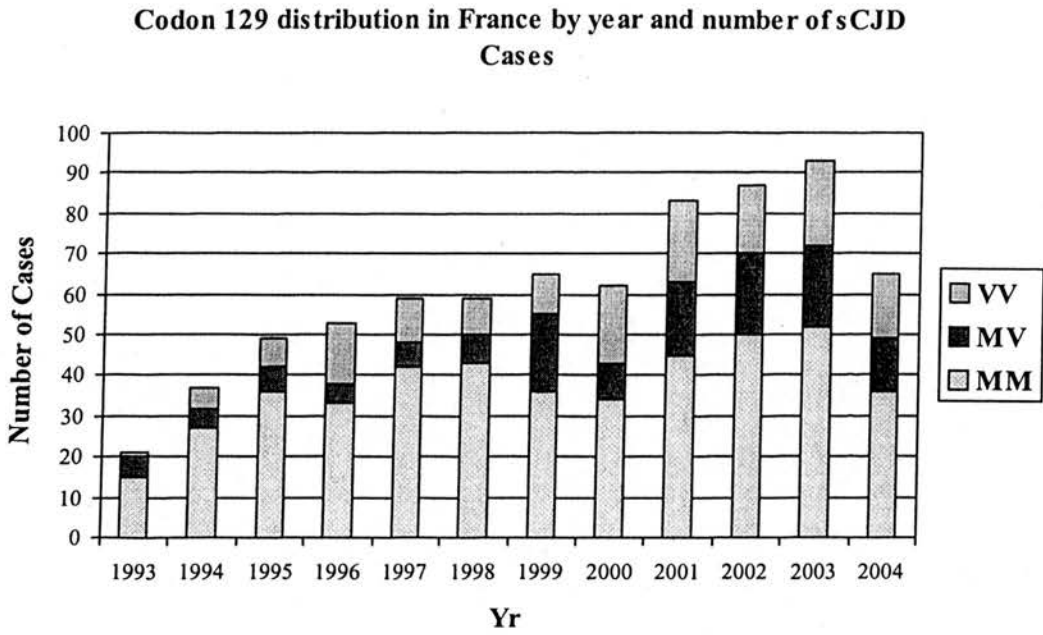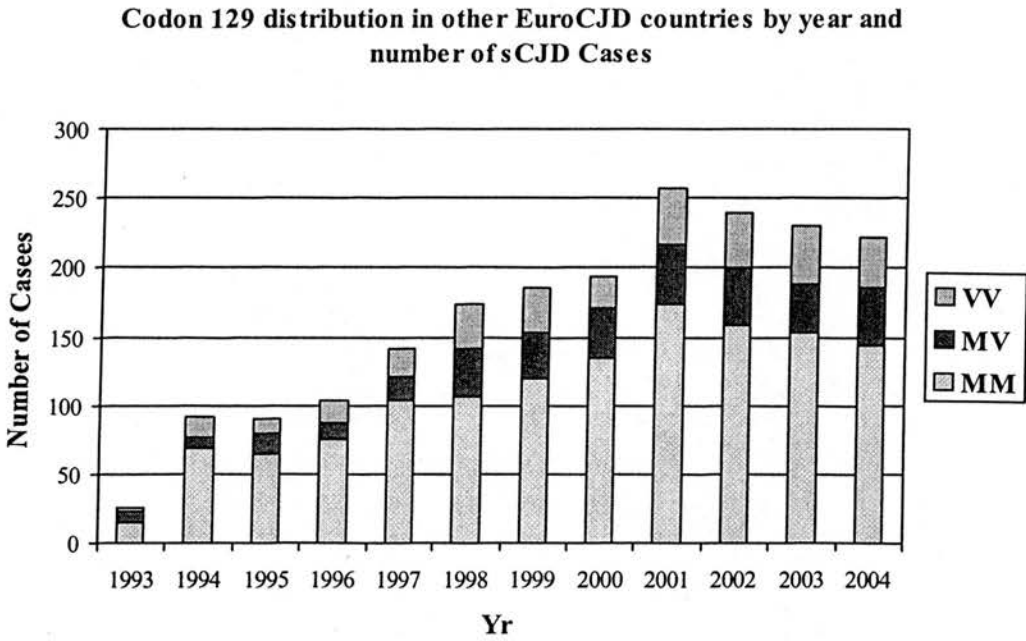
PrP isotype was compared between the UK, France and 'other countries' between 1993 and 2004. However, conclusions are limited by the fact that PrP type was known in less than a third of sCJD cases in each geographical data set. Generally PrP type 1 predominated, particularly in 'other countries', with a smaller proportion being PrP

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type 2A and a minority having a mixture of type 1 and 2A (figs 3.76, 3.77 and 3.78). No cases were identified as having PrP type 2B, which is associated with vCJD. There were no statistically significant geographical differences (χ^2 p = 0.1).

Fig 3.76

PrP isotype in sCJD Cases in the UK[1] by year of death
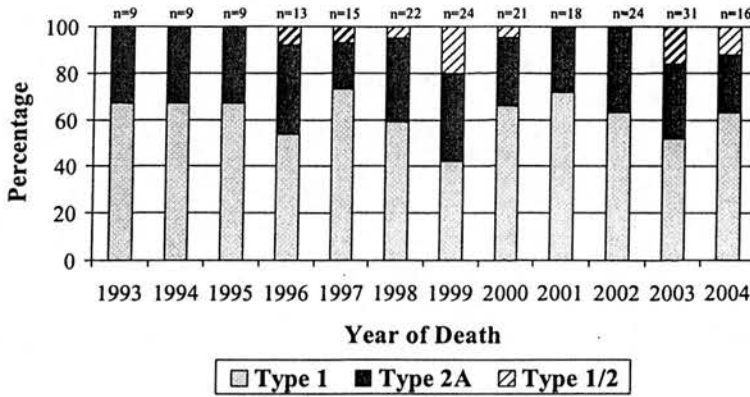
*PrP isotype is available for 32% of the UK sporadic cases

Fig 3.77

PrP isotype in sCJD Cases in France[1] by year of death
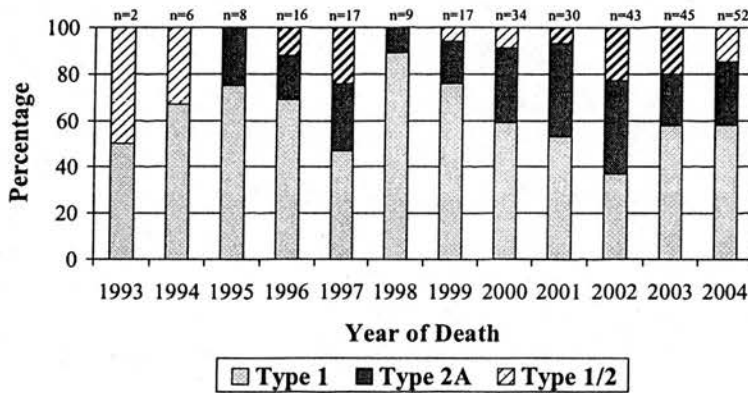
*PrP isotype is available for 29% of the French sporadic cases

Fig 3.78

PrP isotype in sCJD Cases in 'other countries'[1] by year of death
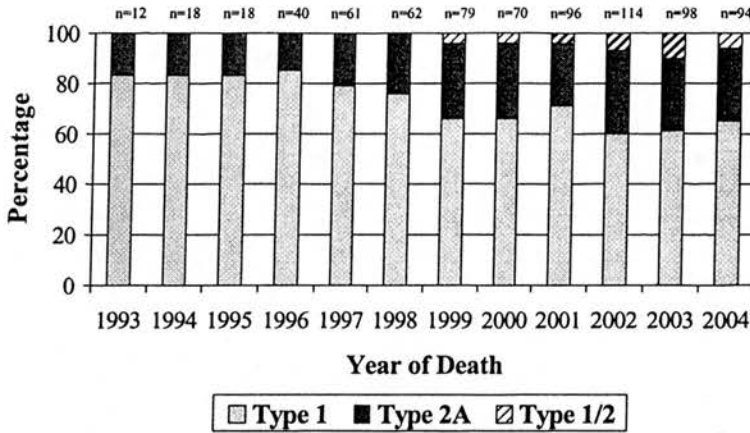
*PrP isotype is available for 25% of the sporadic cases in the other countries
(Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

Full Parchi subtype was only available for small percentage of sCJD cases (32% from UK, n = 209; 24% from France, n = 234; 21% from 'other', n = 661), and hence the absolute numbers of each subtype were relatively small. The UK Parchi type distribution was not significantly different from either France or 'other countries' (χ^2 p = 0.2). In each data set MM1 was most common, followed by VV2 and MV2, with the remainder of the subtypes generally comprising 5% or fewer of the cases (fig 3.79). A higher proportion of French patients were MM1/2 than elsewhere, probably reflecting the slightly higher incidence of mixed PrP isotypes in France.
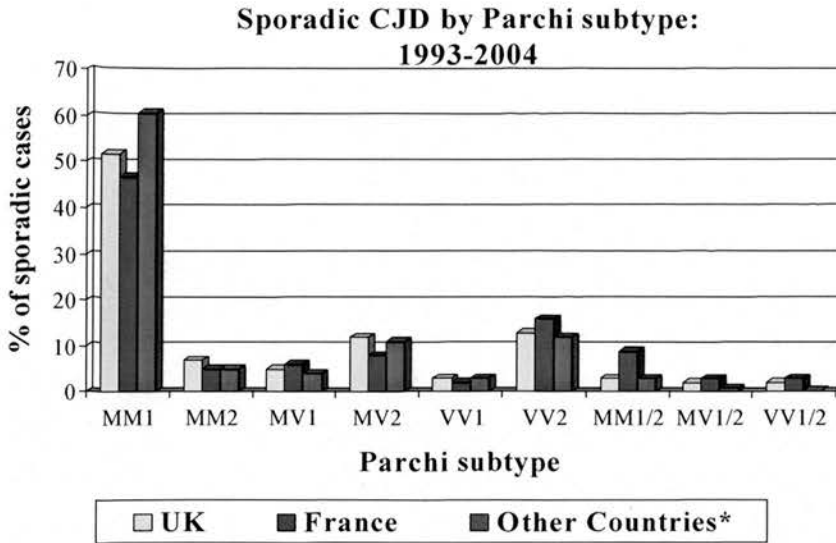
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Fig 3.79

Sporadic CJD by Parchi subtype: 1993-2004

*Other countries = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

Summary of comparison between UK, France and 'other' EuroCJD data between 1993 and 2004

- Overall the sCJD data obtained from the UK, France and 'other' EuroCJD nations were similar.

- There were no significant differences in age of onset, disease duration, PrP type or Parchi subtype distribution between the three geographical areas.

- In the UK and France the proportion of codon 129 methionine homozygotes decreased with time. This was not seen in 'other' EuroCJD countries.

Chapter 4: Discussion and Conclusions

A. Discussion

4.1 The study population

The principal study group comprised patients referred to the NCJDSU in 1993, 1994, 2003 and 2004. The latter two years were chosen because data collection began in 2005 and these were the most recent completed years. 1993 and 1994 were selected to represent suspect sCJD referrals prior to identification of vCJD, plus they provided a study period spanning a decade of CJD surveillance. The UK population was probably exposed to BSE from as early as 1980 (224) but it was not possible to use referrals from this time as UK - wide prospective surveillance was only commenced in 1990. Prior to 1990 surveillance was either retrospective or confined to England and Wales so meaningful comparisons with current data would be limited. The earliest years of UK - wide prospective surveillance were not chosen simply because it takes time for a surveillance programme to become established and by selecting the very early years one might miss many suspected cases due to doctors' lack of awareness of the NCJDSU. Two year time periods pre and post vCJD were used rather than a single year in order to increase the amount of available data.

A more restricted data set was collected on all sCJD Cases dying between 1993 and 2004 inclusively, in order to assess trends over this period. Ideally a full data set would have been collected for each year but this was not possible due to time constraints. The restricted UK data from 1993 to 2004 was compared with corresponding figures from the EUROCJD database for the same time period. The aim was to identify any trends confined to the UK, or possibly the UK and France, that might be attributable to BSE exposure. EUROCJD Cases are collated by date of death rather than referral date, so date of death was also used for UK Cases between 1993 and 2004 inclusively in order to facilitate direct comparison of data. However, date of referral was used for the principal study group (1993/4 and 2003/4) because individuals that ultimately were felt not to have sCJD (Non Cases) were included and might have otherwise been missed because they recovered or had extremely prolonged illnesses. Similarly a key aim of the study was to identify changes in sCJD

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characteristics with time, particularly those that might relate to BSE, so it was sensible to use date of referral rather than death in case disease duration has become more prolonged with time akin to vCJD.

Data collection based on referrals to the NCJDSU may potentially bias towards patients suspected and referred by neurologists as opposed to other clinicians, because only neurologists receive letters reminding them of the existence of the unit. Therefore it is possible that cases not referred to neurology are being missed, potentially including older individuals who may be more likely to see geriatricians, and individuals with a psychiatric onset who are managed by psychiatrists. However, it is unlikely that significant numbers are being overlooked. A systematic study reviewed autopsies on 308 patients with dementia in a geriatric hospital and 137 elderly patients with dementia in a psychiatric institution and only one case of sCJD was confirmed (225). In another study one physician visited all Parisian nursing homes searching for previously unidentified cases of sCJD and found none (226).The characteristic rapidity of the disease course in sCJD and the evolving neurological picture means that most affected individuals will be brought to the attention of a neurologist at some stage, even if the onset is not clearly neurological. This assumption is supported by the fact that a neurologist saw over 90% of all suspect sCJD referrals in this study. A review of French CJD patients between 1968 and 1977 found that all were reviewed by a neurologist, although admittedly this might be a self-fulfilling prophecy as other cases might be missed (227).

There are also a number of safety nets to reduce the chances of missed referrals. Any patient who has a death certificate diagnosis of 'CJD' or 'dementia in CJD' (ICD 10 codes A81.0 and F02.1) will be automatically notified to the NCJDSU, the notes obtained and the case classified according to the diagnostic criteria. Even if the diagnosis is not suspected in life UK neuropathologists are aware of the need to notify cases they identify at autopsy. Neuropathology remains an important component of cases ascertainment, particularly in atypical presentations. Obviously if the diagnosis of prion disease was never suspected in life and no post mortem was performed then such individuals would not be identified in this study, but this is unavoidable and likely to be a rare scenario. (The overall post mortem rate in CJD suspects in the UK is approximately 70%).

Use of the NCJDSU database implies that the only Non Cases included are those where there was a reasonably high suspicion of sCJD. There are likely to be many

more patients where sCJD was briefly considered but excluded on clinical or investigation grounds prior to a referral being made. However, this in itself is not a significant flaw of the study as the Non Cases clinicians are particularly interested in are those where there is real diagnostic confusion rather than more straightforward cases where an alternative diagnosis is readily apparent.

For the purposes of this study Cases were defined as individuals fulfilling WHO criteria for Definite or Probable sCJD (see appendix for definitions). Cases were then scrutinised both as one group and separately as Definites and Probables. This was to minimise potential bias from concentrating on either Definite or Probable patients in isolation. For example, Definite sCJD patients may differ from sCJD as a whole because younger individuals and those with less typical disease courses may be more likely to undergo autopsy and hence be classified as Definite. Conversely relying on Probable patients may bias towards those with characteristic clinical features. There is the additional problem that the WHO definitions of Probable and Possible sCJD are based on various clinical features and investigation results. Therefore it is difficult to study frequency of these same features in these classifications, as it becomes a self-fulfilling prophecy. In order to assess validity of the diagnostic criteria Definite sCJD patients must be used as neuropathology remains the gold standard in diagnostic terms. However, it is not sensible to rely on Definite, pathologically proven sCJD cases when a new BSE phenotype is being sought, because if this phenotype is associated with novel pathology then this might exclude the very individuals that the study is aiming to identify.

As a result of these potential problems this study evaluates Definite, Probable, Possible, Unclear and Non Cases either separately or in combination depending on the question being addressed.

Genetic analysis to exclude familial prion disease was only performed in around half (52%) of all suspect sCJD referrals in this study and in 65% of Cases. Therefore it is possible that a small number of genetic CJD patients have been included accidentally. Pathological appearances and family history can also provide clues to genetic CJD but neither is completely reliable. One case had pathological appearances suggesting familial rather than sporadic CJD but underwent formal genetic analysis of the prion protein gene on two occasions with no mutations identified. A further case was initially felt to have a pattern of PrP staining reminiscent of an insertional mutation but on review was deemed pathologically more consistent with atypical sCJD. No

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genetic analysis was performed but the patient had no family history of CJD or other dementia and died at the age of 88.

At the time of referral no individuals included in this study were known to have a family history of CJD but at a later date one individual was identified as having an estranged sister who had died of pathologically confirmed fCJD with the E200K mutation. Unfortunately no genetic material was available on the study case so she remains classified as sCJD, but in all likelihood she too was a familial E200K case. Interestingly her brain pathology was entirely consistent with sCJD as is often the case with E200K mutations, illustrating the point that pathological appearances do not reliably discriminate between sporadic and genetic prion disease. Thus it is probable that one familial CJD patient has been included in this study but it is unlikely that many other genetic cases have been included. Therefore this is not likely to significantly impact on the conclusions.

4.2 Limitations related to data collection and documentation

There are numerous potential pitfalls inherent in any surveillance system that relies on collecting data provided by a third party, in this case usually the next of kin. Whilst various strategies were applied to try and minimise these problems they were not altogether avoidable.

4.2.1 Quality of data

First and foremost the quality of the data varies widely between individual cases. This is influenced by a number of factors including the degree of closeness of the next of kin and their ability to recall and recount a clear history in an often emotionally charged interview. Usually the NCJDSU registrar interviewed a partner or adult offspring who was frequently, but not invariably, in close contact with the patient. Occasionally the relative was more distant and could provide a less detailed history, particularly if they lived many miles away and relied on telephone calls to keep in touch. Given the nature of sCJD it was rarely possible to elicit any reliable story from the patient directly. Obviously less information was available on the minority of Cases that were never visited but this should not alter the conclusions when comparing Cases in 1993/4 and 2003/4 as similar numbers were not visited (6.1%, n =

6, and 5.4%, n = 7 respectively). It is more relevant when comparing Cases and Non Cases as significantly fewer Non Cases were visited by the NCJDSU registrar (94% of Cases visited versus only 34% of Non Cases).

To try and reduce these problems hospital notes were used as a source of back up information but again the information available was of variable quality. This was influenced by the thoroughness of the doctor admitting the patient, the degree of speech and cognitive problems at admission and the standard of documentation generally. It was not possible to eliminate these variables. Some patients were initially admitted to a district general hospital before being transferred to a tertiary centre, and occasionally the initial set of hospital notes were incomplete or unavailable, despite being requested by letter.

4.2.2 Modifications to the questionnaire

The NCJDSU registrar uses a questionnaire during the interview to provide a partially standardised approach. However, the bulk of the information still comes from a general, unstructured conversation with the family and is recorded as free text. Specific questions are posed in the questionnaire and should therefore be addressed in all cases. These questions have been modified with time, due to the questionnaire being altered in 1997 to a more detailed format. For instance the original questionnaire set up in 1990 asked specifically about weight loss, depression, odd behaviour and sleep disturbance. The revised questionnaire introduced in 1997 omits weight loss and sleep disturbance but includes extra questions on symptoms including visual disturbance, speech disturbance, hallucinations and dizziness. The 1997 questionnaire also has a section on physical signs where the registrar documents presence / absence / unsure for each sign. In contrast the earlier questionnaire was less structured with a free space for examination on admission and progression of signs (see appendix for copies of questionnaires). Therefore, it is likely that certain clinical features are documented with greater or lesser accuracy at different times, reflecting changes in the interview process rather than any real differences in the underlying disease. However, this is unlikely to be a problem with the most characteristic clinical features of sCJD (such as dementia and myoclonus) as these will be inquired about and documented in the vast majority of cases, irrespective of the questionnaire.

4.2.3 Inter - registrar variability in data collection

Different NCJDSU registrars have slightly different approaches to the interview. The sCJD referrals used in this study have relied on the work of ten doctors, but predominantly five registrars who covered 1993/4 and 2003/4. There is some 'on the job' training such that a new registrar accompanies an established registrar on a visit to watch an interview and to standardise techniques and data collection where possible. However, it is inevitable that each registrar will work slightly differently and interpret information in subtly different ways. To a degree this is minimised by the consultant input, which has remained relatively stable since the NCJDSU was established, with one consultant being present since 1990 (RGW), and the other since 1997 (RK).

4.2.4 Dates

It was frequently difficult to precisely date the onset of various sCJD symptoms and the illness itself. This was due both to the lack of definite history from relatives plus the inherent difficulty in dating onset of an illness beginning with subtle features such as altered personality and mild forgetfulness. In most instances I accepted the decision of the registrar who visited the patient, only altering their estimates of dates if further information was available at a later time which clearly contradicted their opinion. An approximate system was used to record dates (to the nearest 1st, 15th or 30th of the month) as anything more precise was judged unreliable.

4.2.5 Clinical features

Whilst some symptoms and signs were relatively clear cut (e.g. headache, myoclonus) others were more subjective. Precise definitions were employed to minimise this subjectivity; for instance to be classified as having pyramidal signs a patient required at least two of increased tone (and / or clonus), hyperreflexia, extensor plantar (s) and pyramidal pattern weakness. However, some signs were less easy to define and required the examining doctor to make a judgement (e.g. akinetic mutism, cortical blindness). It is possible that different registrars have been more or less stringent when assessing these features, thus introducing potential bias.

4.2.6 Absence of a clinical feature versus insufficient information

An additional problem is that lack of documentation of a sign does not necessarily equate to absence of that sign. It may be that the registrar omitted to record a positive finding, particularly with 1993/4 referrals when the questionnaire was less structured. Thus more signs may have been erroneously analysed as being absent in 1993/4. Similarly suspect sCJD patients that were never visited by the NCJDSU may be more likely to have negative results, and this is particularly relevant because 66% of Non Cases were not visited, compared to only 6% of Cases.

Timing of the visit also influences this. For instance patients seen only in the earlier stages of disease are less likely to demonstrate late signs such as akinetic mutism. The amount of extra information obtained after the visit is usually minimal, especially if a diagnosis has been made. Conversely suspected sCJD cases seen in the late stages may not demonstrate certain signs due to the limitations of the examination; e.g. cerebellar signs. It is plausible that patients with a more rapidly progressive disease course and those that are referred late are therefore getting a skewed assessment. Ideally the hospital notes provide extra information about signs in the earlier stages of the illness but this is not infallible.

For the purposes of analysis absence of a sign, insufficient information and 'unsure' were all treated as a single category. However, one has to remain aware of the limitations of this strategy.

4.3 Overview of 1993 to 2004 and demographic data in 1993/4 and 2003/4

4.3.1 Incidence

The annual number of referrals to the NCJDSU has gradually increased between 1993 and 2004, with the exception of a dip in 2004. This pattern might reflect a true increase in disease incidence or simply improved case ascertainment. The latter explanation appears more likely for a number of reasons.

Fig 4.1
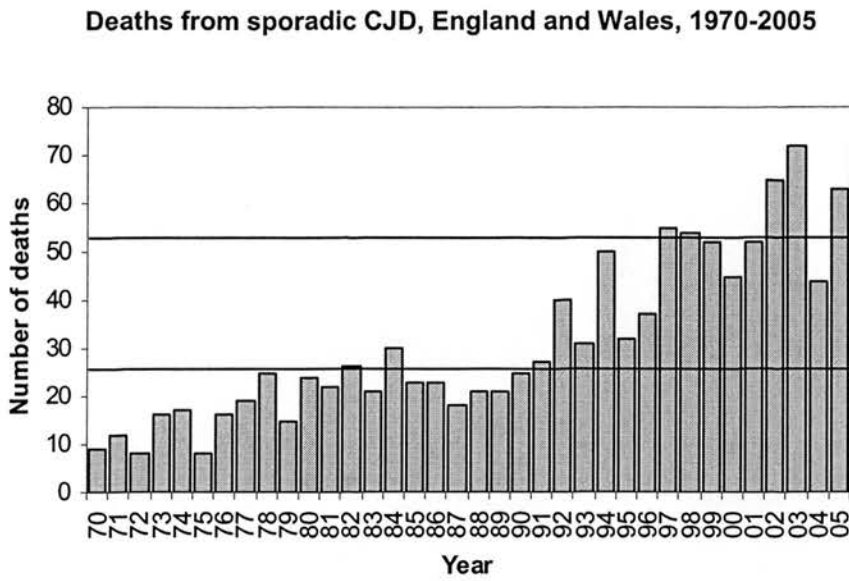
Deaths from sporadic CJD, England and Wales, 1970-2005

With time the NCJDSU has become established and clinicians are more aware of its existence and the need to refer suspected CJD cases. The number of reported deaths from sCJD has actually been increasing in the UK since surveillance began in 1970 (fig 4.1). Other countries' CJD surveillance programs have experienced similar increases in referral rates over the early years as they become established (69, 228, 229). The emergence of vCJD in 1996 may have also contributed to the apparent rise in incidence in the UK as it prompted a letter to all clinical neurologists, further increasing the profile of the surveillance unit. In addition vCJD was hitting the headlines in the media, increasing public awareness of prion disease in general. It is worth noting that the biggest increase in referrals occurred in 1997, just after vCJD was identified.

Investigations and diagnostic tests for sCJD have also improved with time, in particular the introduction of CSF 14-3-3 testing and increased sensitivity and availability of MRI. All these factors help explain an increase in sCJD case ascertainment with time.

Alternatively the increase in the figures may represent a real rise in disease incidence, either of sCJD itself or a new, possibly BSE - related illness, that is being misdiagnosed as sCJD. However, there is little evidence to support this. Other western countries with surveillance systems have observed similar increases in sCJD case load despite a low frequency of BSE in the cattle population (228, 230). This would be against a BSE associated condition, where one might predict a more isolated increase in the UK. Underlying this is the problem that the aetiology of sCJD remains obscure. Therefore it is possible that sCJD incidence is truly increasing throughout Europe due to some, as yet, unidentified factors. One analysis has shown that the time dependant increase in sCJD in the UK since 1970 would fit equally well with two statistical models; either improved case reporting with time or an increase in an (unidentified) cohort factor over time (131).

When the 1993/4 and 2003/4 figures are analysed in more depth it is apparent that much of the increase is due to a rise in Probable classifications (from 13 to 53). This is likely to partly reflect the introduction of 14-3-3 testing in December 1996, resulting in Possible classifications being reclassified as Probables. However, this does not fully explain the increase as the number of Possibles has only dropped slightly (from 18 to 7).

The number of Non Cases has not changed significantly with time.

The slight dip in figures for 2004 is harder to explain but there are a number of possible interpretations. It may just be a one-off blip of no particular significance, but the NCJDSU figures for 2005 also show slightly fewer referrals than in 2002 and 2003, as do those from 2006 although these may still be incomplete. Alternatively it could be the start of a downward trend in referral figures. This might be due to worsening case ascertainment, possibly reflecting waning public and medical interest in CJD now the threat of a 'vCJD epidemic' seems remote, or a real reduction in sCJD numbers for some unknown reason. Certainly the practice of the NCJDSU has not significantly changed to explain any reduction. It is also unlikely to be an artefact of the study design because figures are based on annual referrals and deaths and data were collected up until the end of July 2005. For cases not referred in life date of death was used as referral date. By July 2005 all death certificate referrals coded for CJD in 2004 should have been received and all autopsy results from deaths until the end of 2004 would be expected to be available. However, reviewing the NCJDSU database up until May 2006 has revealed two further patients referred by death

certificate in 2003/4 as suspect sCJD. They were not included in the study database as the certificates were delayed and there was no information on these individuals at the time data collection stopped. Subsequently one has been provisionally classified as Possible sCJD and the other as a Non Case, but the information remains limited and neither family was visited. No new sCJD Cases referred in 2003/4 have been identified. As of January 2006 two individuals in the study database have been reclassified due to extra information becoming available. One patient was reclassified as Unclear diagnosis from Probable sCJD (based on clinical features and a positive 14-3-3 result), because disease duration exceeded two years. Another was changed from Unclear diagnosis to Probable because a characteristic EEG developed. Neither of these alterations significantly change the findings of this study.

Other countries with sCJD surveillance systems have occasionally reported years with reduced numbers of cases but there has not been a sustained decrease in any country (69).

The general overview data from 1993 to 2004 inclusively were identified by date of death whereas the more detailed data from 1993/4 and 2003/4 were collated by date of referral and the rationale for this was explained in section 4.1 of the discussion. However, it is worth noting that these differences in data collection did not significantly impact on the final results, trends and conclusions, as demonstrated in figs 3.1 and 3.2 of the results section looking at disease incidence by year of referral and by year of death. Given the short mean duration of sCJD of well under one year one would not anticipate any major differences with these minor alterations in data collection.

4.3.2 Gender

A slight excess of referrals and sCJD Cases were female, but this did not change significantly between 1993/4 and 2003/4. The gender differences were small and not significant. Similar minor differences have been reported in other studies e.g. Australia CJD surveillance 1970 - 2003 (52.4% female, 47.6% male), England and Wales 1970-79 (230, 74). There is no known scientific explanation as to why more females than males might contract sCJD and generally it is not considered to be a condition influenced by gender. In the USA the mortality rate from sCJD was slightly increased in women but this gender difference disappeared once death rates were

corrected for age, implying the increased female incidence related to their increased longevity (232). Female sex has been reported as a good prognostic factor and predictor of relatively prolonged survival in sCJD (72) but this should not significantly influence the study results as they refer to incidence rather than prevalence.

4.3.3 Age at onset and death and disease duration

The mean age at onset of sCJD has remained stable in the UK at 65 - 66 years without any significant change between 1993 and 2004. This finding is similar to the experience of other countries' surveillance programmes (233, 234, 235). If a novel BSE related disease was occurring and being misdiagnosed as sCJD one might expect the average onset age to decrease, as we know that vCJD tends to affect younger individuals with a mean age of 28 years (150, 158). However, there is no evidence for this. Similarly vCJD is associated with a longer median disease duration of 14 months (158, 161) but there is no suggestion that median disease duration is increasing in sCJD with time. It has remained constant at 4 to 5 months. Mean age at death from sCJD is also steady at approximately 66 years, reflecting the unchanging age at onset and illness duration.

There are differences between 1993/4 and 2003/4 referrals with respect to disease duration in Non Cases. In 1993/4 suspect sCJD referrals that were ultimately classified as Non Cases had significantly longer illness duration than equivalent Non Cases in 2003/4. The most likely explanation for this is improved awareness of the typical sCJD phenotype and therefore more informed referrals in 2003/4. If the disease duration for Non Cases is compared to Cases (for 1993/4 and 2003/4 combined) then overall Non Cases had a longer illness. This probably relates to the underlying diagnoses in the Non Cases. The commonest diagnoses in Non Cases are Alzheimer's disease and Dementia with Lewy Bodies and both of these are typically slower illnesses than sCJD.

Interestingly mean onset age was identical for Cases and Non Cases in 1993/4 and 2003/4 being 66 years in all categories. Possible referrals in 2003/4 and 'Unclear diagnosis' referrals in 1993/4 appeared to be slightly older with a mean of 72 years. However, these results were not statistically significant and were not sustained (in that Possible referrals in 1993/4 and 'Unclear diagnosis' patients in 2003/4 were not

associated with older age at onset). They are likely to simply reflect the small number of referrals in these categories with inevitable susceptibility to skewing of the mean by one or two outliers.

4.3.4 Post mortem rates

The annual post mortem rate for sCJD Cases was steady at approximately 85% until 2001 and since then there has been a decline to a low of 61% in 2003. However, this downward trend is not currently statistically significant. It reflects a more general trend of decreasing autopsy rates for all causes of death in the UK which has been variably attributed to declining clinical interest in autopsies, greater confidence in the diagnosis in life due to improved investigations, and recent organ retention 'scandals' (236). However, the sCJD post mortem rate is still significantly higher than most terminal illnesses including cancer and most types of dementia and this raises a potential problem. Whilst the majority of suspect sCJD cases still undergo autopsy this is not the case for many other neurodegenerative diseases. Conceivably sCJD might be missed if it was masquerading as a typical presentation of Alzheimer's disease for example. This is unlikely but cannot be fully excluded.

Diminishing post mortem rates in sCJD are not unique to the UK. One study based in New York state found that neurologists rarely or never used autopsy to confirm suspected CJD, due to a combination of family reluctance, infection control concerns and inadequate facilities (237).

The UK sCJD post mortem rate peaked at 95% in 1997 and it is possible this relates to the emergence of vCJD because the need for a definitive diagnosis was heightened at this time.

There are concerns that a CJD surveillance system concerned with identifying cases of vCJD may bias towards the identification of atypical presentations of sCJD, particularly young onset cases with prolonged illness courses. We know that such individuals are less likely to have the *PRNP* MM genotype. Interestingly this study did not detect any significant differences in the post mortem rate for the three different genotypes (results section 3.4.5). Similarly when UK data for sCJD autopsy rates by genotype are reviewed for all years between 1993 and 2006 there is no consistent difference between the three *PRNP* types (fig 4.2, data courtesy of Jan Mackenzie, NCJDSU).

Fig 4.2

Percentage of sCJD Cases with autopsy performed, by codon 129 genotype: 1993-2006
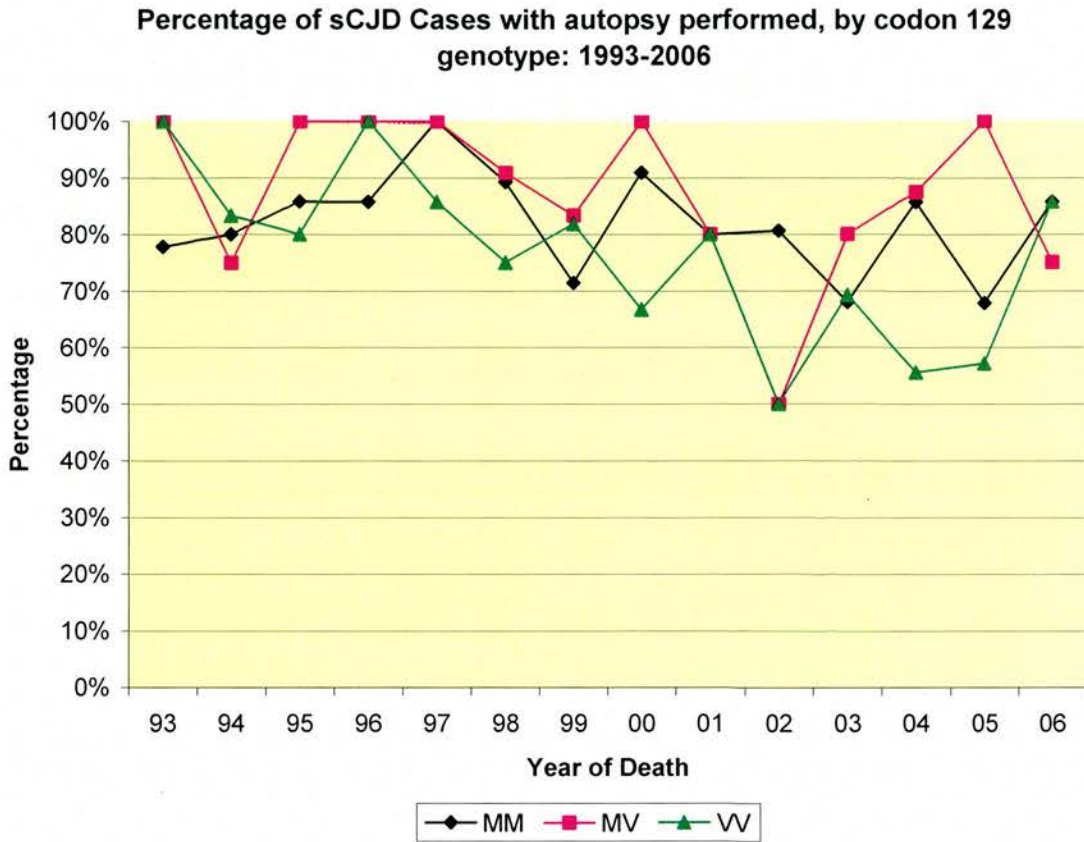
4.3.5 Referral Source

The majority of sCJD Cases referred to the UK NCJDSU between 1993 and 2004 were referred in life, predominantly by neurologists. Overall the proportion referred after death has diminished with time and this is largely attributable to a decrease in neuropathology referrals. Only a small number of Definite or Probable sCJD patients were referred by death certificate in any one year between 1993 and 2004 (fig 4.3). Notably in 2003/4 only a single certified case of sCJD had not already been identified by the NCJDSU.

Fig 4.3

Number of sCJD Cases referred annually by death certificate: 1993-2004
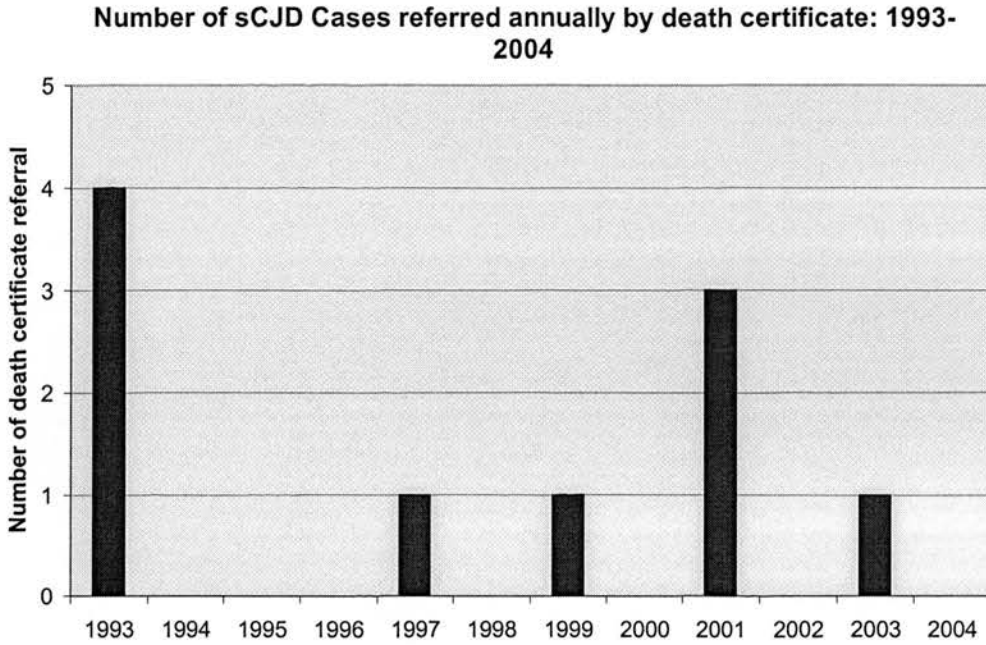
If all suspected sCJD patients in 1993/4 and 2003/4 are compared the percentage referred by neuropathology and death certificate has fallen, with a corresponding increase in the proportion of neurology and physician referrals. This can be partially explained by the general decline in autopsy rates as discussed above. Alternatively it may reflect increasing clinician awareness of either the sCJD phenotype or the existence of the surveillance unit, such that more diagnoses are being suspected and referred promptly in life. One concern was that death certificate referrals from 2003/4 were artificially low due to the timing of data collection, and that death certificate cases were being missed. However, this is unlikely to be the case as discussed in section 4.3.1.

The proportion of psychiatry referrals amongst Cases has not increased with time, despite increased awareness of CJD amongst the psychiatric community because of the prominent psychiatric features of vCJD. This is reassuring as it suggests that large numbers of sCJD patients are not presenting with psychiatric symptoms - obviously a potential concern if one is postulating that a novel BSE phenotype is being misdiagnosed as sCJD.

When referral sources of Cases and Non Cases were compared there were two main findings. Significantly more Non Cases than Cases were being referred by psychiatry. This might be because Non Cases have a more psychiatric presentation than Cases. Against this, when clinical phenotypes of Cases and Non Cases were compared the latter did not have more psychiatric symptoms (see results section 3.3.3). It could reflect the fact that old age psychiatrists follow up more elderly patients with dementia than neurologists and other physicians, and hence are exposed to more atypical cases of Alzheimer's disease and Lewy body dementia (the most frequent final diagnoses in Non Cases (69). Alternatively psychiatrists as a group might be less accurate at diagnosing sCJD than neurologists.

Disproportionately more Non Cases than Cases were referred by death certificate. This is probably due to the well recognised inaccuracy of death certificate diagnoses, that can often be attributed to the fact the forms are left to busy, inexperienced junior doctors who may have only just met the patient before they died (238). Also referrals made in life are inevitably more critically evaluated by the CJD registrar who takes the phone call, and if they feel the history is incompatible with prion disease they might simply offer advice rather than including them as a suspect case. Such safeguards are obviously not possible with death certificate referrals, which are simply sent to the NCJDSU at a later date.

4.3.6 Suspecting the diagnosis of sCJD

As might be anticipated the people first suspecting the diagnosis of sCJD are similar to those making the referral. A slightly higher proportion of Cases were suspected by neurology than were referred, implying that sometimes a neurologist makes the diagnosis but fails to alert the surveillance unit. Possible explanations include the neurologist deferring this task to other clinicians, being unsure about the diagnosis so opting to watch and wait, or simply not referring in life because they forget or prefer not to involve other units. However, against the first theory there is no excess of physician / geriatrician referral over physician / geriatrician suspected diagnosis. More Cases were referred by neuropathology than were initially suspected by pathology, supporting the idea that some of the neurologist - diagnosed sCJD patients were not being referred in life. However, this discrepancy was less marked in 2003/4 than in 1993/4, consistent with increased awareness of the NCJDSU.

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4.3.7 Time to suspect sCJD and refer

The diagnosis of sCJD was suspected quickly in the majority of sCJD Cases, with a median of 2.5 - 3 months. This is consistent with the typical aggressive disease course. However, the range was wide and one notable Case in 2004 was only suspected after 5 years of illness, although this was very much the exception. Despite a detailed review of this individual's history and neuropathology no additional neurological diagnosis was made and she appears to have had a very slowly progressive form of sCJD with a correspondingly delayed diagnosis. In contrast in some instances sCJD was diagnosed after only two weeks of symptoms.

The diagnosis was suspected after similar lengths of time for Cases and Non Cases in 2003/4. However, in 1993/4 Non Cases had been unwell for considerably longer than Cases by the time sCJD was raised as a possibility. This was the only significant difference between 1993/4 and 2003/4 referrals. One interpretation is that in 1993/4 clinicians were less aware of the typical disease course of sCJD and hence were referring patients with quite prolonged illnesses, whereas this had improved by 2003/4.

The data for time to referral mirrors that for time to suspect sCJD, with only brief delays (less than a month) between suspecting sCJD and contacting the NCJDSU in most instances.

4.4 Clinical phenotype in 1993/4 and 2003/4

Overall the clinical phenotype was remarkably similar in Definite, Probable and Possible / Unclear sCJD referrals in 2003/4 compared with a decade earlier. The commonest mode of presentation was rapidly progressive dementia, comprising around two thirds of Cases. Similarly the commonest single presenting symptom was confusion / forgetfulness and if the entire illness was reviewed forgetfulness and dementia were essentially universal. A small number of Definite or Probable Cases were never documented to be demented but this probably reflects insufficient notes / documentation as no individual was recorded as definitely not having cognitive impairment. Unsteadiness and speech disturbance were also extremely common symptoms and were present at some stage in over 80% of Cases, irrespective of year of referral. The most common signs apart from dementia were myoclonus and

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cerebellar signs. These findings concur with the body of literature on the characteristic clinical features of sCJD (74, 227, 239).

Despite the similarities between 1993/4 and 2003/4 referrals some statistically significant differences were noted. However, many can be explained by changes in the questionnaire, differing registrar practice or the effect of applying multiple tests of significance and using p = 0.05, such that one in twenty tests would be expected to be positive just by chance. The Bonferroni correction factor can be used to take account of multiple statistical tests on a single data set but it was not appropriate to apply it in this study because different outcomes were being analysed (i.e. different clinical features), and it is possible that these outcomes were not entirely independent of each other. E.g. There might be correlation between presence of hallucinations and other psychiatric symptoms. Even when multiple tests are performed highly significant results (e.g. p < 0.001) are likely to remain significant despite applying correction factors. For example in this study akinetic mutism would remain significantly more common in 1993/4 than 2003/4 whilst any apparent difference in dyspraxia incidence between 1993/4 and 2003/4 might be eliminated because the p value was only 0.048. Differences that are present in all three sCJD classification groups (Definite, Probable and Possible / Unclear) are more likely to be real than those just detected in one category. E.g. akinetic mutism and cortical blindness.

Weight loss was more frequently recognised in 1993/4 than in 2003/4 but this is probably an artefact of the questionnaire, as the 1993/4 format asked specifically about weight loss whilst this was omitted in the later version. Conversely sensory symptoms were more prevalent in 2003/4 Cases and again this can be explained by changes in the questionnaire. In 2003/4 there were specific questions on sensory symptoms and signs whereas in 1993/4 only sensory abnormalities found on examination were detailed. Alternatively this could be interpreted as weak evidence supporting emergence of a BSE phenotype given that sensory features are prominent in vCJD. However, it is more likely that clinicians and particularly CJD registrars in the post vCJD era are more likely to ask about sensory disturbance in all suspected CJD patients. This phenomenon may also explain why hallucinations appear more common in 2003/4 Cases, although depression and anxiety, the other psychiatric features most frequently associated with vCJD (160) have not increased which is reassuring. Also in 2003/4 there was a question on presence or absence of hallucinations whilst a decade earlier hallucinations were not specifically mentioned.

Akinetic mutism and cortical blindness appear to be significantly more common in 1993/4 in Definite and Probable sCJD patients, and also in Possible / Unclear diagnoses in the case of akinetic mutism. Initially this is difficult to explain as the current questionnaire used in 2003/4 still includes specific questions as to the presence or absence of these signs. One possibility is that these are usually late clinical signs and the 2003/4 patients were being assessed by the CJD registrar earlier in their disease course, but the data on timing of visits does not support this. Both akinetic mutism and cortical blindness can be difficult signs to confirm in a sick patient and are open to clinical interpretation. Therefore the finding might reflect different registrar practice with time, such that the registrars in 1993/4 used less stringent criteria to diagnose akinetic mutism and cortical blindness, or were better at detecting these signs. This is difficult to retrospectively prove or disprove. Alternatively there may have been a real change in the disease phenotype and sCJD patients in 2003/4 are less likely to become akinetic, mute and blind. If this is true the reason is unclear, although interestingly cortical blindness and akinetic mutism are thought to develop later and possibly be less common in vCJD (162). In addition cortical blindness is more common in sCJD cases homozygous for methionine at codon 129(82), and although there was no statistically significant difference in *PRNP* type between 1993/4 and 2003/4 there was a trend away from methionine homozygotes in 2003/4.

4.5 Investigations

Investigation of suspected sCJD has evolved over the past decade. In 1993/4 the most popular form of brain imaging was CT and less than 50% of Cases underwent MRI. This trend was reversed by 2003/4, presumably reflecting both increased availability of MRI and improved understanding of the utility of MRI in sCJD. CSF 14-3-3 analysis was introduced in December 1996 and this probably explains the increased use of lumbar puncture, from 73% in 1993/4 to 88% in 2003/4. One might have anticipated a reduction in EEG testing, because more patients are being classified as Probable sCJD on the basis of the 14-3-3 result and clinical features. However, this has not been the case and EEG use has remained extremely high at around 90% without any significant decrease in the mean number of EEGs performed per case.

4.5.1 CSF

(i) CSF white cell count

The CSF white cell count was normal in the vast majority of sCJD Cases in 1993/4 and 2003/4. In those where the white cell count was elevated it was only minimally raised with no individual having greater than 10×10^9 / mm^3 white cells in their CSF. This contrasts with Non Cases for the same time period where 13% (4 / 31) had CSF white counts above 10×10^9 / mm^3. One can conclude that significant CSF leucocytosis is atypical for sCJD and should prompt the diagnosis to be reassessed. A recent publication from a multinational study on CSF in CJD has confirmed this finding, with only 3 of 298 sCJD patients having a CSF white cell count greater than 5×10^9 / mm^3 (90)

(ii) CSF protein

CSF protein was normal or mildly elevated in the majority of sCJD Cases with no significant differences between 1993/4 and 2003/4 referrals. Only five individuals had CSF protein values greater than 1g / L and in other respects they appeared fairly typical Cases with acellular CSF and characteristic sCJD clinical features, except one individual with a more prolonged illness lasting 20 months. Unfortunately *PRNP* genotype at codon 129 was only tested in two of the five patients (one MM, one MV), so it is difficult to make any assessment of genotype effect. The range of CSF protein levels in this study is similar to previous findings in sCJD in the UK (74). It confirms the clinical impression that CSF protein is often modestly raised in sCJD but is rarely very high, and is not a particularly useful or specific investigation in this context.

(iii) CSF 14-3-3

CSF 14-3-3 protein has been widely reported as a sensitive and relatively specific marker for sCJD, when interpreted in an appropriate clinical context (97, 240, 241, 242). This study found 14-3-3 had a sensitivity of 73% which is rather lower than the values quoted in the literature. Previously most studies reported sensitivities of 90 – 97% (95, 96, 97) but a recent large multinational review also reported a lower sensitivity at 85%, admittedly still significantly higher than the result in this study. (104). Sanchez-Juan et al questioned if their lower than expected sensitivity reflected their rigid strategy in defining a positive 14-3-3 result, or was related to the large

number of patients tested (104). The lower sensitivity in my study is most likely to relate to patient selection. Only pathologically proven sCJD patients could be considered in the calculation and they may be more likely to be clinically atypical, prompting the need for pathological confirmation. The literature suggests that sCJD Cases with less classical histories are less likely to have positive 14-3-3 result (121). There is also evidence that the sensitivity of 14-3-3 diminishes with prolonged disease duration (240) but pathologically proven and unproven Cases had similar durations in this study. A limitation of 14-3-3 is the qualitative, subjective nature of the assay, which relies on visual interpretation of the western blot. It is possible that the individual (AG) interpreting the vast majority of UK 14-3-3 results uses particularly stringent criteria but this same individual has participated in previous studies with higher 14-3-3 sensitivities (243). There have not been recent changes in experimental technique that might explain a drop in sensitivity. Bias is always a potential problem with subjective tests but in most cases 14-3-3 was interpreted with minimal knowledge of clinical details.

Despite these caveats 14-3-3 remains an extremely useful disease marker and was more sensitive than EEG or MRI in this study.

All 14-3-3 negative, pathologically confirmed sCJD patients referred in the UK between December 1996 (introduction of 14-3-3 testing) and December 2004 were reviewed and produced some interesting findings. They were compared with 14-3-3 positive Definite sCJD patients from 2003/4 only because comparable clinical data was available on this cohort. However, this should not alter the conclusions significantly as there is little evidence to support major differences between referrals confined to 2003/4 and 1996 – 2004. It is apparent that 14-3-3 negative sCJD is uncommon and appears to be associated with atypical clinical and pathological features. 14-3-3 negative sCJD patients tend to have significantly prolonged disease duration with a mean of 15 months, and a non significant trend to young age of onset. They are less likely to demonstrate myoclonus or visual disturbance. These unusual features are probably in keeping with the underlying codon 129 genotype / PrP isotype. MM1, which is associated with a typical sCJD presentation, was rare in 14-3-3 negative patients whereas MM2 and MV2 were over - represented. Overall the *PRNP* codon129 distribution was significantly different in 14-3-3 negative sCJD Cases compared to positive Cases. The German TSE reference centre have recently

published their results of molecular subtype-specific diagnosis of CJD and they also identified lower 14-3-3 sensitivity in certain subgroups such as MV2 (69).

Other investigations may also be unhelpful in 14-3-3 negative sCJD, with only a minority having characteristic EEG changes and just a third having a supportive MRI in this study. Again this might reflect *PRNP* genotype / PrP isotype. However MRI has been reported to be a useful diagnostic tool irrespective of genotype, but particularly in this clinically difficult MV2 sCJD (143, 244), so it was disappointing that more MRI scans were not positive. The cause is unclear and may be a real finding or relate to reliance on T1 and T2 MRI sequences, particularly in the early years, as these are now recognised to be less sensitive than FLAIR or Diffusion Weighted imaging (see section 4.5.2) (108, 112).

One conclusion from the data is that a negative 14-3-3 does not exclude sCJD, and unfortunately the assay appears more sensitive in typical sCJD patients where there is less pre- test diagnostic uncertainty. It is a less helpful investigation in the atypical cases where you really need it.

Previously Castellani et al have reported that the sensitivity of 14-3-3 analysis varies with sCJD subtype and they identified PrP2 as the main factor reducing sensitivity (140). Zerr et al also identified PrP type 2, and particularly MV2 cases, as less likely to have a positive 14-3-3 result (119,141). This study provides some support for this finding although the small numbers limit the strength of the results. The rarity of sCJD itself, and particularly 14-3-3 negative sCJD, means limited data are almost inevitable as illustrated here, despite using all known UK cases. Ongoing European collaboration on CSF markers in CJD is addressing this problem.

The observation that 2 of the 25 negative 14-3-3 patients subsequently had a positive result raises the question that a negative result might relate to testing too early. Repeated CSF analysis has been reported to increase the diagnostic sensitivity of 14-3-3, particularly in methionine valine heterozygotes (104, 245). However, there is also evidence that testing after prolonged disease duration is more associated with a negative 14-3-3 result, and 14-3-3 concentrations are lowest at both disease onset and the end stage (240). Also in this study the median time to perform the assay was longer in the 14-3-3 negative group than the positive group, and a similar proportion through the illness as a whole. Of note the 14-3-3 assay has only been validated up to 2 years after disease onset so one needs to be cautious in interpreting results outwith this timeframe.

A crucial and incompletely understood issue is why CSF 14-3-3 is positive in sCJD at all, and hence negative in a minority. There are two principal theories; one relating to dynamics of neuronal damage, one relating to localisation of the sCJD pathology. Previously cortical disruption was believed to be more strongly associated with 14-3-3 than subcortical basal ganglia and thalamic pathology (119). However, a recent study identified a negative correlation between positive 14-3-3 and extensive cortical spongiform change, and between positive 14-3-3 and severe neuronal loss in the thalamus suggesting a more complex relationship between CSF protein levels and the location of brain pathology (246). Presumably 14-3-3 protein leaks into the CSF as neurones are damaged so an assay performed once there is established, extensive damage may be too late to detect significantly elevated protein levels (93, 101, 246). The analysis in this thesis is potentially consistent with both theories on positive CSF 14-3-3, as the longer disease duration of negative 14-3-3 patients may imply slower neuronal damage and a high proportion of these patients had predominantly subcortical pathology consistent with underlying codon 129 / PrP type.

(iv) CSF S100

In this study CSF S100 was abnormally high in 95% of Cases (all from 2003/4 as not available in 1993/4) but it ranged from normal to grossly elevated. Therefore an isolated S100 result in suspected sCJD is not particularly useful although, as a group, sCJD patients have elevated levels (247). The main value of performing S100 assays is to aid interpretation of the 14-3-3 test (A Green personal communication). Usually in sCJD both these CSF markers are abnormal but if either one is strongly abnormal and the other normal this raises a question about the diagnosis. It may reflect a problem with one or other assay, or indicate a diagnosis other than sCJD. Elevated S100 with normal 14-3-3 is rarely seen in sCJD and is more likely to reflect an alternative cause of dementia such as Alzheimer's disease or be associated with malignancy or cerebrovascular disease. (248, 249, A Green personal communication).

4.5.2 MRI

Many more 2003/4 Cases had MRI appearances supporting a diagnosis of sCJD than in 1993/4 (45% v 9%). The most likely explanation is that awareness of the significance of these subtle MRI signal changes had increased by 2003/4 so they were

being reported more frequently. The NCJDSU was aware of the value of MRI in 1993/4 but, despite invariably requesting imaging, only 2 scans were received in the unit for review. Both were classified as positive on the basis of caudate / putamen high signal whereas only a further 2 of the other 44 MRIs performed were thought to be positive by the reporting radiologist. This suggests bias was introduced when the referring clinicians selected scans for review. The experience from both variant and sporadic CJD is that the characteristic MRI changes were under-reported in the early days, and detection improved with neuroradiology review in a specialist centre (250, 170). One study estimated 80% of sCJD MRI changes were overlooked by the initial radiologist reviewing the images (107). Therefore the small numbers of suspect sCJD MRIs reviewed in the NCJDSU in 1993/4 may well have contributed to the apparent low rate of typical changes. The quality of MRI scanners has improved over the last decade and this may also have been influential, together with refinement of scanning techniques and increased use of diffusion weighted imaging (DWI) and FLAIR sequences which are most sensitive for sCJD (108, 112, 251, 252). In this study a pragmatic approach was taken and any available MRI sequence was reviewed and taken into account when classifying the MRI appearances. Whilst we now believe DWI is the most sensitive sequence for the radiological diagnosis of sCJD it was not appropriate to rely on this as often DWI was not performed. T2 -sequences were done in all cases but if T2 films alone were reviewed then this would underestimate sensitivity. In the literature some studies have confined analysis to T2 MRI sequences whereas others have considered FLAIR and DWI too, and this will potentially impact on reported sensitivity and specificity rates.

Alternatively the disparity between 1993/4 and 2003/4 in this study might reflect a change in the underlying disease itself. MRI sensitivity for sCJD has been reported at between 58% and 79% by the German CJD Surveillance group (106, 107, 108). Somewhat surprisingly their sensitivities have been decreasing with time, in contrast to the findings of this study. They attribute the decline in sensitivity to performing more scans in the early stages of illness, less pre-selection of good quality images and introduction of a policy to review all MRIs (108). The German experience of declining sensitivity would be against a Europe - wide shift to more sCJD cases with supportive MRI appearances. Of course the situation may be different in the UK but it seems unlikely that we are experiencing a UK- limited change in sCJD and MRI sensitivity, particularly as the MRI sensitivity from this UK based study is still lower

than the most recent German data. Unfortunately there is no earlier available UK data on the sensitivity of MRI in sCJD for comparison (DS, DC personal communication). One difficulty in exploring the MRI data is the incomplete understanding of the relationship between the MRI appearances and the clinical and pathological features of sCJD. It is likely that the high signal on T2 weighted imaging is secondary to increased free water due to gliosis and / or spongiform change (253). Animal studies suggest increased T2 signal corresponds with gliosis and reduced attenuation represents spongiform change (254). However, correlation between the degree of severity of radiological and neuropathological damage has been poor (255) although this might partly reflect the inevitable time delays between performing an MRI and autopsy. One might expect sCJD MRI changes to correlate with extrapyramidal features given the basal ganglia involvement, but there is not strong evidence supporting this theory and there have even been reports of a negative association between extrapyramidal signs and typical MRI appearances (244). This study did not find a positive association between extrapyramidal signs and caudate / putamen hyperintensity.

MRI appearances were weakly correlated with *PRNP* codon 129 although this was not statistically significant. Cases homozygous for valine at *PRNP* codon 129 were more likely to have basal ganglia hyperintensity on MRI than methionine homozygotes or methionine valine heterozygotes. PrP type also appeared to influence the MRI although the numbers were small and again the result was not significant. A higher proportion of PrP 2 cases had caudate / putamen high signal on MRI than PrP 1 cases. There are a number of studies addressing the relationship between MRI and *PRNP* or PrP type (121, 141). However, most papers refer to complete molecular subtypes (codon129 type in combination with PrP type) whereas too few cases in the current study had sufficient data to reliably assess this. Sensitivity of MRI imaging has been found to be particularly reliable in the diagnosis of MV2 patients; a useful finding as this uncommon subgroup are often clinically atypical and less likely to have other supportive investigations (119, 143, 243). MRI is also frequently abnormal in valine homozygotes, with VV2 cases tending to show thalamic hyperintensity whereas VV1 patients are more likely to have cortical or basal ganglia signal changes (144, 256). The typical sCJD MRI appearance of basal ganglia hyperintensity is seen least frequently in the classic sCJD subtypes, MM1 and MV1, and in MM2, but cortical hyperintensity is increasingly recognised in these patients (121, 141, 142). The results

of this study partially concur with the literature: as predicted basal ganglia signal change was most strongly associated with VV cases and observed least frequently in MM patients. MV1 and MV2 cases were largely evaluated together due to small numbers and this limits any meaningful conclusions as the reported high sensitivity of MRI in MV2 is likely to be cancelled out by the reported low sensitivity in MV1. Isolated cortical hyperintensity was rarely recognised (7% in 2003/4 sCJD cases) yet a recent paper found cortical signal change was common (141). This may reflect technical improvement in MRI with time, and suggests that subtle cortical changes may be increasingly recognised in the future. Their specificity and significance remain unknown.

The characteristic MRI appearance of vCJD, the pulvinar sign, was not observed in any sCJD case in this study. Whilst this remains an effective means of discriminating between sporadic and variant CJD there have been reports of false positive pulvinar signs in sCJD suggesting it is not entirely specific (171). Prominent thalamic hyperintensity has also been noted in sCJD, particularly in the MV2 subtype (143) but also in VV2 cases (144). However, in most instances it is not classified as the pulvinar sign because the thalamic signal change is no brighter than that in the head of caudate and putamen.

4.5.3 EEG

The principal finding when EEGs were compared between 1993/4 and 2003/4 Cases was that significantly fewer 2003/4 patients had characteristic sCJD EEGs (33% versus 52%). The obvious assumption is that there is now less reliance on EEG due to the introduction of CSF 14-3-3, which supports the clinical diagnosis and permits classification of an individual as a Probable case. To a lesser extent the increased availability of MRI may have also reduced the need for EEG, particularly as the significance of basal ganglia hyperintensity is better recognised. However, these theories do not explain the change in EEG results with time in this study because interestingly no fewer EEGs were done in 2003/4 than a decade earlier. Therefore an alternative explanation must be sought.

One possibility is that fewer EEGs were available for review at the NCJDSU in 2003/4, and hence less likely to be classified as characteristic of sCJD. Again this is disproved because more 2003/4 EEGs were actually reviewed in the unit. The same

individuals (RGW, RK) reviewed the EEGs blind to clinical details and applied the same diagnostic criteria so this cannot explain the observed difference. The timing of the EEG was also similar in 1993/4 and 2003/4.

Could it relate to a change in the underlying disease, possibly influenced by a novel disease phenotype or changing *PRNP* genotype distribution? This study has not demonstrated any significant change in *PRNP* codon 129 genotype between 1993/4 and 2003/4 (results section 3.4.5) so it seems unlikely to be the full explanation. However, there has been a non significant trend towards more atypical Parchi subtypes (non MM1 / MV1) which are less associated with the characteristic periodic EEG, and correspondingly fewer methionine homozygotes so this may be a factor. Variant CJD is not generally associated with periodic sharp wave complexes and it is possible that misdiagnosis of vCJD or a similar BSE related disease could reduce the frequency of typical sCJD EEGs, but in the absence of other evidence for a novel phenotype this seems unlikely to be the answer.

The most plausible explanation is that it is an artefact of classification and Case definition. The percentage of characteristic EEGs was calculated in all sCJD Cases, namely all patients meeting criteria for Definite or Probable sCJD. In 1993/4 all the Probable Cases would have typical EEGs, whereas in 2003/4 a significant proportion would fulfil Probable criteria on the basis of clinical features and a positive 14-3-3 alone. Therefore it is more accurate to assess EEG findings in Definite Cases only. When this calculation is performed there is no significant difference between 1993/4 and 2003/4, although the trend to fewer characteristic EEGs in 2003/4 persists (38% in 1993/4 versus 28% in 2003/4; $p = 0.18 \chi^2$).

EEGs were also reviewed in the referrals classified as Possible sCJD or 'Unclear Diagnosis'. The numbers were extremely small but there was no apparent difference in the proportion of typical EEGs with time. A significant minority (14%) had EEGs characteristic for sCJD in both referral periods. They were not classified as Probable sCJD because of insufficient clinical features, but it is likely that some do represent sCJD cases, particularly as no alternative diagnoses were made.

The current study has shown an association between the characteristic sCJD EEG and methionine homozygosity, and also between the characteristic EEG and PrP 1 isotype. This has previously been reported in the literature. Zerr et al found EEG changes of periodic sharp and slow waves predominantly with MM1 and MV1 genotypes (119).

Conversely valine homozygosity has a negative association with a typical EEG (118, 256). The data on MV2 genotype and EEG is mixed, with some reports suggesting MV2 is not associated with typical EEG changes (143) whereas others report a positive association (128).

The reason for the links between genotype / PrP isotype and EEG changes is unclear, not least because the aetiology of the periodic sharp wave complexes themselves is incompletely understood (257). It is important to point out that the associations are not absolute, and a number of non-specific EEGs were recorded in MM1 Cases (n = 4). Whether these patients would have ultimately demonstrated periodic sharp wave complexes is unknown, although it is clear that such changes are by no means universal in sCJD, even with repeated EEGs performed up to the final stages of illness. In fact there is evidence that the characteristic EEG is less common in the preterminal stage of the illness as periodic activity disappears, at least at the level of scalp electrodes, and diffuse flattening occurs (258, 259, 260). Frontal intermittent delta wave activity (FIRDA) has also been reported as an early EEG finding in sCJD but was not observed in this study (260).

Periodic sharp wave complexes are not unique to sCJD. Fortunately the majority of diseases producing sCJD - like EEGs are clinically distinct from sCJD so should not cause too much of a diagnostic dilemma (e.g. hepatic encephalopathy, lithium and baclofen related encephalopathy), although this does stress the importance of interpreting the EEG in the light of the clinical picture. However, this study identified 3 pathologically proven Non Cases with EEGs that were typical or highly suggestive for sCJD and potentially compatible clinical histories. Their final diagnoses were Alzheimer's disease, Lewy body dementia and normal pressure hydrocephalus. These three conditions have all been reported in association with EEG periodic sharp wave complexes, albeit rarely (122, 123, 124, 261). The experience of this study confirms that the characteristic EEG appearances associated with sCJD are not entirely specific for this disease, even when the EEGs are reviewed blindly by NCJDSU consultants following stringent criteria (see appendix). The combination of rapidly progressive dementia and periodic sharp wave complexes can still rarely be due to illness other than sCJD.

4.5.4 Brain and tonsil biopsy

A minority of sCJD Cases underwent brain biopsy as part of their investigative work up. It is difficult to draw firm conclusions on these patients because of small numbers, but they were generally younger and had more prolonged illnesses than sCJD Cases who did not get biopsied. These two factors may not be independently significant because there is a known inverse association between age and disease duration (262). One might anticipate biopsy cases to be younger as we know young patients are more thoroughly investigated in many illnesses and are also more likely to have an autopsy (as reported by the Office of National Statistics for England and Wales). The unusually long mean disease duration could be explained partly by the correlation with age, and also because any deviation from the typical sCJD disease course might prompt more extensive investigation. Similarly this might explain why three of the ten biopsy patients had odd presenting features (although the remaining seven had fairly characteristic disease onsets), and the unusual codon 129 genotype distribution of the ten cases. Methionine homozygotes were underrepresented in the biopsy cohort compared to sCJD patients not undergoing brain biopsy (25% v 64%), although this did not reach statistical significance, possibly reflecting the small numbers involved.

Whether the biopsies were necessary or justified remains debatable. Without biopsy 4 of the Cases were classified as Probable sCJD and a further 4 were Possible whereas 2 were 'Unclear diagnosis'. sCJD was suspected in all instances before biopsy. The decision to perform a biopsy is guided by a risk - benefit analysis, with the potential risks of the procedure weighed against the chance of altering management. In this study no major complications were reported from any of the procedures. Obviously no treatable conditions were identified in the 10 individuals biopsied, but a definitive diagnosis was made and this in itself can be useful. It provides families with a name for their relative's condition and can guide clinicians away from repeated investigations and futile attempts at treatment. The fact that 80% of the biopsy patients were seen in a single centre implies that different units have different practises and thresholds at which they believe cerebral biopsy is indicated.

A recent analysis of 90 brain biopsies undertaken for the investigation of dementia found that 57% were diagnostic but in only 11% was treatment directly modified by the biopsy findings (263). In all cases the biopsy was requested to exclude potentially reversible pathology (inflammation, infection) but this was identified in only a

minority (11%) and the commonest diagnoses were neurodegenerative (including Alzheimer's disease 18% and CJD 12%). It reported a complication rate of 11% including intracranial haemorrhage, infection and seizures but no biopsy - related deaths.

6 of the 54 young onset sCJD Cases studied in this thesis had a tonsil biopsy to help support or exclude a diagnosis of vCJD. It was negative in all 6 cases, with no evidence of PrP^{Sc} in the lymphoreticular tissue. None of the older onset sCJD patients referred in 1993/4 and 2003/4 underwent tonsil biopsy. Tonsil biopsy is a valuable diagnostic tool in suspected vCJD, particularly as tonsillar tissue is more accessible than brain and therefore the biopsy can usually be performed under local anaesthetic and it is associated with a lower morbidity than cerebral biopsy. There is evidence that lymphoid PrP^{Sc} is detectable in the pre-symptomatic phase of the disease so tonsil biopsy could potentially be used to identify asymptomatic vCJD carriers or as an early disease marker.

However, there are a number of disadvantages associated with tonsil biopsy. It is not an entirely risk free procedure, particularly in critically ill patients, and significant haemorrhage can occur. Similar to brain biopsy there are significant public health implications, and use of disposable instruments is recommended. A positive tonsil biopsy does not definitively prove a diagnosis of vCJD and the individual remains classified as Probable (although to date no patient with a positive tonsil result has had an alternative diagnosis made subsequently). Therefore one can argue tonsil biopsy adds little in a patient with the characteristic vCJD clinical features and pulvinar sign on MRI, as they already fulfil Probable criteria. The major disadvantage to tonsil biopsy compared to brain biopsy is it simply confirms or helps exclude a diagnosis of vCJD. It has no role in the diagnosis of alternative causes of rapidly progressive dementia. Therefore in an individual where the differential diagnosis remains wide and includes both vCJD and sCJD cerebral biopsy may be more helpful.

4.5.5 Pathology and codon 129 genotype

There was no significant difference in *PRNP* 129 distribution in sCJD Cases in 1993/4 compared to 2003/4. However, there was a trend towards fewer methionine homozygotes and more valine homozygotes in 2003/4. Given the lack of statistical significance this may be a chance observation, but it does correspond to the UK and

French findings of a general decline in MM frequency with time when all years between 1993 and 2004 are reviewed (see section 3D). Up to date UK figures from the NCJDSU suggest this trend is being sustained (fig 4.4 and 4.5).

Fig 4.4

UK sCJD codon 129 distribution: 1990 - 2007

Fig 4.5

UK sCJD codon 129 distribution by %: 1990-2007
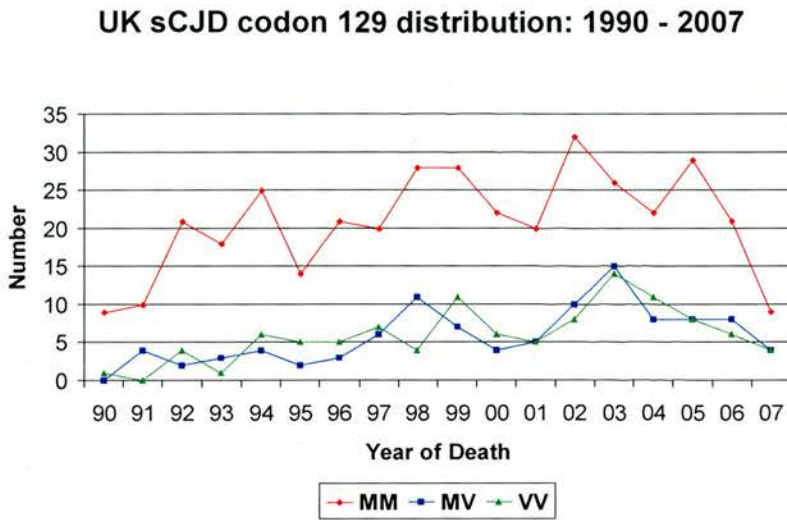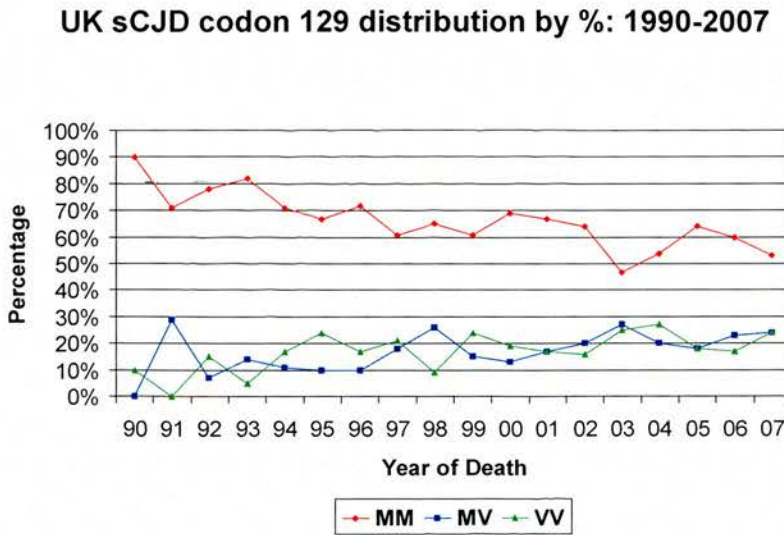
There are a number of possible explanations. It may reflect a real change in the disease genotype profile, possibly due to altered prion pathogenesis or host susceptibility. Alternatively it may relate to case ascertainment. The CJD surveillance system particularly aims to identify young and atypical presentations of sCJD, particularly since the advent of vCJD. Young onset sCJD has a higher proportion of *PRNP* VV genotype (262). Similarly the classic sCJD phenotype is associated with Parchi type MM1 and atypical cases are more likely to be non MM (134). MM cases may also be less likely to undergo genotyping due to lack of time as their disease tends to be more rapid (section 3.4.5). The introduction of the CSF 14-3-3 test may have improved detection rates for VV sCJD, because the majority will have a positive 14-3-3 whereas previously they might have been missed when there was more reliance on EEG (228, 229). All these explanations might bias against identifying and genotyping MM patients and favour detection of VV cases.

It was not possible to compare PrP isotypes or full Parchi subtypes in 1993/4 and 2003/4 because only two 1993/4 referrals underwent PrP typing.

When sCJD neuropathology was compared between the two time periods there were significantly more individuals with kuru type plaques in 2003/4, although they were still uncommon. As expected from the literature most of these patients were Parchi subtype MV2 (134). It is not clear why the incidence of kuru plaques has increased, particularly as the proportion of MV Cases has remained stable. The numbers are small and therefore susceptible to unexpected results so it would be interesting to see if this finding is borne out in a larger neuropathological study. There is currently great interest in amyloid plaques due to the recent identification of an atypical cattle BSE strain with pathological similarities to MV2 sCJD (4). Therefore any sustained increase in sCJD patients with kuru plaques might be extremely important. Reassuringly no case was identified with the florid plaques characteristic of vCJD.

4.6 The differential diagnosis of sCJD

The number of Non Cases referred to the NCJDSU increased annually between 1993 and 2000 but has since decreased with time. The proportion of Non Cases compared to total annual referrals is small and is also diminishing with time, particularly since 2001. This suggests that diagnostic accuracy of referrers has improved. Possible explanations include increased awareness of the characteristic sCJD phenotype and

better availability and specificity of investigations, both for CJD and the alternative diagnoses seen in Non Cases. The percentage of pathologically confirmed Non Cases (as opposed to those defined only on clinical grounds) has also decreased with time. This probably reflects the general trend away from post mortem.

The differential diagnosis of sCJD is wide and the diagnosis is not always straightforward in life. In this study the commonest alternative pathological diagnosis amongst patients referred as suspected sCJD was Alzheimer's disease. Other pathologically proven alternatives included dementia with Lewy bodies / Parkinsonism with dementia, cerebrovascular disease (including vascular dementia) and encephalitis of unknown cause. In the Non Cases identified only on a clinical basis the commonest diagnosis was again Alzheimer's disease, followed by unclassified dementia and Lewy body dementia. However, this group is particularly difficult to study because there is no definitive means of proving the diagnosis, which depends on clinical judgement. In this study the diagnosis was based on information from the referring clinician, both at referral and follow-up, and on the opinion of the visiting registrar. When there was significant clinical doubt it was discussed with one or both NCJDSU consultant neurologists (RGW, RK) and a consensus was reached. An alternative diagnosis to sCJD was not always made but the individual was only classified as a Non Case if the features were felt incompatible with CJD; otherwise they were classified as 'Unclear diagnosis'. Therefore one study weakness is that a significant number of Non Cases have no definite diagnosis other than 'not CJD' (even including some who had post mortems). This has been a problem in the past when evaluating the differential diagnosis of sCJD (R.G. Will - personal communication) and there is no obvious solution, other than to minimise the problem by limiting analysis to pathologically proven Non Cases. However, this is not a satisfactory reflection of real life practise and significantly limits the amount of information available, particularly as fewer autopsies are being performed nowadays.

In this study there were single cases of numerous diagnoses including the expected such as hypoxic encephalopathy, the rare such as multifocal calcifying leucoencephalopathy and the surprising such as acute confusion in the context of shingles. A significant number of the Non Cases recovered, either spontaneously or with steroids. However, in the pathological Non Cases the autopsy rarely revealed any potentially reversible diagnoses. One individual had previously unidentified viral encephalitis that might have been amenable to therapy and three others had

encephalitis of unknown aetiology. This concurs with the body of literature where the majority of conditions misdiagnosed as CJD are neurodegenerative and just a small minority are treatable (including multiple sclerosis and herpes encephalitis) (264).

The literature on the differential diagnosis of sCJD is relatively limited with numerous isolated case reports but few large studies. The largest reviews support the current study, identifying rapidly progressive Alzheimer's disease as the condition most commonly mistaken for sCJD (69, 74, 123, 124, 265). Tschampa et al reviewed patients with Alzheimer's disease or Lewy body dementia misdiagnosed as sCJD because of rapidly progressive dementia and focal neurological signs (122). They concluded that sCJD should be the primary diagnosis in this clinical situation, but identified long duration as a pointer towards Alzheimer's disease, whereas extrapyramidal signs and fluctuations favoured dementia with Lewy bodies. A Belgian study of possible sCJD patients with an alternative final diagnosis had similar findings, identifying Parkinsonism and fluctuations as markers of Lewy body dementia, duration greater than a year as a predictor of Alzheimer's disease and focal onset and compatible imaging as a pointer towards vascular dementia (124). However, as the current study shows, these rules are not absolute and long duration sCJD patients certainly exist, with one proven case surviving 62 months.

Interestingly the German CJD surveillance unit found chronic inflammatory neurological disease was the commonest alternative in young patients and they highlighted Hashimoto's encephalopathy in particular (123). No cases of Hashimoto's encephalopathy were diagnosed in my study, or in the other reviews. One possible explanation is that many neurologists will check thyroid autoantibodies prior to referring to the NCJDSU, thus eliminating these patients. Alternatively it might reflect different interpretation in the UK and Germany of the poorly understood disease entity that is Hashimoto's encephalopathy (266).

Genetic, iatrogenic and variant CJD are also in the differential diagnosis of sCJD but were excluded in this study.

Patients ultimately classified as either Possible sCJD or 'Unclear diagnosis' are an interesting but challenging group. The 'Unclear diagnosis' cohort appear to be a mixture including patients strongly suspected of having sCJD who do not fulfil diagnostic criteria despite supportive EEG, MRI or CSF results (often because disease duration exceeds two years), individuals thought clinically to have an alternative, non

CJD diagnosis but with insufficient evidence to prove this and lastly patients where no confident diagnosis has been made at all. Diagnostically the limiting factor is generally the lack of data to substantiate the clinical impression, whether in terms of long term follow up or neuropathology.

Individuals classified as Possible sCJD are a little different. The most likely diagnosis for all the Possible patients referred in 1993/4 and 2003/4 was considered to be sCJD. However, there are a number of caveats to assuming that all Possibles truly had sCJD. A 'best guess' diagnosis is, by definition, unproven and can never equate to a proven neuropathological diagnosis. A number of Non Cases were clinically thought to be sCJD before autopsy and it is likely that this would also be true for the Possible cohort. There is classification bias such that two patients may fulfil criteria for Possible sCJD but one may be designated a Possible by the NCJDSU registrar whilst the other is reclassified as 'Unclear diagnosis' or a Non Case based on the clinical suspicion of an alternative diagnosis. Thus the final Possibles are a highly selected group of patients reflecting the judgement of the NCJDSU. Finally bias may occur related to information made available to the NCJDSU. An individual may be classified as Possible sCJD initially but as their illness evolves over months or years the diagnosis of sCJD may become untenable. However, the local doctor may be less likely to update the NCJDSU than if the clinical progress favoured CJD, and therefore this patient would remain classified as Possible sCJD based on the available information.

4.7 Assessing the diagnostic criteria

From this study current diagnostic criteria for a Probable classification have a sensitivity of 72%, specificity of 79%, positive predictive value of 89% and negative predictive value of 56%, using autopsy confirmed sCJD patients as the gold standard. No other reports assessing these criteria were found in the literature so it is not possible to compare how they fare in the UK compared to other countries. In comparison with diagnostic criteria for other neurological conditions they perform reasonably well. For example the clinical criteria of the Consortium of dementia with Lewy bodies for probable Lewy body dementia quote a lower sensitivity and positive predictive value at 61% and 48% respectively, but higher specificity (84%) and

negative predictive value (90%) (267). One small study validating the NINCDS-ADRDA clinical criteria for probable Alzheimer's disease found specificity to be comparable with the current criteria for sCJD (82% v 79%), but the Alzheimer's disease criteria had a lower positive predictive value (61%) and better negative predictive value (93%) and sensitivity (80%) (268).

When the current WHO diagnostic criteria for sCJD are compared with those prior to the introduction of CSF 14-3-3 (Rome 1993) it is apparent that the sensitivity has increased significantly (42% to 72%), but at the expense of a moderate drop in specificity (97% to 79%) and a small reduction in the positive predictive value (97% to 89%). This is probably a reasonable compromise as previously over half the Definite sCJD patients were classified as Possible or less in life based on this study data. Brandel et al assessed the same Rome 'Probable' criteria in French patients and found the sensitivity to be higher than this study at 65%, with similar specificity and positive predictive values. (269). The reason for the discrepancy between sensitivities is unclear, but could potentially reflect more EEGs being performed in France and hence more characteristic EEGs being identified.

The impact of incorporating MRI changes into the diagnostic criteria was also evaluated. The numbers were relatively small but the addition of MRI did not appear to make a major difference, irrespective of whether basal ganglia hyperintensity alone or basal ganglia or cortical hyperintensity were used. Sensitivity and positive predictive value did increase marginally but specificity was unchanged. This might reflect the small numbers, particularly of Non Cases with MRI imaging, and it would be useful to address the utility of MRI further in a larger study. It would be especially interesting to look at the false positive rate of the typical MRI changes. In this study three Non Cases demonstrated basal ganglia high signal although it did not impact on their classification. However, this may well be a concern if MRI is incorporated in the future, particularly with increasing use of the more sensitive MRI sequences, DWI and FLAIR. In particular, the specificity of cortical signal change will need to be reviewed. The findings in this thesis do not support using MRI in the diagnostic criteria but this has been recommended by members of the German CJD Surveillance unit although they did not formally assess the impact of introducing MRI criteria (108).

Irrespective of the precise diagnostic criteria used the negative predictive value was low. This implies that failure to fulfil Probable criteria does not reliably exclude a diagnosis of sCJD.

There are a number of limitations when validating the diagnostic criteria. The main problem is the reliance on pathologically confirmed sCJD patients as the gold standard, because they are a highly selected group and may not be representative of sCJD in general. As previously discussed some may have a post mortem because they are clinically atypical, and it is plausible that the more typical patients who already fulfil Probable classification will be less likely to undergo autopsy as their clinicians and families already have a relatively secure diagnosis. This will artificially skew the findings towards lower sensitivity and predictive values. In this study both pathological and clinical Non Cases were used when evaluating the criteria but one could argue that this should have been confined to the autopsy proven Non Cases. However, the numbers would have been too small for any meaningful analysis. Also individuals were only classified as Non Cases if there was felt to be no possibility of sCJD, otherwise remaining as 'Unclear diagnosis', so it seemed reasonable to include all Non Cases in the analysis.

It is important to validate the diagnostic criteria for a number of reasons. It is helpful for families and health professionals if a label of Probable sCJD can be translated into everyday language. E.g. Probable sCJD implies that we are around 90% certain that this is the diagnosis (based on the positive predictive value of 89%). Validation is also useful on a population basis. A key role of any surveillance centre is to monitor disease incidence and this is obviously highly dependent on the reliability of the diagnostic criteria. From time to time criteria will be modified and one needs to predict the likely effect on diagnostic accuracy to avoid misinterpreting any changes in incidence. Clearly defined criteria provide consistency so that data from different countries can be compared. This has been particularly useful with sCJD and the various European collaborations. Simple, clearly defined diagnostic criteria are also useful for research purposes, to select and categorise patients entered into trials.

4.8 Utility of individual clinical features in the diagnosis of sCJD

As one might anticipate dementia was almost universal amongst referrals to the NCJDSU, irrespective of whether the patient ultimately had CJD. Therefore this was

not a good discriminating feature. Similarly myoclonus was not particularly useful with high sensitivity of 87% but poor specificity at 45%. This probably reflects the population studied. Myoclonus is probably the best-recognised sign associated with sCJD and its very presence may trigger referral to the NCJDSU, so it is not surprising a significant proportion of Non Cases also had myoclonus. If a less selected population was studied (e.g. any patient with rapidly progressive dementia) then it might prove more discriminating.

The most useful clinical feature to differentiate sCJD from non-CJD was visual disturbance, with a positive predictive value (PPV) of 93%. This is clinically relevant, particularly as visual symptoms are often an early feature of sCJD. Unfortunately visual disturbance is an imprecise term but it reflects real life practice, as frequently sCJD sufferers are unable to precisely define their visual problems. It encompasses numerous visual symptoms that have been reported in sCJD including micropsia, macropsia, metamorhopsia, field defects and simple blurred vision (83). Akinetic mutism was also useful if present (PPV 89%) although sensitivity was low at just 53%. However, its utility in everyday practise might be less than visual disturbance as it tends to be a feature of late disease. Parkinsonism was generally not a helpful diagnostic pointer to sCJD (sensitivity 20%, PPV 60%). This might reflect the significant numbers of Non Cases with Dementia with Lewy bodies or Parkinson's disease with dementia. Negative predictive values were generally low implying absence of any single feature does not reliably exclude a diagnosis of sCJD, so it is important to look at the clinical picture as a whole.

When the Non Cases mistaken for sCJD were evaluated visual disturbance at onset, cortical blindness and akinetic mutism were all significantly less common than in sCJD patients, concurring with the above conclusions on the diagnostic utility of these clinical features. However, numerous other symptoms and signs were also rarer in the Non Cases (including cerebellar signs, myoclonus and primitive reflexes). Whilst this may be real one has to be wary of over-interpreting the data on Non Cases. They were less likely to be visited by the NCJDSU registrar and follow up information was often scarce, meaning that the quality and quantity of data may not have been comparable with the sCJD cases. Despite this, three clinical features were more common in the Non Case population: sensory symptoms at onset, symptoms suggesting a seizure and parkinsonism. Parkinsonism has already been discussed. Seizures are well recognised in sCJD but are infrequent and generally a late feature (227, 270, 271). Presentation

with seizures would be atypical for sCJD (with the possible exception of epilepsy partialis continua) (272). Non convulsive status is sometimes reported in sCJD on the basis of the altered mental state and EEG findings, but frequently this is a misinterpretation of the early periodic sharp wave complexes of sCJD itself (273).

It is not immediately clear why early sensory symptoms were more prominent in Non Cases than in sCJD. The commonest final diagnoses in Non Cases in this study were Alzheimer's disease and Parkinson's disease with dementia / Dementia with Lewy bodies; not conditions characteristically associated with sensory symptoms. sCJD cases may have been questioned more rigorously about sensory symptoms because of the association between vCJD and painful sensory disturbance, resulting in better documentation. However, this should not explain the extra sensory symptoms in Non Cases as absence of a symptom and insufficient information were analysed together.

4.9 Young onset sCJD

In this study young onset sCJD (defined as onset aged 50 or less) was rare but well recognised, typically with 5 or fewer Cases per year. The number of young patients was essentially stable with time, with the exception of an unexplained and non-sustained rise in 1999 when there were 12 young sporadic Cases. The majority were aged between 40 and 50 years but extremely young cases were identified, including one 15 year old and one 25 year old. However, this is well-recognised with seven cases of adolescent onset sCJD reported in the literature (70, 173, 274, 275, 276, 277). The concern with such young cases is the potential for diagnostic confusion with vCJD, which has a mean onset age of 28 years (158).

Unsurprisingly a number of the young sCJD referrals were initially suspected of having vCJD, not only by the referring team but also by the visiting NCJDSU registrar. However, when the clinical phenotypes of the young cases were compared with older sCJD patients they were reassuringly similar. Dementia and myoclonus were present in the vast majority of young cases and overall clinical presentations were similar in the two groups. Features that are particularly associated with vCJD, such as psychiatric symptoms, chorea and dystonia, were not seen significantly more often than in older patients, with the exception of sensory symptoms. Sensory disturbance was commoner in young onset sCJD than older onset sCJD (35% v 11%).

Sensory disturbance in vCJD is typically painful and persistent and this was the case in 19% of the young sCJD cohort. This is most likely to be an artefact of reporting, as the visiting CJD registrar is likely to search harder for sensory disturbance in any young suspected CJD patient in case they have vCJD. Another possible explanation relates to the longer disease duration in the young cases, meaning they were examined at a relatively earlier stage of their illness and therefore their ability to report sensory problems might still be preserved. Thirdly young sporadic patients may have a subtly different phenotype to older sCJD cases, related to *PRNP* type or an unidentified factor. Finally the higher than expected proportion of young cases with sensory disturbance could represent misdiagnosed vCJD, but against this the clinical features are otherwise consistent with sCJD.

One notable difference between the two age cohorts was the average disease duration, which was significantly longer in the young patients and reminiscent of the duration seen in vCJD. Possible explanations include better premorbid health, more aggressive supportive care (feeding, antibiotics), genetic background related to *PRNP* 129 or misdiagnosis of vCJD as sCJD. This latter possibility is unlikely in view of the typical sCJD phenotype and pathology. A study has identified early age of onset as a major factor influencing sCJD survival (72). In comparison older onset cases of vCJD do not appear to have dramatically more rapid illnesses than young onset patients, with the eight UK variant cases aged over 50 at onset having a mean duration of 11.6 months compared to the vCJD average of 14 months. The German CJD Surveillance group has recently published a review of their young sCJD patients (defined in the same manner as this study) and they too identified an association between prolonged illness duration and young age (262). They found this persisted with all three codon 129 genotypes suggesting *PRNP* type is not the full explanation.

The German study's findings on clinical phenotype were also similar to this study, except for a preponderance of early psychiatric symptoms in young sCJD not corroborated by this study. Interestingly they identified 52 young cases between 1993 and 2003 compared to this study's figures of 54 between 1993 and 2004. Given the smaller UK population this suggests a higher incidence of young onset sCJD in the UK compared with Germany. The cause for this is unclear. It might simply be a chance finding given the number of young cases is small. Alternatively it could reflect better case ascertainment in the UK in light of vCJD concerns, but it seems unlikely that significant numbers of young onset sCJD cases would be missed in Germany

given the devastating nature of the condition. Lastly it might reflect a real difference between the UK and Germany, either BSE related given the higher BSE exposure in the UK or for another unidentified reason. There is no evidence to support a BSE related cause and laboratory transmission studies performed in the youngest sCJD patient in this study did not demonstrate the characteristic lesion profile and incubation period seen with vCJD. Instead the results were typical of sCJD with *PRNP* MV background, and were indistinguishable from transmission studies from older, pathologically confirmed MV sCJD patients (70).

Potentially as yet unidentified environmental, dietary or genetic factors could influence the incidence of young onset sCJD, but Germany and the UK have similar genetic and environmental backgrounds so a chance or surveillance related finding seems more likely.

Generally investigations were less helpful in establishing a diagnosis of sCJD in the young compared to the older cohort. Significantly fewer EEGs showed typical changes, a smaller proportion of 14-3-3s were positive and there was a trend towards fewer characteristic MRI appearances in the young cases. No MRI scans in the young patients showed the pulvinar sign to suggest vCJD. These results are similar to the German CJD experience (262). One explanation is again the genetic background of the young patients. Whilst there were no significant differences in terms of codon 129 genotype in this study there was a trend towards valine homozygosity in the young cohort (also present in the German study). It is well recognised that periodic sharp wave complexes are rarely seen with VV homozygotes (120, 121, 141). Alternatively the reduced sensitivity of investigations might reflect the longer, slower disease course in young onset sCJD, particularly with 14-3-3 which is postulated to rise due to rapid neuronal death (93).

Invasive investigations including cerebral and tonsil biopsy were performed more frequently in young onset sCJD. This is hardly surprising given the lower sensitivity of the conventional investigations, plus the great pressure to provide a diagnosis in young patients who are deteriorating quickly. 6 young cases underwent tonsil biopsy compared with no older sCJD cases. In view of the similar clinical phenotypes of young and old sCJD patients this suggests tonsil biopsies are sometimes being recommended on the basis of age and in the absence of other features to suggest vCJD. Tonsil biopsy carries risks and a negative result in this situation is not particularly helpful, so this procedure should not be rushed into lightly.

There is a single case report in the literature of a young onset sCJD patient who fulfilled the diagnostic criteria for both Probable sCJD and Probable vCJD (173). Her illness began at the age of 19 with sensory symptoms but otherwise she had a fairly classical disease course for sCJD, culminating in myoclonus and akinetic mutism. Similar to the young Cases in this study she had a prolonged disease duration surviving for almost two years. Brain biopsy and ultimately post mortem confirmed sCJD of the VV1 type, whilst tonsil biopsy was negative. An unusual finding was that her MRI reportedly showed the pulvinar sign, suggesting this is not as specific as previously hoped in the context of prion disease. However, reassuringly no young cases with a positive pulvinar sign were identified in this study despite 87% of patients (47/54) undergoing MRI.

A limitation of the young sCJD data is that genetic analysis was not performed in all instances so it is possible that genetic CJD cases are mistakenly included in the young sporadic cohort. However, this is unlikely as 80% of patients did undergo genotyping and the remainder had no significant family history, and frequently genetic cases look different pathologically, the main exception being E200K mutations which rarely present in the very young.

4.10 Comparison between sCJD Cases in UK, France and other EuroCJD countries

Data from UK, France and 'other'* EUROCJD databases was compared searching for any variation between countries, and particularly any differences in the UK and possibly France that might be attributed to increased BSE exposure. Overall there were few significant differences, and therefore no good evidence of a BSE related effect on sCJD characteristics between countries.

Age at sCJD onset and death was similar in all three geographical areas, as was mean disease duration. *PRNP* codon 129 distribution was comparable when the entire period 1993 – 2004 was reviewed in UK, France and 'other' EUROCJD countries.

*'other' = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Switzerland, Spain

However, if codon 129 genotype was analysed by percentage and individual year there was a significant trend towards fewer methionine homozygous cases with time in the UK and France, which was not shared in the 'other' countries. There are a number of possible explanations. It might be a real shift in sCJD genotype distribution, although limited to the UK and France. This could be due to alterations in sCJD susceptibility but the geographical variation is not explained, or it potentially could be a BSE related disease affecting MV and VV individuals and being misdiagnosed as sCJD. However, the rest of this study does not support this, and certainly the UK Cases have a phenotype consistent with sCJD rather than a novel illness attributable to BSE. The most plausible explanation for the decrease in MMs in the UK and France is a shift in the population being genotyped. Previously smaller numbers of Cases were undergoing *PRNP* analysis and they were largely typical MM presentations of sCJD. Recently more MV and VV Cases have been genotyped, possibly due to improved ascertainment of atypical, non MM patients in the UK and France with the heightened concerns regarding vCJD in these countries. This theory is supported by the graphs looking at actual numbers of each codon 129 type annually in France and the UK, compared to other EUROCJD nations (results section 3D, fig 3.73, 3.74, 3.75).

The racial and genetic backgrounds of the different countries studied here are not necessarily comparable, and there is evidence supporting a worldwide *PRNP* 129 west to east gradient with a higher frequency of methionine homozygotes in the normal population as you travel eastwards (278, 279, 280). However, this is unlikely to explain the different patterns in sCJD *PRNP* 129 distribution between UK / France and 'other' EUROCJD countries as most European countries have a similar pattern of codon 129 distribution in the normal population (222, 278, 281). Also one study found that previously *PRNP* genotype frequencies in sCJD were not statistically different across seven European countries (UK, France, Germany, Italy, Netherlands / Belgium, Slovakia). (281). Individual countries have differing rates of *PRNP* analysis and this may be relevant. E.g. Slovakia has extremely high levels of familial CJD so any suspected sCJD patient is likely to undergo genetic analysis whereas other countries are less rigorous (282, 283). In the context of this study UK and 'other' countries had similar levels of *PRNP* typing (66% and 63%) whereas France was higher (76%). This might mean more Cases presenting in an atypical manner are likely to be genotyped in France.

Interestingly the trend towards decreased MM frequency with time is not statistically significant when UK data for referrals in 1993/4 and 2003/4 only were analysed (results section 4.5.5), presumably reflecting the smaller numbers tested.

PrP isotype and Parchi subtype were also compared between the UK, France and 'other' EUROCJD countries, but unfortunately the relatively small numbers available limit conclusions. A further concern is that the cases tested were not representative of all sCJD patients as, by definition, they underwent neuropathological examination and therefore might be younger or have less characteristic histories or investigation results than the cases that did not undergo PrP testing. However, against this UK Cases that were PrP typed did not have significantly different illness durations or ages at death from those where testing was not performed (data from NCJDSU, table 4.1).

Despite these caveats there does not appear to be any significant difference between PrP type and Parchi subtype distribution in the UK, France and 'other' EUROCJD countries. PrP type 1 and MM1 patients were most prevalent in all three regions.

Table 4.1

UK sCJD deaths 1990-2007	PrP type available n = 284 (31%)	PrP type not known n = 639 (69%)
Mean age at death / yrs	67 (range 20 – 87)	67 (range 40 – 95)
Median illness duration / mo	5 (range 1 – 54)	4 (range 1 – 74)

One concern with respect to UK, French and 'other' EUROCJD results is whether the data sets are truly comparable. All the countries participating in the EUROCJD programme collect cases prospectively, use the same sCJD diagnostic criteria and have categorised cases by year of death. However, there are inevitably disparities between different countries' surveillance programmes. These include variable access to neurologists and investigations, differing awareness of the surveillance units with corresponding dissimilar referral rates, and different autopsy rates. For instance the post mortem rate in the UK was noticeably higher than France or 'other' EUROCJD countries, at least until 2001, and this may have influenced patient classification and

sCJD detection rate (fig 4.6). As mentioned earlier the genetic composition will vary between countries, both with respect to *PRNP* and other genes, and this may impact on sCJD susceptibility and phenotype. Notwithstanding these limitations there is no evidence of an emergent BSE related phenotype being misdiagnosed as sCJD in the UK.

Fig 4.6
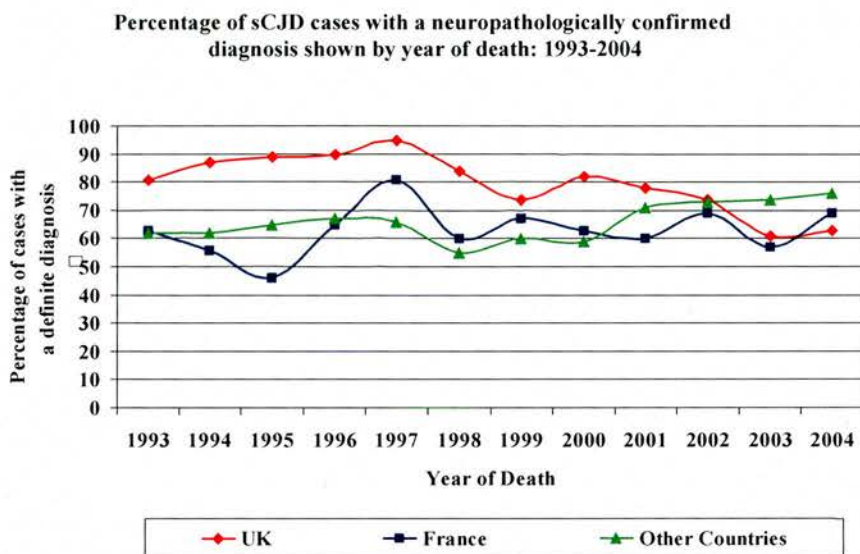
Percentage of sCJD cases with a neuropathologically confirmed diagnosis shown by year of death: 1993-2004

Other countries = Australia, Austria, Canada, Germany, Italy, Netherlands, Slovakia, Spain, Switzerland

B. Conclusions

Sporadic CJD is a rare, universally fatal neurodegenerative disease and a member of the family of transmissible spongiform encephalopathies. The emergence of BSE in cattle followed by variant CJD in humans has highlighted concerns that other, possibly BSE related, forms of human prion disease are being missed. This study provides a comprehensive review of UK sCJD cases between 1993 and 2004, concentrating particularly on 1993/4 referrals predating the first recognised vCJD patient, and 2003/4 referrals after the peak in vCJD incidence. The sCJD clinical phenotype has remained similar between the two time periods with most differences being readily explicable by changes in data collection, case ascertainment or investigation use. There is no convincing evidence supporting a novel BSE related phenotype. Similarly when young onset sCJD cases are studied their clinical characteristics are comparable to older onset sCJD patients, with the exception of a more prolonged disease duration and more frequent sensory disturbance, although this latter finding is likely to reflect reporting bias. A comparison of sCJD databases in the UK, France and other European countries does not support any major geographical differences attributable to BSE exposure. In the UK and France there is a suggestion that the proportion of sCJD patients with the *PRNP* MM genotype is diminishing with time but the most plausible explanation is improved detection and genotyping of atypical sCJD cases.

This study has validated the WHO sCJD diagnostic criteria in the UK population and found them to be generally useful with the classification Probable sCJD having a positive predictive value of 89%. Incorporation of CSF 14-3-3 result has resulted in improved sensitivity at 72% but at the expense of moderate reduction in specificity to 79%. There is currently insufficient evidence to support inclusion of MRI results in the diagnostic criteria. More research is required to fully evaluate the impact of including MRI, using larger numbers of sCJD patients and Non Cases and also studying the sensitivity and specificity of different MRI sequences.

In the UK sCJD population rapidly progressive dementia is the commonest mode of presentation, and the most frequently reported clinical features are dementia, myoclonus and cerebellar signs. However, amongst the patients referred to the NCJDSU the most useful features to discriminate between sCJD and non CJD are

visual disturbance and akinetic mutism. The differential diagnosis of sCJD is wide and includes many rarities, but in line with the literature this study identified Alzheimer's disease as the most common condition mistaken for sCJD. A number of Non sCJD Cases never get a diagnosis and in a minority this is despite post mortem neuropathology.

Overall results from this study are reassuring, with no evidence of an emergent BSE related phenotype being misdiagnosed as sCJD in the UK. However, ongoing surveillance is vital to promote early and accurate disease recognition and expand our knowledge of sCJD, its risk factors, relevant investigations and the diseases it can mimic. The recent developments with experimental atypical BSE strains highlight the many unanswered questions that still remain in the study of transmissible spongiform encephalopathies and emphasize the need for disease surveillance.

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Appendix

A. Historical and Current Diagnostic Criteria for sCJD

1. Masters et al 1979

Definite: Neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia with at least one of:

    (i)   Myoclonus

    (ii)   Pyramidal signs

    (iii)   Extrapyramidal signs

    (iv)   Cerebellar signs

    (v)   Characteristic EEG

Probable: Neuropathologically unconfirmed but progressive dementia with all 5 of (i) – (v)

Possible: Progressive dementia with either:

    Myoclonus and course < 3 years

            or

    Any least 2 of (i) – (v) plus prominent, early signs of lower motor neurone involvement (amyotrophic variety)

2. Matthews 1984

Definite: Neuropathologically confirmed spongiform encephalopathy in progressive dementia with at least 1 of:

Probable: Progressive dementia and at least 2 of:

    (i)   Myoclonus

    (ii)   Cortical blindness

    (iii)   Pyramidal / extrapyramidal / cerebellar signs

    (iv)   Akinetic mutism

And characteristic EEG

Possible: Progressive dementia and at least 3 of the above without characteristic EEG

3. Rome 1993

Definite: Neuropathological confirmation

Probable: Rapidly progressive dementia and at least 2 of:

- (i) Myoclonus
- (ii) Visual or cerebellar problems
- (iii) Pyramidal or extrapyramidal features
- (iv) Akinetic mutism

And characteristic EEG

Possible: Rapidly progressive dementia and at least 2 of (i) – (iv) and duration < 2 years (without characteristic EEG or positive 14-3-3)

4. Rotterdam 1998 (current)

Definite: Neuropathological confirmation

Probable: Rapidly progressive dementia and at least 2 of:

- (v) Myoclonus
- (vi) Visual or cerebellar problems
- (vii) Pyramidal or extrapyramidal features
- (viii) Akinetic mutism

And characteristic EEG and / or positive 14-3-3 CSF protein

Possible: Rapidly progressive dementia and at least 2 of (i) – (iv) and duration < 2 years (without characteristic EEG or positive 14-3-3)

B. EEG classification used by the NCJDSU

1. Typical
General deterioration / loss of normal background.

Truly periodic generalised synchronous bi/tri phasic discharges occurring throughout the whole record or at least one quarter of it, and in relatively long segments (15 seconds minimum)

2. Highly suggestive
General deterioration / loss of normal background.

Intermittent bi / tri phasic discharges similar to those seen in sCJD being truly periodic and generalised at times

BUT either

    a) Occurring in bursts of only relatively short duration (<15 seconds) and occupying less than a quarter of the record

    b) Not being truly generalised and synchronous in all portions of the record where they occurred

3. Suggestive
General deterioration / loss of normal background.

Intermittent bi / tri phasic discharges similar to those seen in sCJD

BUT

    a) Occurring in bursts of only relatively short duration (<15 seconds)

And either b) or c) or both

    b) Not being truly generalised and synchronous

    c) Without true periodicity

4.Non specific
Non specific deterioration in normal background activity

Non specific excessive slow or fast wave activity

5. Normal

C. Patient Questionnaires

1. Current version

Patient Review and Examination Form

1. Identification information		**Id number**	

1.1   What is the patient's name: First name

                                               Surname

1.2   Name of the patient's consultant:

1.3   Hospital address   Name of hospital

                                               Street

                                               Town

                                               Postcode

                                               Telephone number

       Patient's hospital record number

1.4   Who is the patient's G.P.?   Surname+initial

1.5   G.P.'s address   Street

                                                 Town

                                               Postcode

                                               Phone number

1.6   Patient's NHS number: old:

                                                 new:

1.7   Date of examination (dd/mm/yyyy):   _____/_____/_____

1.8   Examination performed by:

iv

2. Clinical history
(note the source of the information: e.g. hospital notes, relative, etc.)

3. **State of patient at admission/first examination by a neurologist**

3.1   General appearance:

3.2   Mental state/speech functions:

3.3   Cranial nerves:

3.4   Motor system:

          Involuntary movements:

3.5   Sensory system:

3.6   Reflexes:

          primitive:

          tendon:

          plantar:

3.7   Cerebellar function/coordination:

3.8   General examination:

4. Previous medical history

Complete this section of the form using the medical notes available. All questions refer to the patient's history prior to the onset of the current illness.

4.1   Does the patient have a record of previous hospital admissions unrelated to the present illness? (1=yes, 2=no)

☐

(*If yes*), on how many occasions has the patient been admitted to hospital? (88=not applicable)

☐☐

(*If yes*) record the hospital's name, the date(s) of admission and the reason(s) for the admission?

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

4.2	Has the patient ever had a diagnosis of inflammatory bowel disease? (1=yes, 2=no)	☐
	(*If yes*) record date of first diagnosis (dd/mm/yyyy)	____/____/_____
4.3	Has the patient ever been diagnosed as diabetic? (1=yes, 2=no)	☐
	(*If yes*) record date of first diagnosis (dd/mm/yyyy)	____/____/_____
	(*If yes*) has the patient received insulin? (1=yes, 2=no)	☐
	(*If patient has received insulin*) record date of first and last prescription (dd/mm/yyyy)	____/____/_____First ____/____/_____Last
4.4	Has the patient ever undergone surgery requiring a general anaesthetic? (1=yes, 2=no)	☐
	(*If yes*) record the date of the surgery, the procedure(s) performed, and the name of the hospital where the procedure(s) took place.	_____ _____ _____ _____
4.5	Has the patient ever undergone surgery without general anaesthetic? (1=yes, 2=no)	☐
	(*If yes*) record the date of the surgery, the procedure(s) performed, and the name of the hospital where the procedure(s) took place.	_____ _____ _____ _____
4.6	On how many occasions in all has the patient undergone surgery (with or without general anaesthetic)?	☐☐

4.7 Has the patient ever received an organ transplant (including corneal or bone marrow transplant)? (1=yes, 2=no)

☐

(If yes) record the date, organ received and name of hospital.

_____

_____

_____

_____

_____

_____

4.8 Has the patient ever received blood or blood products? (1=yes, 2=no)

☐

(If yes) record the date, type of product, name of hospital and reason.

_____

_____

_____

_____

_____

_____

4.9 Has the patient ever received a treatment involving a course of injections (excluding any treatments related to the current illness)? (1=yes, 2=no)

☐

(If yes) record the year of the treatment, the medication(s) involved and the reason.

_____

_____

_____

_____

_____

4.10	Non-injectable treatments lasting more than 4 weeks: record the start date of the treatment, the duration, the medicine and the reason for the treatment

1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	
11.	
12.	
13.	
14.	
15.	
16.	
17.	
18.	
19.	
20.	
4.11	**Has the subject ever been exposed to one of the medications of bovine origin withdrawn in 1990?** (1=yes, 2=no)

x

6. Recording/coding of history and examination

6.1 What were the first symptoms of illness noted by the patient or their family?

_____

_____

When did these symptoms first occur? (dd/mm/yyyy) _____/_____/_____

6.2 When did the patient first seek medical attention for the illness? (dd/mm/yyyy) _____/_____/_____

6.3 When was the patient first referred to a neurologist? (dd/mm/yyyy) _____/_____/_____

6.4 When was the patient first admitted for the current illness? (dd/mm/yyyy) _____/_____/_____

6.5 Since the start of the illness, until the current time, has the patient exhibited the following neurological symptoms/signs: (_if yes record the date of the first appearance of the symptom/sign_)

Coding: 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909

rapidly progressive dementia ☐ _____/_____/_____

cerebellar signs ☐ _____/_____/_____

visual signs ☐ _____/_____/_____

oculomotor signs ☐ _____/_____/_____

pyramidal signs ☐ _____/_____/_____

extrapyramidal signs ☐ _____/_____/_____

primitive reflexes ☐ _____/_____/_____

seizures ☐ _____/_____/_____

myoclonus ☐ _____/_____/_____

other involuntary movements ☐ _____/_____/_____

headache ☐ _____/_____/_____

pain ☐ _____/_____/_____

other sensory disturbances ☐ _____/_____/_____

☐

6.5	(continued)
	vertigo/dizziness □ ___/___/___
	pseudobulbar signs □ ___/___/___
	neurogenic muscle wasting □ ___/___/___
	akinetic mutism □ ___/___/___

6.6 Since the start of the illness, until now, has the patient exhibited the following clinical symptoms/ signs: (*if yes record the date of the first appearance of the symptom/sign*)

Coding: 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909

gait disturbances □ ___/___/___

speech disturbances □ ___/___/___

visual disturbances □ ___/___/___

forgetfulness □ ___/___/___

6.7 Since the start of the illness, has the patient been seen by a psychiatrist? (1=yes, 2=no) □

(*If yes*) record the date of the first consultation (dd/mm/yyyy)   ___/___/___

6.8 Since the start of the illness until now, has the patient exhibited the following psychiatric symptoms/signs: (*if yes record the date of the first appearance of the symptom/sign*)

Coding: 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909

___/___/___

clinical depression □

___/___/___

social withdrawal □

___/___/___

low mood and apathy □

___/___/___

anxiety □

___/___/___

delusions □

___/___/___

hallucinations □

___/___/___

aggression □

7. Investigations

7.1 Has the patient undergone an EEG? (1=yes, 2=no)

(*If yes*), on how many occasions?

(*If yes*), record date of most recent EEG (dd/mm/yyyy)   ___ / ___ / _____

Are EEG records/copies available in the Unit? (1=yes all, 2=yes some, 3=no, 8=not applicable)

Have the EEGs been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)

7.2 Has the patient recorded an EEG characteristic of CJD (generalized triphasic periodic complexes with frequency about 1/s)?(1=yes, confirmed by Unit staff, 2=yes, reported by local staff, EEG not available for confirmation by Unit staff, 3=no, 8=no EEG performed)

What was the basis for the classification of the EEG? (1=informal, 2=Oxford criteria, 3=Gottingen criteria, 4="WHO" criteria, 8= no EEG performed)

(*If yes*) record the date on which the first characteristic EEG was recorded (dd/mm/yyyy)   ___ / ___ / _____

7.3 Has the patient ever had a CT scan? (1=yes, 2=no)

(*If yes*), on how many occasions?

(*If yes*), record date of most recent scan (dd/mm/yyyy)   ___ / ___ / _____

Are CT scan results available in the Unit (1=yes all, 2=yes some, 3=no, 8=not applicable)

Have the CT scans been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)

7.4 Has the patient ever had an abnormal CT scan? (1=yes, confirmed by Unit staff, 2=yes, reported by local staff, scan not available for confirmation by Unit staff, 3=no, 8=no scans performed)
(*If yes*) record the date on which the first abnormal scan was performed (dd/mm/yyyy)   ___ / ___ / _____

(*If yes*) specify what abnormalities have been observed

_____

_____

7.5   Has the patient ever had an MRI scan? (1=yes, 2=no)

☐

(*If yes*), on how many occasions?

☐☐

(*If yes*), record date of most recent scan (dd/mm/yyyy)

____/____/_____

Are MRI scan results available in the Unit (1=yes all, 2=yes some, 3=no, 8=not applicable)

☐

Have the MRI scans been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)

☐

7.6   Has the patient ever had an abnormal scan? (1=yes, confirmed by Unit staff, 2=yes, reported by local staff, scan not available for confirmation by Unit staff, 3=no, 8=no scans performed)

☐

(*If yes*) record the date on which the first abnormal scan was performed (dd/mm/yyyy)

____/____/_____

(*If yes*) specify what abnormalities have been observed

_____

_____

_____

_____

7.7   (*If an abnormal MRI scan has been reported by someone outside the unit*) who reported the abnormal scan?

Name: _____

Address: _____

_____

7.8   CSF findings (fill coding boxes with 8s if test results are not available)

Date of first CSF collection (dd/mm/yyyy)   ____ / ____ / _____

Results: protein   ☐☐ ☐ mg/L

                                   glucose   ☐☐ ☐ mmol/L

                                   cell count   ☐☐☐☐ count/mm^3

                                   14-3-3   ☐ (1=negative, 2=equivocal, 3=positive)

                                   NSE   ☐☐☐ ☐ ng/ml

                                   S100b   ☐☐☐ ☐ ng/ml

                                   tau   ☐☐☐☐ pg/ml

Ig oligoclonal bands in: CSF   ☐ 1=positive, 2=negative

                                   blood   ☐ 1=positive, 2=negative

Date of second CSF collection (dd/mm/yyyy)   ____ / ____ / _____

Results: protein   ☐☐ ☐ mg/L

                                   glucose   ☐☐ ☐ mmol/L

                                   cell count   ☐☐☐ count/mm^3

                                   14-3-3   ☐ (1=negative, 2=equivocal, 3=positive)

                                   NSE   ☐☐☐ ☐ ng/ml

                                   S100b   ☐☐ ☐ ng/ml

                                   tau   ☐☐☐☐☐ pg/ml

Ig oligoclonal bands in: CSF   ☐ 1=positive, 2=negative

                                   blood   ☐ 1=positive, 2=negative

7.9 Has the patient had any abnormal liver function test results recorded? (1=yes, 2=no)

☐

(If yes) specify abnormality and give date of first abnormal test:_____

___/___/_____

_____

_____

7.10 Does the patient have any abnormalities on other routine biochemical/haematological investigations? (1=yes, 2=no)

☐

(If yes) give describe the investigation(s) and the abnormalities

_____

_____

_____

_____

_____

7.11   Has the patient undergone a brain biopsy? (1=yes, 2=no)

☐

(*If yes*) what was the result? (1=no evidence of spongiform change, 2=spongiform change without florid plaques, 3=spongiform change with florid plaques, 4=result not yet available, 8=no biopsy performed)

☐

Name of neuropathologist:

———————————————

7.12   Has the patient undergone a tonsil biopsy? (1=yes, 2=no)

☐

(*If yes*) what was the result? (1=no evidence of PrP immunostaining, 2=equivocal, 3=PrP positive, 4=result not yet available, 8=no biospy performed)

☐

———————————————

8.   Specimens collected

	1=yes, 2=no	Quantity (mls)

8.1   Blood: frozen for general use

☐ ☐☐

separated and frozen for transmission studies

☐ ☐☐

8.2   Urine

☐ ☐☐

8.3   CSF

☐ ☐

9.   Patient classification

9.1   On the basis of the available information, what is the classification of the patient? (1.0=definite CJD, 2.0=probable CJD, 3.0=possible CJD, 4.1=diagnosis unclear, 4.2=CJD thought unlikely, 4.3=definitely not CJD, 5=GSS)

☐☐

(*If patient is classified as at least possible CJD or GSS*) which category of disease is suspected? (S=sporadic CJD, N=nvCJD, F=familial CJD, I=iatrogenic CJD, G=GSS, 8=not applicable)

☐

2.Original CJD study questionnaire

1. Patient number

2. a) Case   Source:
   b) Control

3. Date of interview

4. Place of interview

5.   Patient (Maiden Name)   Interviewee

   Name:

   Address:

   Tel:

   Relationship:

6. Sex

7. Date of birth

8. Hospital:

   Ward:

   Hospital No:

   Consultant:

9. GP:

   Address:

   Tel:

xx

10. Country of origin

11. Skin Colour

PRODROMAL PHASE

12a. Has the patient ever seen a doctor in the last year?

Reason:

Date:

Doctor:

12b. Has the patient ever seen a dentist in the last year?

Reason:

Date:

Dentist:

13. Had the patient, prior to this admission been:

a) Depressed

b) Tired and exhausted

c) Unable to sleep

d) Behaving oddly; specify:

e) Sweating abnormally

f) Eating abnormally

g) Losing weight

h) Gaining weight

14. In the last 3 months prior to this admission, had the patient had:

a) Cough

b) Cold

c) "Flu"

d) Diarrhoea

e) Other illness; specify:

15. When did the patient first see the doctor about the present illness?

    Date:

    Reason:

    Doctor:

PAST MEDICAL HISTORY

16. Has the patient every been in hospital prior to this illness?

If so:	Date	Reason	Hospital
1.			
2.			
3.			
4.			

17. Does the patient either regularly attend hospital or GP?

Date	Practitioner	Reason

18. Has the patient ever had an operation?

If so: Hospital	Date	Type of operation	Reason
1.			
2.			
3.			
4.			

19a. Has the patient ever had an eye operation?

    If so: Reason:

                  Date:

                  Hospital:

19b. Has the patient ever been tested for glaucoma?

20. Has the patient ever had a head injury (with loss of consciousness or skull fracture)?

    If so: Details:

21. Has the patient ever been jaundiced?

    If so: Details:

22. Has the patient ever had an epileptic fit?

    If so: Details

23. Has the patient ever attended a psychiatrist?

    If so: Date:

                  Doctor:

                  Reason:

24a. Has the patient ever had a blood transfusion?

    If so: Details:

24b. Has the patient ever been a blood donor?

    If so: Details:

25. Has the patient ever had an organ transplant

    If so: Specify organ and give details:

26. Has the patient ever been in contact with any person with a serious dementing illness?

    If so, details

27. Is the patient left or right handed?

28. Has the patient ever suffered from:

a)	Glandular fever?		e)	Rheumatoid arthritis
b)	Polio?		f)	Diabetes Mellitus
c)	Shingles?		g)	Allergies
d)	Herpes Simplex?			

29. What medications has the patient been exposed to:

	Duration	Name (including dose and freq)	Reason
(a) Prescribed			

Hormone supplement:

Please specify type and route of administration:

(b) OTC
Purchases

(c)   Homeopathic/Herbal

(e)   Eyedrops

30a. What injectable therapy, or vaccinations has the patient received in the past?

        Name   Date   Reason   Frequency

30b. Has the patient ever had an EMG

       If yes, age at first EMG:
       If yes, age at last EMG:
       If yes, specify reason:
       (eg myopathy, neuropathy etc)

31   Smoking habits:

Never	=	1
Ex (>12/12)	=	2
Current cigs	=	3
Current pipe/cigar	=	4
Not Known	=	9

Drinking habits:

Never	=	1
Ex drinker (>12/12)	=	2

Current   =   3

Not Known   =   9

Tatooing:

Ear piercing:

Acupunture:

FAMILY HISTORY

32.1   Father   Mother   Sp

a)   Country of birth?

b)   Is relative alive now?

c)   If no: Age at death:

                  Cause of death

                  Place of death

                  Prior to death was relative
                  confused or unconscious?

                  Did relative suffer any
                  other disease or illness?

32.2   Paternal   Paternal   Maternal   Maternal
                          Grandfather Grandmother   Grandfather   Gran

a)   Country of birth?

b)   Is relative alive now?

c)   If no: Age at death:

                  Cause of death   =   3

Place of death

Prior to death was relative
confused or unconscious?

Did relative suffer any other disease or illness?

33. Siblings

	1st name	Age	Full/half sib	Alive/Dead	Age at death	Cause of death
1.						
2.						
3.						
4.						
5.						

34. Patient's marital status

35. Has the patient been married more than once?

36. Children

	Name	Age	Sex	Alive/Dead	Cause of Death
1.					
2.					
3.					
4.					
5.					

SOCIAL HISTORY

37. Residential history

Address	Dates	Local characteristics (eg proximity to farms, hospitals,

factories etc.)

    1.

    2.

    3.

    4.

    5.

    6.

    7.

    8.

    9.

    10.

38.   Occupational history

	Type of job	Employer	Location	Dates
1.				
2.				
3.				
4.				
5.				
6.				

39. Occupation of partner:

40. Occupation of parents:

41. Educational history

	Institution	Town	Dates
1.			
2.			
3.			

42. Eating habits

a)   How often does the patient eat the following
      Never   =   1
      < 1 yr   =   2
      Several times/year =   3
      > 1/12   =   4
      > 1/week   =   5
      Not Known   =   9

                                              <u>Ever</u>   <u>After 1985</u>

      (i)   Lamb/mutton

      (ii)   Pork/bacon/ham

      (iii)   Beef

      (iv)   Venison

      (v)   Veal

      (vi)   Poultry

      (vii)   Fish

      (vii)   Shellfish

      (i)   Sausages

      (ii)   Tripe

      (iii)   Liver (state origin)

      (iv)   Kidneys (origin)

      (v)   Sweetbreads

      (vi)   Tongue

      (vii)   Brains

      (viii)   Trotters

      (ix)   Puddings

      (x)   Eyes

      (xi)   Haggis

      (xii)   Heart

xxx

c) Does the patient ever eat rare or undercooked meat?

d) Does the patient have any dietary restrictions or eccentricities?
    (NB: If vegetarian, did they ever eat meat, and if so, for how long?)

e) Does the patient consume dairy products?

	Ever	After 1985
Milk		
Cheese		

EXPOSURE TO ANIMALS

43. Has the patient ever had personal contact with the following animals:

		Y/N	Age first exposed	Duration	Ever Bitten	Age Bite	No. of Bites
(i)	Cats						
(ii)	Ferrets						
(iii)	Live mink						
(iv)	Cattle						
(v)	Sheep						
(vi)	Deer						
(vii)	Horses						
(viii)	Pigs						
(ix)	Rabbits						
(x)	Rodent/hamster						

44. Has the patient had contact with fur or leather other than normal contact with every

45. Has the patient ever lived or worked on a farm?

46. Hobbies:

47. Has the patient ever had contact with the following:

   (a) Fertiliser
   (b) Bonemeal
   (c) Hoof and Horn
   (d) Dried blood

48. Has the patient any domestic animals now or has he/she had any in the past?

   a) Species

   b) Was animal allowed to
      mix freely with other
      animals outside the
      house?

   c) Did animal sleep in
      house? -bed?

      1. Always

      2. Usually

      3. Rarely

      4. Never

   d) Did animal ever have a
      serious illness?

   e) Age of patient when
      animal in house

49. Has the patient ever travelled abroad?

    If so: Location and dates

50. Does the patient regularly travel within Britain?

    If so: Location, frequency and reasons

51. Has any other relative had a similar disease? (OMIT THIS
    QUESTION IN THE CASE OF CONTROLS)

CLINICAL HISTORY

EXAMINATION ON ADMISSION

1. General appearance:

2. Mental state/speech functions:

3. Cranial nerves:

4.   Motor system:

5.   Reflexes:

6.   Sensory system:

7.   General examination:

REVIEW OF PROGRESSION OF PHYSICAL SIGNS

EXAMINATION

1.   General appearance:

2.   Mental state/speech functions:

3.   Cranial nerves:

4.   Motor system:

5.   Reflexes:

6.   Sensory system:

7.   General examination:

INVESTIGATIONS

a)   Abnormalities on routine biochemical/haematological investigation:

b)   LFT's

c)   CSF:

d)   EEG results:

e)   CT scan:

f)   MRI scan:

e)   Other investigations:

TREATMENT

OUTCOME

a)   Date of death:

        Place of death:

        Cause of death:

b)   Review of clinical course:

c)   EEG progression:

d)   Abnormalities in other investigations:

e)   Post-mortem: Yes/No

        Histology

f)   Blood taken for genetic studies?   Yes/No

        Analysing Centre:

CLASSIFICATION

                                                        Present
        Absent

1.   Rapidly progressive dementia:

2.   a)   Myoclonus

        b)   Cortical blindness

        c)   Pyramidal/extra-pyramidal/
                cerebellar signs

        d)   Akinetic mutism

        e)   Early onset of neurogenic
                muscle wasting

        f)   Characteristic EEG
3.   Histology:

Classification   1.   CJD   -   Definite

- Probable
- Possible

2.   Other

Late Referral Form

---

1. Identification information   **Id number**   ☐☐☐☐☐

1.1   What was the patient's name: First name   _____

                                        Surname   _____

1.2   Who was patient's consultant: _____

1.3   Hospital address(last) Name of hospital   _____

                                Street   _____

                                Town   _____

                                Postcode   _____

                                Telephone number   _____

         Patient's hospital record number   _____

1.4   Name of preceding hospital/hospice (if any)   _____

         Patient's hospital record number   _____

         Other preceding hospital/hospice (if any)   _____

         Patient's hospital record number   _____

1.5   Patient's G.P. (surname & initial)   _____

         G.P.'s address   Street   _____

                                Town   _____

                                Postcode   _____

Telephone	_____

1.6	NHS number of patient:	old:
		new:

1.7	Date of death of patient (dd/mm/yyyy)

1.8	ICD coding on death certificate:	I. A
		B
		C
		D
		II.

1.9	Sources of information:
	Hospital notes
	Information from GP
	Information from relatives

Coding: 1=yes, 2=no

1.10	Date this review closed (dd/mm/yyyy)
1.11	Review closed by:

2. Clinical history
(note the source of the information: e.g. hospital notes, relative, etc.)

3. **State of patient at admission/first examination by a neurologist**

3.1   General appearance:

3.2   Mental state/speech functions:

3.3   Cranial nerves:

3.4   Motor system:

        Involuntary movements:

3.5   Sensory system:

3.6   Reflexes:

        primitive:

        tendon:

        plantar:

3.7   Cerebellar function/coordination

3.8   General examination

4. Previous medical history

Complete this section of the form using the medical notes available. All questions refer to the patient's history prior to the onset of the final illness. If notes are not available then enter 8s in coding boxes

4.1   Did the patient have a record of previous hospital admissions unrelated to the last illness? (1=yes, 2=no)

(*If yes*), on how many occasions was the patient admitted to hospital? (88=not applicable)

(*If yes*) record the hospital's name, the date(s) of admission and the reason(s) for the admission?

4.2 Was the patient ever diagnosed as having inflammatory bowel disease? (1=yes, 2=no)	☐
(*If yes*) record date of first diagnosis (dd/mm/yyyy)	____/____/_____
4.3 Was the patient ever diagnosed as diabetic? (1=yes, 2=no)	☐
(*If yes*) record date of first diagnosis (dd/mm/yyyy)	____/____/_____
(*If yes*) did the patient receive insulin? (1=yes, 2=no)	☐
(*If patient received insulin*) record date of first and last prescription (dd/mm/yyyy)	____/____/_____First ____/____/_____Last
4.4 Did the patient ever undergo surgery requiring a general anaesthetic? (1=yes, 2=no)	☐
(*If yes*) record the date of the surgery, the procedure(s) performed, and the name of the hospital where the procedure(s) took place.	_____ _____ _____ _____
4.5 Did the patient ever undergo surgery without general anaesthetic? (1=yes, 2=no)	☐
(*If yes*) record the date of the surgery, the procedure(s) performed, and the name of the hospital where the procedure(s) took place.	_____ _____ _____ _____
4.6 On how many occasions in all did the patient undergo surgery (with or without general anaesthetic)?	☐☐

4.7	Did the patient ever receive an organ transplant (including corneal or bone marrow transplant)? (1=yes, 2=no) (*If yes*) record the date, organ received and name of hospital.	☐ _____ _____ _____ _____ _____ _____
4.8	Did the patient ever receive blood or blood products? (1=yes, 2=no) (*If yes*) record the date, type of product, name of hospital and reason.	☐ _____ _____ _____ _____ _____ _____
4.9	Did the patient ever receive a treatment involving a course of injections (excluding any treatments related to the final illness)? (1=yes, 2=no) (*If yes*) record the year of the treatment, the medication(s) involved and the reason.	☐ _____ _____ _____ _____

	4.10	Non-injectable treatments lasting more than 4 weeks, excluding treatments related to the final illness: record the start date of the treatment, the duration, the medicine and the reason for the treatment
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		
13.		
14.		
15.		
16.		
17.		
18.		
19.		
20.		

4.11	**Was the subject ever exposed to one of the medications of bovine origin withdrawn in 1990?** (1=yes, 2=no)	☐

5.	**Recording/coding of history and examination**	
5.1	What were the first symptoms of illness noted by the patient or their family?	_____ _____
	When did these symptoms first occur? (dd/mm/yyyy)	___/___/_____
5.2	When did the patient first seek medical attention for the illness? (dd/mm/yyyy)	___/___/_____
5.3	When was the patient first referred to a neurologist? (dd/mm/yyyy)	___/___/_____
5.4	When was the patient first admitted for the current illness? (dd/mm/yyyy)	___/___/_____
5.5	Did the patient, at any time during the course of the illness, exhibit the following neurological symptoms/signs: (*if yes record the date of the first appearance of the symptom/sign*)	**Coding:** 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909

rapidly progressive dementia	☐	___/___/_____
cerebellar signs	☐	___/___/_____
visual signs	☐	___/___/_____
oculomotor signs	☐	___/___/_____
pyramidal signs	☐	___/___/_____
extrapyramidal signs	☐	___/___/_____
primitive reflexes	☐	___/___/_____
seizures	☐	___/___/_____
myoclonus	☐	___/___/_____
other involuntary movements	☐	___/___/_____
headache	☐	___/___/_____
pain	☐	___/___/_____

☐

5.5 (continued)	
other sensory disturbances	☐ ___/___/___
vertigo/dizziness	☐ ___/___/___
pseudobulbar signs	☐ ___/___/___
neurogenic muscle wasting	☐ ___/___/___
akinetic mutism	☐ ___/___/___

5.6 Did the patient, at any time during the course of the illness, exhibit the following clinical symptoms/signs: (*if yes record the date of the first appearance of the symptom/sign*)

Coding: 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909

gait disturbances	☐ ___/___/___
speech disturbances	☐ ___/___/___
visual disturbances	☐ ___/___/___
forgetfulness	☐ ___/___/___

5.7 Since the start of the illness, was the patient seen by a psychiatrist? (1=yes, 2=no)   ☐

(*If yes*) record the date of the first consultation
(dd/mm/yyyy: enter 08/08/0808 if not applicable)   ___/___/___

5.8 **Since the start of the illness until death, did the patient exhibit the following psychiatric symptoms/signs:** (*if yes record the date of the first appearance of the symptom/sign*)

Coding: 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909: if no enter date as 08/08/0808

clinical depression	___/___/___
social withdrawal	☐ ___/___/___
low mood and apathy	☐ ___/___/___
anxiety	☐ ___/___/___
delusions	☐ ___/___/___
hallucinations	☐ ___/___/___
aggression	☐ ___/___/___
	☐

6.   Investigations

6.1   Did the patient undergo an EEG? (1=yes, 2=no)

☐

(*If yes*), on how many occasions?

☐☐

(*If yes*), record date of most recent EEG (dd/mm/yyyy)

_____/_____/_____

Are EEG records/copies available in the Unit? (1=yes all, 2=yes some, 3=no, 8=not applicable)

☐

Have the EEGs been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)

☐

6.2   Did the patient record an EEG characteristic of CJD (generalized triphasic periodic complexes with frequency about 1/s)?(1=yes, confirmed by Unit staff, 2=yes, reported by local staff, EEG not available for confirmation by Unit staff, 3=no, 8=no EEG performed)

☐

What was the basis for the classification of the EEG? (1=informal, 2=Oxford criteria, 3=Gottingen criteria, 4="WHO" criteria, 8= no EEG performed)

☐

(*If yes*) record the date on which the first characteristic EEG was recorded (dd/mm/yyyy)

_____/_____/_____

6.3   Did the patient ever have a CT scan? (1=yes, 2=no)

☐

(*If yes*), on how many occasions?

☐☐

(*If yes*), record date of most recent scan (dd/mm/yyyy)

_____/_____/_____

Are CT scan results available in the Unit (1=yes all, 2=yes some, 3=no, 8=not applicable)

☐

Have the CT scans been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)

☐

6.4   Did the patient ever have an abnormal CT scan? (1=yes, confirmed by Unit staff, 2=yes, reported by local staff, scan not available for confirmation by Unit staff, 3=no, 8=no scans performed)

☐

(*If yes*) record the date on which the first abnormal scan was performed (dd/mm/yyyy)

_____/_____/_____

(*If yes*) specify what abnormalities have been observed

_____

6.5   Did the patient ever have an MRI scan? (1=yes, 2=no) ☐

     (*If yes*), on how many occasions? ☐☐

     (*If yes*), record date of most recent scan (dd/mm/yyyy)   ____/____/_____

     Are MRI scan results available in the Unit (1=yes all, 2=yes some, 3=no, 8=not applicable) ☐

     Have the MRI scans been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable) ☐

6.6   Did the patient ever have an abnormal scan? (1=yes, confirmed by Unit staff, 2=yes, reported by local staff, scan not available for confirmation by Unit staff, 3=no, 8=no scans performed) ☐

     (*If yes*) record the date on which the first abnormal scan was performed (dd/mm/yyyy)   ____/____/_____

     (*If yes*) specify what abnormalities have been observed _____

     _____

     _____

     _____

6.7   (*If an abnormal MRI scan has been reported by someone outside the unit*) who reported the abnormal scan?

     Name: _____

     Address: _____

     _____

1

6.8   CSF findings (fill coding boxes with 8s if test results are not available)

Date of first CSF collection (dd/mm/yyyy)   ____/____/_____

Results: protein   [ ][ ] [ ] mg/dl

                                      glucose   [ ][ ] [ ] mmol/L

                                      cell count   [ ][ ][ ][ ] count/mm³

                                      14-3-3   [ ] (1=negative, 2=equivocal, 3=positive)

                                      NSE   [ ][ ][ ] [ ] ng/ml

                                      S100b   [ ][ ] [ ] ng/ml

                                      tau   [ ][ ][ ][ ][ ] pg/ml

Ig oligoclonal bands in: CSF   [ ] 1=positive, 2=negative

                            blood   [ ] 1=positive, 2=negative

Date of second CSF collection (dd/mm/yyyy)   ____/____/_____

Results: protein   [ ][ ] [ ] mg/dl

                                      glucose   [ ][ ] [ ] mmol/L

                                      cell count   [ ][ ] [ ][ ] count/mm³

                                      14-3-3   [ ] (1=negative, 2=equivocal, 3=positive)

                                      NSE   [ ] . ng/ml

                                      S100b   [ ][ ] . [ ] ng/ml

                                      tau   [ ][ ] [ ][ ] pg/ml

                                      CSF   [ ] 1=positive, 2=negative

Ig oligoclonal bands in: CSF   [ ] 1=positive, 2=negative

                            blood   [ ]

li

6.9 Did the patient have any abnormal liver function test results recorded? (1=yes, 2=no)

☐

(*If yes*) specify abnormality and give date of first abnormal test:_____

___/___/_____

_____

_____

6.10 Did the patient have any abnormalities on other routine biochemical/haematological investigations? (1=yes, 2=no)

☐

(*If yes*) give describe the investigation(s) and the abnormalities

_____

_____

_____

_____

_____

6.11	Did the patient undergo a brain biopsy during life? (1=yes, 2=no) (*If yes*) what was the result? (1=no evidence of spongiform change, 2=spongiform change without florid plaques, 3=spongiform change with florid plaques, 4=result not yet available, 8=no biopsy performed)	☐ ☐
	Name of neuropathologist:	_____
6.12	Did the patient undergo a tonsil biopsy? (1=yes, 2=no)	☐
	(*If yes*) what was the result? (1=no evidence of PrP immunostaining, 2=equivocal, 3=PrP positive, 4=result not available, 8=no biopsy performed)	☐

7. Material available

		1=yes, 2=no	Quantity (mls)
7.1	Blood: frozen for general use	☐	☐☐
	separated and frozen for transmission studies	☐	☐☐
7.2	Urine	☐	☐☐
7.3	CSF	☐	☐
7.4	Was a post mortem performed? (1=yes, 2=no)	☐	
	(*If yes*) is neuropathological material available? (1=yes, 2=no, 8=not applicable)	☐	
	(*If material is available*) is material available in Edinburgh? (1=yes, 2=no, 8=not applicable)	☐	
7.5	Are post mortem results available? (1=yes, 2=no, 8=no post mortem performed) (*If yes*) what is the result? (1=no evidence of spongiform change, 2=spongiform change without florid plaques, 3=spongiform change with florid plaques, 4=result not yet available, 8=no post mortem performed)	☐ ☐	
	Name of neuropathologist:	_____
7.6	Are PrP genotype data available? (1=yes, 2=no)	☐	
	(*If yes*) did the patient carry a mutation? (1=yes (specify), 2=no)	☐ _____	
	(*If yes*) what was the patient's codon 129 genotype? (1=MM, 2=MV, 3=VV)	☐	

☐☐

8.	**Patient classification**	
8.1	At notification to the CJDSU, what was the patient's classification? (1.0=definite CJD, 2.0=probable CJD, 3.0=possible CJD, 4.1=diagnosis unclear, 4.2=CJD thought unlikely, 4.3=definitely not CJD, 5=GSS) (*If patient was classified as at least possible CJD/GSS*) which category of disease was suspected? (S=sporadic CJD, N=nvCJD, F=familial CJD, I=iatrogenic CJD, G=GSS, 8=not applicable)	.
8.2	What was the highest classification on the basis of clinical information alone? (2=probable CJD, 3=possible CJD, 4=neither probable nor possible CJD, 5=GSS)	
8.3	At the time of completion of this review, what is the patient's classification? (1.0=definite CJD, 2.0=probable CJD, 3.0=possible CJD, 4.1=diagnosis unclear, 4.2=CJD thought unlikely, 4.3=definitely not CJD, 5=GSS) (*If patient was classified as at least possible CJD/GSS*) which category of disease is suspected? (S=sporadic CJD, N=nvCJD, F=familial CJD, I=iatrogenic CJD, G=GSS, 8=not applicable)	.
8.4	(*If patient was classified as at least possible CJD/GSS*) what was the clinical presentation of subject at onset of symptoms? (1= rapidly progressive dementia, 2= Heidenhain, 3=pure psychiatric onset, 4=slowly progresive dementia, 5= pure cerebellar onset, 6= extrapyramidal onset, 6=stroke like onset, 7=other, 8=not applicable, 9= unable to ascertain/missing)	

D. NATIONAL CJD REPORTING FORM

FAX TO:

Patient details

Surname:.. Forename(s):...

Postal Address:..
....
....
Postcode:..

Telephone number:...............................

Fax Number:.......................................

Email Address:.....................................

NHS Number, if known:...

Family, carer or independent representative details (if appropriate*)

* This may be appropriate if the approach is made via a lead family member, carer or independent representative (i.e. when a patient is too ill to be approached directly or has a preference for this route).

Surname:.. Forename(s):...

Postal Address:..
....
....
Postcode:..

Telephone number:...............................

Fax Number:.......................................

Email Address:.....................................

Neurologist details (or other hospital clinician)

Surname:.. Forename(s):...

Hospital Postal Address:..
....
....
Postcode:..

Telephone number:...............................
Fax Number:.......................................

```
┌─────────────────────────────────────────────────────────────┐
│                       CCDC details                          │
│                                                             │
│   Surname:....................................  Forename(s):.................................  │
│                                                             │
│   Postal Address:.................................................................................  │
│   ..............................................................................................  │
│   Postcode:......................................................  │
│                                                             │
│   Telephone number:................................  │
│                                                             │
├─────────────────────────────────────────────────────────────┤
│ GP Details                                                  │
│                                                             │
│   Surname:....................................  Forename(s):.................................  │
│                                                             │
│   GP Practice Postal Address:.................................................................  │
│   ..............................................................................................  │
│   ..............................................................................................  │
│   Postcode:......................................................  │
│                                                             │
│   Telephone number:................................  │
│   Fax Number:.........................................  │
└─────────────────────────────────────────────────────────────┘
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Brief clinical details: (please attach recent letter or discharge summary)

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Consent:
*please delete as appropriate

I have been provided with the patient information
leaflet which explains the role of the National | YES / NO |
CJD Surveillance Unit and the National Prion
Clinic.

I agree to my/the patient's* details being
forwarded to the National CJD Surveillance Unit | YES / NO |
and the National Prion Clinic.

I agree that staff from the National CJD Surveillance Unit in Edinburgh and the National Prion Clinic in London can visit myself/the patient* and my/their* relatives at a mutually convenient time for clinical assessment and surveillance purposes and to provide the opportunity, should we wish, to discuss ongoing research, including clinical trials of potential treatments.

YES / NO

I understand that this may mean providing further information to help in the organisation of my/the patient's* care, and to contribute to a better understanding of the illness.

YES / NO

Signed: ....
Print: ....
Date: ....
On completion, please fax to NCJDSU 0131 343 1404, NPC 0207 061 9889 and also to your local CCDC

E. Tables of frequencies of symptoms and signs in Definite, Probable and Possible sCJD / Unclear diagnosis in 1993/4 and 2003/4

Table A

Clinical symptoms at onset	Definites 1993/4	Definites 2003/4	Significance
Forgetful	43.9 % (36)	39.5 % (30)	NS
Unsteady	35.4 % (29)	22.4 % (17)	NS
Sleep	25.6 % (21)	22.4 % (17)	NS
Visual	19.5 % (16)	22.4 % (17)	NS
Weight loss	18.3 % (15)	11.8 % (9)	NS
Psychiatric	15.9 % (13)	11.8 % (9)	NS
Speech	9.8 % (8)	7.9 % (6)	NS
Dizzy	12.2 % (10)	11.8 % (9)	NS
Weakness	4.9 % (4)	6.6 % (5)	NS
Sensory symptoms	3.7 % (3)	3.9 % (3)	NS
Headache	2.4 % (2)	2.6 % (2)	NS
Hallucinations	1.2 % (1)	2.6 % (2)	NS
Symptoms suggesting seizure	1.2 % (1)	0 % (0)	NS

Table B

Clinical symptoms at onset	Probables 1993/4	Probables 2003/4	Significance
Forgetful	53.8 % (7)	39.3 % (22)	NS
Unsteady	23.1 % 3	25.0 % (14)	NS
Sleep	15.4 5 (2)	16.1 % (9)	NS
Visual	15.4 % (2)	21.4 % (12)	NS
Weight loss	15.4 % 92)	7.1 % (4)	NS
Psychiatric	7.7 % (1)	17.9 % (10)	NS
Speech	23.1 % (3)	8.9 % (5)	NS
Dizzy	15.4 % (2)	14.3 % (8)	NS
Weakness	0 % (0)	0 % (0)	NS
Sensory symptoms	0 % (0)	3.6 % (2)	NS
Headache	38.5 % (5)	10.7 % (6)	NS
Hallucinations	7.7 % (1)	3.6 % (2)	NS
Symptoms suggesting seizure	0 % (0)	0 % (0)	NS

Table C

Clinical symptoms at onset	Possible / Unclear diagnosis 1993/4	Possible / Unclear diagnosis 2003/4	Significance
Forgetful	50 % (13)	59.4 % (19)	NS
Unsteady	23.1 % (6)	25% (8)	NS
Sleep	11.5 % (3)	9.4 % (3)	NS
Visual	7.7 % (2)	0 % (0)	NS
Weight loss	15.4 % (4)	9.4 % (3)	NS
Psychiatric	15.4 % (4)	12.5 % (4)	NS
Speech	0 % (0)	6.3 % (2)	NS
Dizzy	23.1 % (6)	3.1 % (1)	NS
Weakness	7.7 % (2)	3.1 % (1)	NS
Sensory symptoms	3.8 % (1)	3.1 % (1)	NS
Headache	3.8 % (1)	3.1 % (1)	NS
Hallucinations	7.7 % (2)	6.3 % (2)	NS
Symptoms suggesting seizure	3.8 % (1)	0 % (0)	NS

Table D

Clinical symptoms ever	Definites 1993/4	Definites 2003/4	Significance
Forgetful	95.1 % (78)	97.4 % (74)	NS
Unsteady	89.0 % (73)	94.7 % (72)	NS
Sleep	73.2 % (60)	55.3 % (42)	p = 0.02
Visual	61.0 % (50)	65.8 % (50)	NS
Weight loss	45.1 % (37)	25.0 % (19)	p = 0.01
Psychiatric	41.5 % (34)	31.6 % (24)	NS
Speech	80.5 % (66)	84.2 % (64)	NS
Dizzy	25.6 % (21)	27.6 % (21)	NS
Weakness	34.1 % (28)	35.5 % (27)	NS
Sensory symptoms	4.9 % (4)	17.1 % (13)	p = 0.02
Headache	12.2 % (10)	23.7 % (18)	NS
Hallucinations	36.6 % (30)	52.6 % (40)	NS
Symptoms suggesting seizure	12.2 % (10)	5.3 % (4)	NS

Table E .

Clinical symptoms ever	Probables 1993/4	Probables 2003/4	Significance
Forgetful	100 % (13)	100 % (53)	NS
Unsteady	92.3 % (12)	98.1 % (52)	NS
Sleep	46.2 % (6)	41.5 % (22)	NS
Visual	53.8 % (7)	67.9 % (36)	NS
Weight loss	53.85 (7)	22.6 % (12)	p = 0.04

Psychiatric	30.8 % (4)	26.4 % (14)	NS
Speech	84.6 % (11)	92.5 % (49)	NS
Dizzy	23.1 % (3)	32.1 % (17)	NS
Weakness	15.4 % (2)	26.4 5 (14)	NS
Sensory symptoms	38.5 % (5)	18.9 % (10)	NS
Headache	15.4 % (2)	30.2 % (16)	NS
Hallucinations	38.5 % (5)	49.1 % (26)	NS
Symptoms suggesting seizure	15.4 % (2)	3.8 % (2)	NS

Table F

Clinical symptoms ever	Possible / Unclear diagnosis 1993/4	Possible / Unclear diagnosis 2003/4	Significance
Forgetful	92.3 % (24)	96.9 % (31)	NS
Unsteady	84.6 % (22)	65.6 % (21)	NS
Sleep	46.2 % (12)	43.8 % (14)	NS
Visual	26.9 % (7)	18.8 % (6)	p = 0.003
Weight loss	30.8 % (8)	25.0 % (8)	NS
Psychiatric	23.1 % (6)	31.3 % (10)	NS
Speech	57.7 % (15)	56.3 % (18)	NS
Dizzy	30.8 % (8)	9.4 % (3)	p = 0.04
Weakness	46.2 % (12)	15.6 % (5)	p = 0.008
Sensory symptoms	19.2 % (5)	15.6 % (5)	NS
Headache	23.1 % (6)	18.8 % (6)	NS
Hallucinations	19.2 % (5)	53.1 % (17)	NS
Symptoms suggesting seizure	3.8 % (1)	9.4 % (3)	NS

Table G

Signs on 1st exam.	Definites 93/4	Definites 03/4	Significance
Dementia	56.1 % (46)	63.2 % (48)	NS
Cerebellar	40.2 % (33)	48.7 % (37)	NS
Pyramidal	11.0 % (9)	19.7 % (15)	NS
Extrapyramidal	4.9 % (4)	2.6 % (2)	NS
Myoclonus	9.8 % (8)	19.7 % (15)	NS
Other movt disorder	9.8 % (8)	9.2 % (7)	NS
Oculomotor	11.0 % (9)	25.0 % (19)	NS
Cortical blindness	1.2 % (1)	0 % (0)	NS
Dyspraxia	8.5 % (7)	11.8 % (9)	NS
Akinetic mutism	0 % (0)	0 % (0)	NS
Primitive reflexes	4.9 % (4)	3.9 % (3)	NS
Sensory signs	14.6 % (12)	9.2 % (7)	NS
Neurogenic muscle wasting	1 % (1.2)	1.3 % (1)	NS

Urinary incontinence / catheterised	7.3 % (6)	7.9 % (6)	NS

Mean time to 1st examination for pathologically confirmed cases was 3.3 months for 1993/4 referrals and 4.4 months for 2003/4 referrals.

Table H

Signs on 1st exam.	Probables 1993/4	Probables 2003/4	Significance
Dementia	92.3 % (12)	62.3 % (33)	p = 0.05
Cerebellar	61.5 % (8)	56.6 % (30)	NS
Pyramidal	30.8 % (4)	13.2 % (7)	NS
Extrapyramidal	0 % (0)	1.9 % (1)	NS
Myoclonus	15.4 % (2)	18.9 % (10)	NS
Other movt disorder	0 % (0)	11.3 % (6)	NS
Oculomotor	7.7 % (1)	9.4 % (5)	NS
Cortical blindness	0 % (0)	1.9 % (1)	NS
Dyspraxia	7.7 % (1)	17.0 % (9)	NS
Akinetic mutism	0 % (0)	0 % (0)	NS
Primitive reflexes	7.7 % (1)	5.7 % (3)	NS
Sensory signs	0 % (0)	7.5 % (4)	NS
Neurogenic muscle wasting	0 % (0)	0 % (0)	NS
Urinary incontinence / catheterised	0 % (0)	5.7 % (3)	NS

Mean time to exam for Probable sCJD was 1.3 months in 1993/4 and 3.0 months in 2003/4.

Table I

Signs at 1st exam	Possible / Unclear diagnosis 1993/4	Possible / Unclear diagnosis 2003/4	Significance
Dementia	65.4 % (17)	53.1 % (3)	NS
Cerebellar	46.2 % (12)	21.9 % (7)	p = 0.007
Pyramidal	7.7 % (2)	6.3 % (2)	NS
Extrapyramidal	0 % (0)	9.4 % (3)	NS
Myoclonus	19.2 % (5)	12.5 % (4)	NS
Other movt disorder	7.7 % (2)	3.1 % (1)	NS
Oculomotor	7.7 % (0)	9.4 % (3)	NS
Cortical blindness	0 % (0)	0 % (0)	NS
Dyspraxia	0 % (0)	3.1 % (1)	NS
Akinetic mutism	0 % (0)	0 % (0)	NS

Primitive reflexes	3.8 % (1)	9.4 % (3)	NS
Sensory signs	15.4 % (4)	9.4 % (3)	NS
Neurogenic muscle wasting	0 % (0)	0 % (0)	NS
Urinary incontinence / catheterised	15.4 % (4)	9.4 % (3)	NS

Mean time to first exam for Possible / Unclear diagnosis cases was 2.7 months in 1993/4 and 4.2 months in 2003/4

Table J

Clinical signs ever	Definite 1993/4	Definite 2003/4	Significance
Dementia	93.9 % (77)	97.4 % (74)	NS
Cerebellar	62.2 % (51)	68.4 % (52)	NS
Pyramidal	56.1 % (46)	51.3 % (39)	NS
Extrapyramidal	22.0 % (18)	17.1 % (13)	NS
Myoclonus	85.4 % (70)	88.2 % (67)	NS
Other movt disorder	37.8 % (31)	30.3 % (23)	NS
Oculomotor	36.6 % (30)	46.1 % (35)	NS
Cortical blindness	24.4 % (20)	9.2 % (7)	p = 0.02
Dyspraxia	28.0 % (23)	43.4 % (33)	p = 0.05
Akinetic mutism	69.5 % (57)	35.5 % (27)	p < 0.001
Primitive reflexes	59.8 % (49)	51.3 % (39)	NS
Sensory signs	22.0 % (18)	10.5 % (8)	NS
Neurogenic muscle wasting	8.5 % (7)	2.6 % (2)	NS
Urinary incontinence / catheterised	54.9 % (45)	81.6 % (62)	p < 0.001

Table K

Clinical signs ever	Probable 1993/4	Probable 2003/4	Significance
Dementia	100 % (13)	100 % (53)	NS
Cerebellar	69.2 % (9)	79.2% (42)	NS
Pyramidal	53.8 % (7)	69.8 % (37)	NS
Extrapyramidal	0 % (0)	5.7 % (3)	NS
Myoclonus	92.3 % (12)	98.1 % (52)	NS
Other movt disorder	23.1 % (3)	34.0 % (18)	NS
Oculomotor	30.8 % (4)	45.3 % (24)	NS
Cortical blindness	53.8 % (7)	22.6 % (12)	p = 0.04
Dyspraxia	30.8 % (4)	35.8 % (19)	NS
Akinetic mutism	76.9 % (10)	37.7 % (20)	p = 0.01

Primitive reflexes	61.5 % (8)	58.5 % (31)	NS
Sensory signs	0 % (0)	3.8 % (2)	NS
Neurogenic muscle wasting	0 % (0)	1.9 % (1)	NS
Urinary incontinence / catheterised	69.2 % (9)	79.2 % (42)	NS

Table L

Clinical signs ever	Possible / Unclear diagnosis 1993/4	Possible / Unclear diagnosis 2003/4	Significance
Dementia	92.3 % (24)	93.8 % (30)	NS
Cerebellar	61.5 % (16)	46.9% (15)	p = 0.02
Pyramidal	42.3 % (11)	25.0 % (8)	NS
Extrapyramidal	11.5 % (3)	21.9 % (7)	NS
Myoclonus	76.9 % (20)	78.1 % (25)	NS
Other movt disorder	19.2 % (5)	25.0 % (8)	NS
Oculomotor	30.8 % (8)	25.0 % (8)	NS
Cortical blindness	11.5 % (3)	0 % (0)	NS
Dyspraxia	19.2 % (5)	15.6 % (1)	NS
Akinetic mutism	38.5 % (10)	37.7 % (20)	p = 0.04
Primitive reflexes	42.3 % (11)	40.6 % (13)	NS
Sensory signs	15.4 % (4)	12.5 % (4)	NS
Neurogenic muscle wasting	0 % (0)	3.1 % (1)	NS
Urinary incontinence / catheterised	57.7 % (15)	50.0 % (16)	NS