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THE INFLUENCE OF AGE ON CASE ASCERTAINMENT IN CJD

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ABSTRACT

Ageing is the greatest risk factor for most forms of dementia. Variant Creutzfeldt-Jakob Disease (vCJD) however is predominantly a disease of younger adults and sporadic CJD (sCJD), although a disease of the older population, mainly affects those under 80 years of age. The very low age-specific incidence of both vCJD and sCJD in the oldest age group may, in part, be due to case under ascertainment, perhaps due to a lack of familiarity with CJD, or atypical clinical presentation of CJD

In the UK, suspect cases of CJD are referred by clinicians to the National CJD Research & Surveillance Unit (NCJDRSU) for clinical assessment and epidemiological review. Case ascertainment in CJD is important not only for appropriate clinical care but also, due to the potential for person-to-person transmission of the CJD agent through medical procedures, to help protect public health. In this thesis:

1) I describe the clinical and referral characteristics of CJD patients diagnosed later in their disease progression and determine if these characteristics differ in those diagnosed earlier. A retrospective review of CJD cases referred to the NCJDRSU, for vCJD between 1995 and 2015 (n = 177) and for sCJD between 2010 and 2015 (n = 584) was undertaken. Age was significantly associated with timing of diagnosis, with later diagnoses occurring in older patients, and differences in clinical and referral characteristics between these and younger patients.

2) I also pilot a study of enhanced CJD surveillance in the older population. Since January 2016, patients aged ≥65 years seen in NHS Lothian with a diagnosis of non-CJD dementia but with atypical features (e.g. rapid speed of progression or focal neurology) have been invited to participate in a study to investigate whether atypical CJD might underlie the diagnosis of some patients with dementia. For each participant, a clinical examination was undertaken, with consent, including Addenbrooke's Cognitive Examination–III, the frontal assessment battery, the hospital anxiety and depression scale, Barthel's Index, and the Edinburgh Motor Assessment Scale. In addition, MRI was undertaken (including DWI and FLAIR sequences), a blood sample was taken for codon-129 subtyping and patients were consented for donation of brain tissue in the event of their death. Ten patients were recruited during the initial 6 months of study. Although patients had individual features of CJD there was no evidence of CJD clinically. No patients however reached post-mortem during this initial study period. Barriers to referral, including clinician time pressures, likely impacted study referral.

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GLOSSARY

The following table lists the meanings of abbreviations used throughout this thesis.

Abbreviation	Meaning
ACE-III	Addenbrookes Cognitive Assessment - III
AD	Alzheimer's dementia
ARRNC	Anne Rowling Regenerative Neurology Centre
BI	Barthel Index
BSE	Bovine Spongiform Encephalopathy
CDC	Cognitive Disorders Clinic
CJD	Creutzfeldt Jakob Disease
CPD	Continuing Professional Development
CPN	Community Psychiatric Nurse
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal Fluid
DLB	Dementia with Lewy Bodies
DSM	The Diagnostic and Statistical Manual of Mental Disorders
DWI	Diffusion Weighted Imaging
EEG	Electroencephalogram
EMAS	Edinburgh Motor Assessment Scale
FAB	Frontal Assessment Battery
FFI	Fatal Familial Insomnia
FLAIR	Fluid-Attenuated Inversion Recovery
FTLD	Frontotemporal Lobar Dementia

gCJD	Genetic CJD
GP	General Practitioner
GSS	Gerstmann-Sträussler-Scheinker Disease
HADS	Hospital Anxiety and Depression Scale
hGH	Human Growth Hormone
iCJD	Iatrogenic CJD
IMD	Index of Multiple Deprivation
IQR	Interquartile Ranges
M	Methionine
MATS	Memory Assessment and Treatment service
MFE	Medicine For the Elderly
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NCJDRSU	National CJD Research and Surveillance Unit
NHNN	National Hospital for Neurology and Neurosurgery
NICE	National Institute of Clinical Excellence
NPC	National Prion Clinic
OAP	Old Age Psychiatry
PRNP	Prion gene
PrP^{C}	Prion protein (normal state)
PrP^{Sc}	Prion protein (diseased state)
REH	Royal Edinburgh Hospital
RPD	Rapidly Progressive Dementias
RT-QuIC	Real Time Quaking Induced Conversion

sCJD	Sporadic CJD
SIGN	Scottish Intercollegiate Guidelines Network
SPSS	Statistical Package for Social Sciences
UK	United Kingdom
V	Valine
VaD	Vascular Dementia
vCJD	Variant Creutzfeldt-Jakob Disease
VPSPr	Variably Protease Sensitive Prionopathy

CHAPTER 1: DEMENTIA AND PRION DISEASE IN THE OLDER POPULATION

1.1 Introduction

Creutzfeldt-Jakob Disease (CJD) is a rare but important form of dementia, not least due to its potential for secondary transmission in the healthcare setting. All forms of CJD are important, however, variant CJD (vCJD) has specific implications due to particular infectivity of tissues outwith the central nervous system. Whilst there has been a decline in the number of patients diagnosed with vCJD over the last decade, significant public health concerns remain and CJD surveillance is as important now as it has ever been.

This thesis will consider CJD with a particular focus on older patients, and specifically whether cases of CJD in older patients may be missed by current surveillance activities.

1.2 Dementia

Dementias are generally persistent and, for the majority, progressive syndromes commonly associated with neurodegeneration. A number of types of dementia (or syndromes) exist, all with the core feature of a decline from previous functioning. The Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM – V) definition of dementia (now termed 'major neurocognitive disorders') is detailed in Box 1.

Box 1: DSM-V criteria for the diagnosis of major neurocognitive disorders (2013) [1]

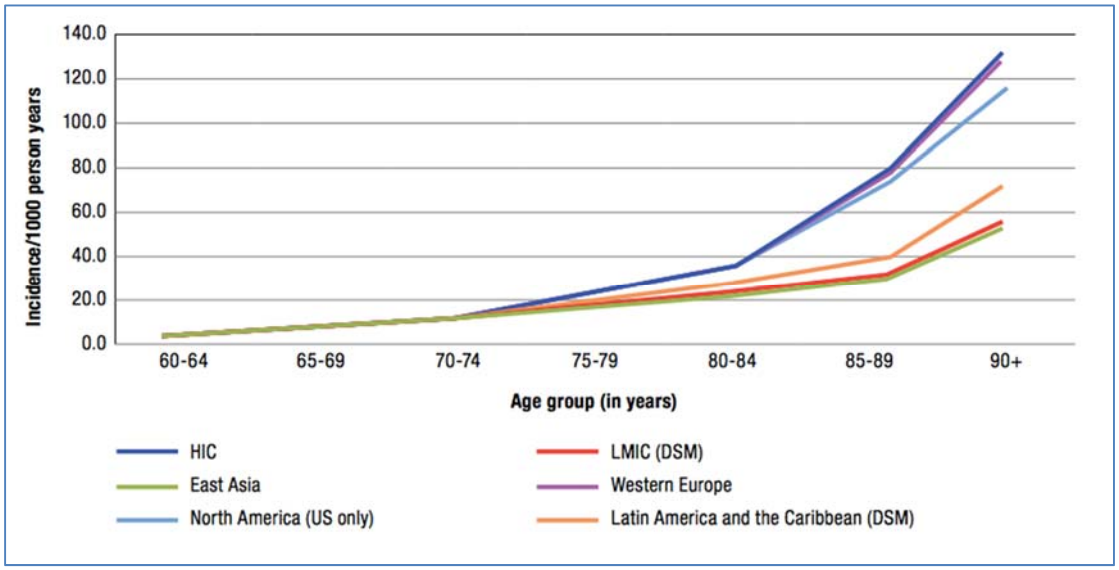
1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: i) concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function and ii) a substantial impairment in cognitive performance, preferably documented by standardised neuropsychological testing or, in its absence, another quantified clinical assessment.
2. The cognitive deficits interfere with independence in everyday activities (ie, at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
3. The cognitive deficits do not occur exclusively in the context of a delirium.
4. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia).

The global prevalence of dementia in 2015 was estimated to be 46.8 million, with an estimated overall incidence of 17.3 cases per 1,000 person years in those aged ≥60 years (equating to approximately 9.9 million new cases per year) [2]. In the United Kingdom (UK), the overall prevalence and incidence in those aged ≥65 years in 2015 was estimated to be 670,000 and 17.7 per

1,000 person years (equating to just under 210,000 new cases per year) respectively [3, 4].

The incidence of dementia has been demonstrated to rise with age both in the UK and globally (Figure 1) [2, 5]. However, in some less commonly encountered dementias this exponential relationship is not seen and a fall in age-specific incidence can occur in older patients [6, 7]. It is not clear whether this observation is a true epidemiological feature or whether it reflects under-recognition of dementia, perhaps as a consequence of less thorough investigation of cognitive symptoms in older patients.

Figure 1: Estimated age specific incidence of dementia; World Alzheimer Report (2015) (permission for use granted) [5]



HIC: High income countries LMIC: lower middle income countries

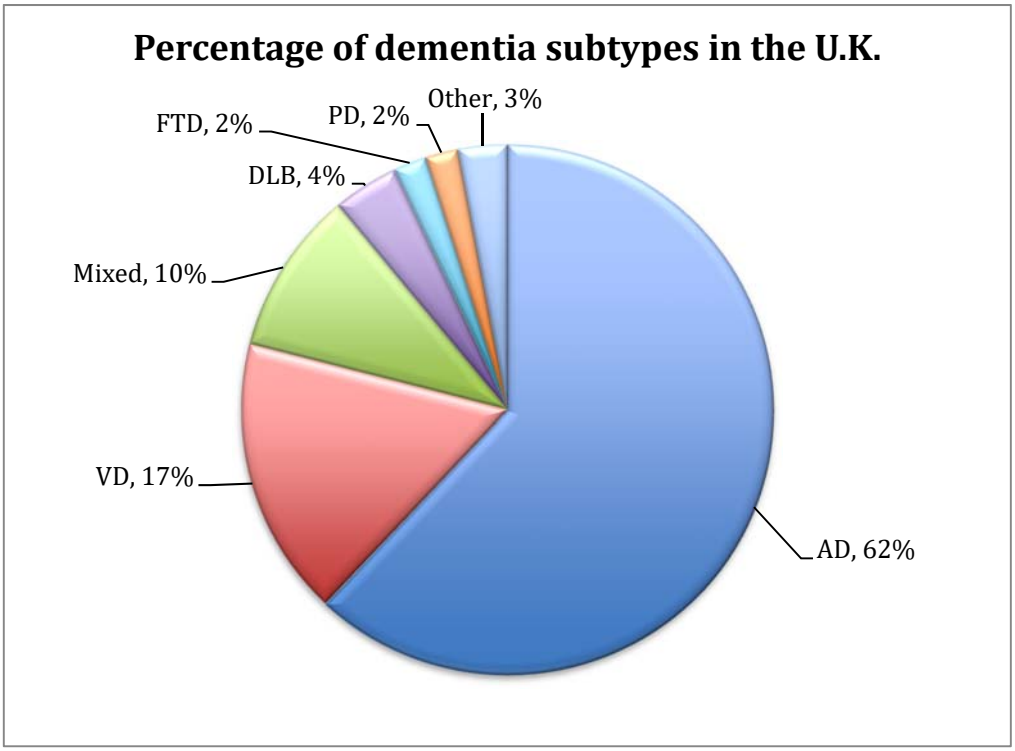
The global prevalence of dementia is predicted to increase by almost three fold by 2050, predominantly due to a rising number of cases in low to middle income countries (most likely reflecting global demographic changes) [2]. High

income countries (including the UK), however has seen a decline in incidence of all cases of dementia in those aged ≥65 years between 1991 and 2011 [4]; reasons for this are not clear, although it may reflect cardiovascular-targeted public health measures [2] and improving literacy / educational attainment in recent generations [8, 9]. This observed decline should not however underestimate the predicted societal impact of dementia in the UK; dementias are associated with increased rates of hospital admissions [10] and institutional care [11], which, given the UK's ageing population poses significant future economical burden.

1.3 Dementia diagnosis and the older population

Dementia can be caused by a range of pathologies. These pathologies are associated with clinical syndromes. The relative percentage of dementia syndromes in all age groups in the UK is demonstrated in Figure 2. In all age groups, the most common form of dementia is Alzheimer's dementia, accounting at least in part for 65-70% of all diagnoses [12, 13]. Other conditions, driven by differing pathological substrates, also contribute to dementia. Each of these can be diagnosed according to well-established consensus diagnostic criteria ([6, 14-17]) and are described in more detail in Appendix A. Symptoms affecting patients include memory disturbance but also deficits in other cognitive domains including language, behaviour and visuospatial functioning. Discriminating between the causes of dementia is challenging with histopathological (or genetic) analysis remaining the gold standard.

Figure 2: Relative percentage of dementia subtypes in the U.K., all ages (2014) [18]



PD – Parkinson's disease; FTD – frontal temporal dementia; DLB – dementia with Lewy Bodies; VD – vascular dementia; AD – Alzheimer's dementia

Discriminating between the different subtypes of dementia in any age group is important; it allows for timely evaluation of potentially reversible conditions and for earlier consideration of the potential role for therapeutic interventions. Importantly, it also allows for planning with an increased likelihood the patient will be able to participate in discussions regarding their own future care.

The diagnosis of a dementia however has its challenges. These include: 1) patient recognition of symptoms; 2) the clinical challenge of attributing patients' cognitive symptoms to a dementia, and ascertaining if these impact

daily functioning; and 3) establishing the underlying pathophysiology of patients' deficits. Both these challenges have additional factors to consider in the older population. Firstly, approximately 50% of individuals with dementia are not registered as such on primary care registries [2, 19, 20]; those who are older are more likely to be missed [19, 21, 22]. A number of reasons suggested as to why this may be the case are detailed in Box 2. Even where dementia is identified, however, consensus criteria for the pathophysiological classification of the dementia often lack utility in clinical practice as criteria are generally designed for recruitment to research trials and therefore favour specificity over sensitivity. This is of particular relevance in older patients, for the following reasons:

1) The relative high prevalence of common dementias.

In general the more common forms of dementia (i.e. Alzheimer's dementia) are over-diagnosed in older patients and the less common forms, under-diagnosed [6, 21, 23, 24]

2) The prevalence of mixed pathology in older patients.

Almost half of older patients with a diagnosis of dementia had evidence of multiple pathologies (generally mixed Alzheimer's pathology and atherosclerosis) at post-mortem [25]

3) An increased likelihood of dissociation of pathology and typical phenotype.

In older patients without a clinical diagnosis of dementia, 49% have been found to have pathological changes at post-mortem that fulfilled the diagnostic

criteria for Alzheimer's dementia [26] with 3% found to have Lewy Bodies [27]. Conversely, 22% of older patients with a clinical diagnosis of dementia had no neuropathological features of dementia at post-mortem [26].

4) The low rate of post-mortem in older patients.

Confirmation of a diagnosis of a particular cause of dementia can only be reached with post-mortem histopathological examination of brain material / a brain biopsy in life (or identification of a disease causing genetic mutation). The general rate of post-mortem, however, is in decline [28, 29] with <1% of deaths now reaching hospital post-mortem in the UK [30]. Post-mortem rates are lowest in the elderly [29], making it difficult to establish numbers of cases (outwith research cohorts), leading to a limited understanding of both clinical features and investigation interpretation in older patients. These problems are particularly pertinent in the less commonly encountered types of dementia, such as prion disease.

Box 2: Possible reasons for missed cases of dementia in the elderly

- Risk factors for delayed presentation more common in elderly (depression / lower socioeconomic status / social isolation [19, 21, 31])
- Cognitive symptoms may be misattributed to normal ageing [32]
- Confounding factors more common in elderly (polypharmacy, remote or current alcohol excess, or poor nutrition) [22, 33]
- Physical co-morbidities are common in elderly; these may be given priority with time / financial constraints limiting full attention to cognitive symptoms [22, 33].
- Poor access to healthcare (physical reasons (e.g. transport), co-morbidities (e.g. pacemaker excluding MRI, anticoagulation limiting lumbar puncture etc.), or a lack of awareness of resources in a less internet savvy / informed generation) [22, 33].
- More likely to be seen by generalists less confident in differentiating between abnormal and normal cognitive ageing [22].

1.4 The prion hypothesis

Prion diseases are neurodegenerative and universally fatal conditions. They are characterised by a post-translational structural change of the naturally occurring prion protein (PrP^{C}) resulting in tissue deposition of an abnormal, mis-folded, and partially protease-resistant form (PrP^{Sc}).

The normal PrP^{C} is found in most tissues throughout the body however is found in highest concentrations in the central nervous system and

lymphoreticular system. The prion-only hypothesis states that all that is required for propagation of the diseased form of the prion protein is the presence of PrP^{Sc} and PrP^{C}. PrP^{C} is recruited as the substrate with conformational change to PrP^{Sc} in an autocatalytic manner [27].

Prion diseases were originally described in animals (with the prototypic illness of scrapie in sheep and goats) with later description in humans.

1.5 Human prion diseases

Human prion diseases consist of Creutzfeldt-Jakob disease (CJD), the most common form, comprising sporadic, genetic, iatrogenic types (including variant CJD [vCJD: a much less commonly encountered acquired form], and Kuru [a historical disease affecting a small part of Papua New Guinea]) and two relatively distinct genetic forms: Gerstmann-Sträussler-Scheinker syndrome & Fatal Familial Insomnia. A more recently described form of uncertain nosology is Variably Protease Sensitive Prionopathy (VPSPr). This review will focus on CJD, and in particular sporadic and variant CJD.

Creutzfeldt-Jakob Disease (CJD) was first described by the neuropathologist, Hans Gerhard Creutzfeldt and neurologist, Alfons Jakob in 1920. It is a highly heterogeneous disorder categorised according to aetiology with differing associated clinicopathological and epidemiological characteristics. There are however key commonalities between all forms of CJD:

a) Clinical features.

Common to all forms of CJD is a characteristic, usually rapidly progressive, intellectual and multifocal neurological decline converging on a terminal akinetic mute stage. In general this is shortest in sporadic and longest in variant and some inherited forms.

b) Codon-129 expression.

Disease susceptibility and phenotypic expression of all forms of CJD are mediated by expression of either methionine or valine at codon-129 on the prion gene (*PRNP*) on chromosome 20. A significant excess of methionine homozygotes are seen; in the normal UK population, 44.1% are homozygous for methionine, however, 61.5 – 67% of sCJD and 99.4% of vCJD cases tested were methionine homozygotes [7, 34, 35].

c) Neuropathological appearances.

Core features include spongiform change, reactive proliferation of astrocytes and microglia, neuronal loss, + / - amyloid plaque deposition. The spongiform change is seen within the neuronal processes throughout the cerebral cortex, and also commonly in other grey matter structures such as the basal ganglia and thalamus. Demonstration of the abnormal isoform, PrP^{Sc}, by immunohistochemistry is also a key diagnostic feature seen in all forms [36].

d) Transmissibility and public health considerations.

All forms of CJD are potentially transmissible, making them unique amongst the neurodegenerative disorders. Further to this, PrP^{Sc} is resistant to standard

autoclaving and sterilisation procedures of surgical equipment. This combined with a lack of a pre-clinical diagnostic / screening test furthers the unique implications for public health posed by CJD

1. *Sporadic CJD*

Sporadic CJD (sCJD) is the most common form of CJD, accounting for >80% of all cases. It is a disease of older patients, affecting those mostly in their late 60s and early 70s, with the median age of onset of 67 years. Cases as young as 15 years old and as old as 94 years have, however, been reported [7].

The exact aetiology of sCJD is unknown. Theories include the spontaneous production of PrP^{Sc} via a random (as yet undetermined) event, the somatic mutation of the prion gene (*PRNP*), or exposure to an as yet unidentified exogenous source of infection. Given what is known about the epidemiology of sCJD, the last of these is unlikely to be the general explanation for sCJD cases, however it is difficult to exclude as the cause of at least some cases.

sCJD is characterised by a rapidly progressive dementia associated with multifocal neurological decline (including ataxia, visual disturbance, pyramidal and extrapyramidal features with later myoclonus and akinetic mutism). The median duration of illness is 4 months (range 1 to 74 months). Approximately 60% of UK patients will die within 6 months of symptom onset [7].

Internationally accepted diagnostic criteria are as detailed in Box 3, and have been recently updated to incorporate the CSF prion protein biomarker, RT-QuIC.

Box 3: Internationally agreed diagnostic criteria for sCJD (as of 31st December 2015) [37]

sCJD
I Rapidly progressive cognitive impairment
II A Myoclonus
B Visual or cerebellar problems
C Pyramidal or extrapyramidal features
D Akinetic mutism
III Typical EEG
IV High signal in caudate/putamen on MRI brain scan

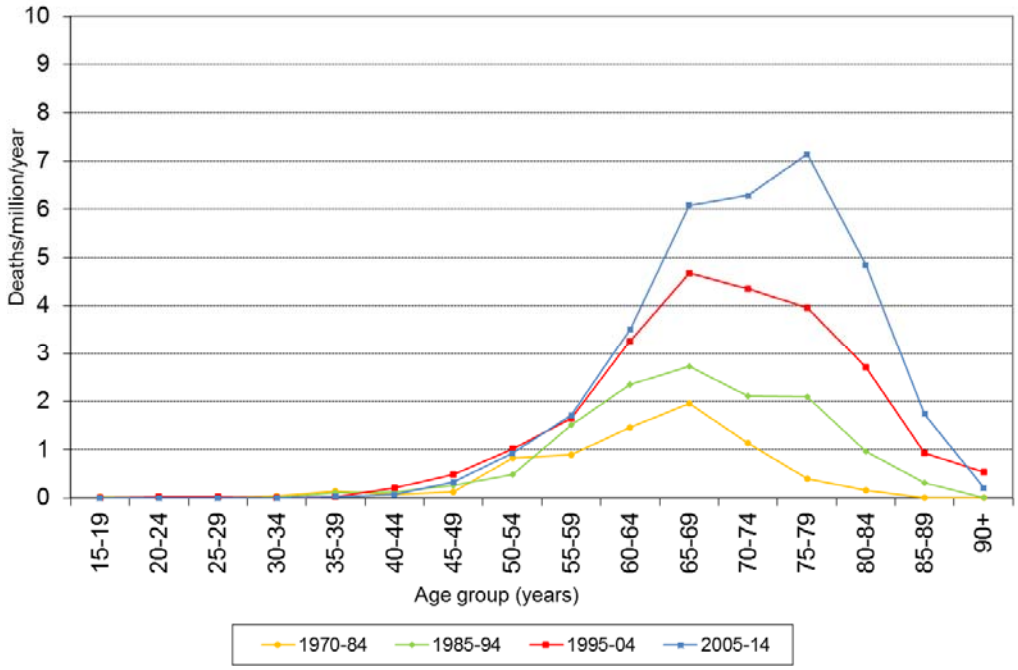
DEFINITE:
Progressive neurological syndrome AND Neuropathologically OR immunocytochemically OR biochemically confirmed

PROBABLE:
I + 2 of II and either typical EEG OR typical MRI brain scan OR positive 14-3-3 OR progressive neurological syndrome and positive RT-QuIC in CSF or other tissues

POSSIBLE:
I + 2 of II + duration <2 years

Worldwide, the annual mortality rate from sCJD is 1-2 cases/million/year [6]; in the UK this increases to 4-5 cases/million/year in those over 65, and then declines, with few cases in those ≥80 years old (Figure 3). These figures are comparable to other countries with established CJD surveillance centres. Similar to other centres also are the age, sex, codon-129 distribution, and the rise seen in the age specific mortality rates of sCJD, particularly in older patients [38, 39].

Figure 3: Age specific mortality rates from sporadic CJD in the UK (1970 – 2014) - As taken from the NCJDRSU 23rd Annual report (2015) [7]



2. *Variably protease sensitive prionopathy*

A newly recognised prion disease has been described: variably protease sensitive prionopathy (VPSPr) [40]. The nosological status of this disease is uncertain however it is most likely a subtype of sporadic CJD.

The frequency of VPSPr in the general population is not known and some reported cases are hard to distinguish from more common dementing illnesses without neuropathological examination.

The literature describing clinical features is limited to small case series meaning it is difficult to draw general conclusions, however like other forms of CJD, VPSPr presents as a relatively rapid onset dementia with associated neuropsychiatric features [40]. Unlike vCJD and sCJD, however, the majority of cases are homozygote for valine at codon-129.

3. *Genetic prion disease*

Approximately 10-15% of human prion diseases are due to autosomal dominantly inherited mutations on *PRNP* [41].

There are 3 recognised forms of genetic prion disease: genetic (previously familial) CJD (gCJD); fatal familial insomnia (FFI) and Gerstmann-Sträussler-Scheinker disease (GSS) (see Table 1).

There is considerable variability in the frequency of different genetic mutations dependent on country of origin and ethnicity, however, overall the most common mutation is the point mutation, E200K (which accounts for 70% of cases of gCJD in the UK [41]). Like most forms of CJD, all forms of inherited CJD are over-represented by methionine homozygotes at codon-129.

Table 1: Inherited CJD (Adapted from Genetic prion disease: the EUROCJD experience (2005) [41])

Condition	sCJD mimic	Positive family history (%)	MRI – basal ganglia restricted diffusion (%)	EEG – slow periodic triphasic complexes (%)	CSF positive 14-3-3 (%)
GSS	No	70	30	10	50
FFI	No	90	20	<5	20
E200K	Yes	50	45	70	90
V210I	Yes	10	15	80	95

4. *Iatrogenic CJD*

CJD may rarely be attributable to iatrogenic exposure (iCJD). The main sources of infection have been past exposure to human growth hormone and dura mater grafts. Rarely contaminated neurosurgical instruments, corneal grafts and gonadotrophins have been implicated [42].

In the UK, 85 cases were reported between 1970 and 2015, with the vast majority (99% of cases) due to contaminated human growth hormone (hGH) (n = 76) and contaminated dura mater grafts (n = 8). Case numbers peaked in the late 1990s and have continued to fall since.

In general, patients present with a cerebellar syndrome (or visual disturbance in dura mater cases) followed by cognitive and multifocal neurological decline. The mean age at death for hGH-derived iCJD in the UK is 35 years old (range 20 – 51 years) with a mean incubation period of 20 years. Dura mater-derived

cases have a later mean age at death of 46.5 years old (range 27 – 78 years) with a shorter incubation period of 12 years [42].

Allele expression at codon-129 influences both disease susceptibility and incubation period of iCJD. Those who present earlier are over-represented by methionine homozygotes with a later 'second wave' of heterozygote cases. This is consistent with other acquired forms of prion disease (e.g. Kuru) [43, 44].

5. Variant CJD

In 1996 the first cases of variant CJD (vCJD) were described in the UK [45]. In total 178 cases of vCJD have been reported between 1996 and December 2017 [6]. The majority of cases have been causally linked to bovine spongiform encephalopathy (BSE) epidemiologically and through molecular analysis and strain linkage of PrP^{Sc} [46, 47]. Three cases have however been associated with infection via contaminated non-leucodepleted red blood cells, with two further instances of transmission of infection identified in asymptomatic recipients of blood/blood products from a donor who subsequently developed vCJD [48, 49].

Variant CJD is characterised by an insidious onset of behavioural change, psychiatric symptoms and sensory disturbance, followed by cognitive decline and ataxia with later myoclonus and terminal decline into akinetic mutism. Internationally accepted diagnostic criteria are as detailed in Box 4. The median duration of illness is longer than sCJD at 14 months (range 6 – 114

months). Distinct from other human forms of CJD (where infectivity is mostly limited to the central nervous system), PrP^{Sc} can also be detected within the lymphoreticular system posing unique public health concerns with cases, as above, transmitted via blood products.

Box 4: Internationally agreed diagnostic criteria for vCJD (as of 31st December 2015) [37]

I
A Progressive neuropsychiatric disorder
B Duration of illness > 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
B Persistent painful sensory
C Ataxia
D Myoclonus or chorea or dystonia
E Dementia

III
A EEG does not show the typical appearances of sCJD in the early stages of illness
B Bilateral pulvinar high signal on MRI scan

IV Positive tonsil biopsy

DEFINITE: 1A and neuropathological confirmation of vCJD

PROBABLE: I and 4/5 of II and IIIA and IIIB
Or I and IV A

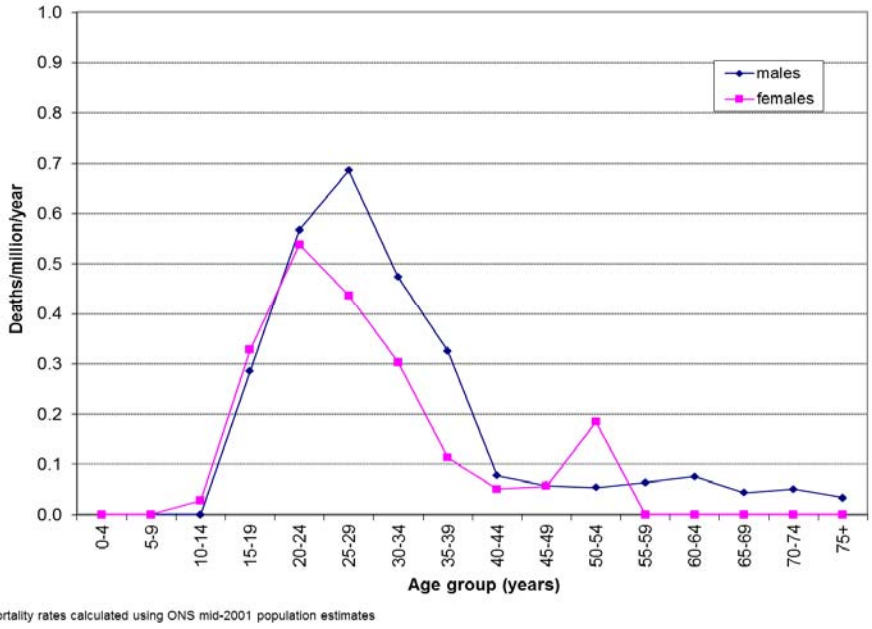
POSSIBLE: I and 4/5 of II and III A

Whilst the general pathology of vCJD is similar to other human prion diseases, the neuronal loss is particularly severe within the pulvinar region

giving rise to distinct MRI characteristics and possibly the sensory symptoms characteristic of vCJD. The pattern of deposition of PrP^{Sc} is characteristically different to sCJD and highly conserved between cases of vCJD [50].

In general, vCJD is a disease of the young, with the median age of onset younger than sCJD at 26 years old (Figure 4) although cases as young as 12 years old, and older cases, up to 74 years old, have been reported. [7].

Figure 4: Age specific incidence of variant CJD in men and women (1996 – 2014) - As taken from the NCJDRSU 23rd Annual report (2015) [7]



As discussed in iCJD, allele expression at codon-129 influences incubation period in acquired cases of prion disease with methionine homozygotes generally presenting earlier and a later, 'second wave', of heterozygotes. There is suggestion of this in vCJD; all cases of probable / definite vCJD (tested for codon-129 polymorphism) up until 2009 were methionine

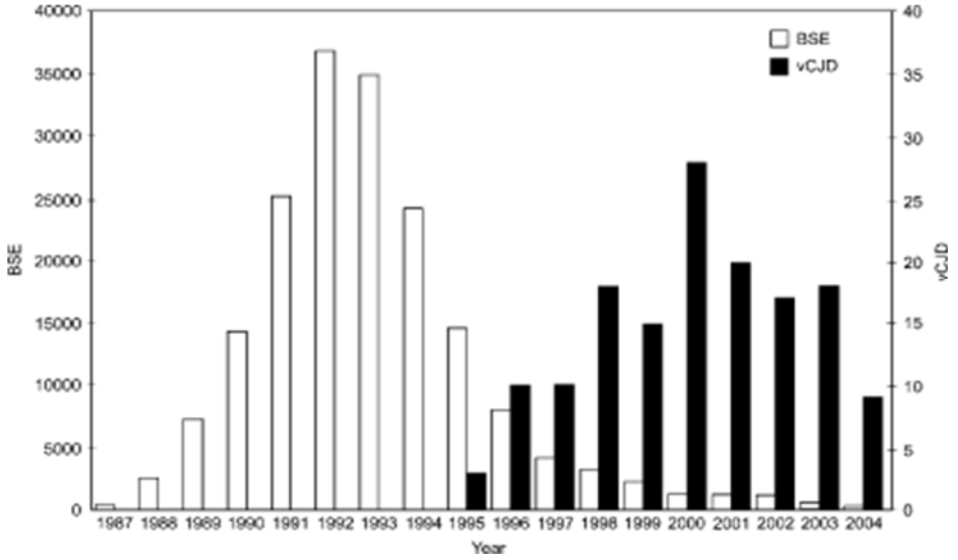
homozygotes. In 2009, the first case of possible MV vCJD was diagnosed [49], with the first case of pathologically confirmed MV vCJD diagnosed in 2016 [51]. Both cases were in their 30s and therefore older than the median age of onset of vCJD. The case of possible vCJD was more in keeping with 'classical vCJD' and presented with a protracted history over 19 months of pain, psychiatric symptoms, cognitive decline and ataxia. The MRI however was equivocal for the pulvinar sign and CSF 14-3-3 was positive. The case of definite vCJD presented with psychiatric and behavioural disturbance and, unusually for vCJD, with visual symptoms. Both disease duration (10 months) and MRI findings (hyperintensity greatest of the basal ganglia plus cortical ribboning) were atypical for vCJD and more compatible with a diagnosis of sCJD. CSF was negative for RT-QuIC and 14-3-3. Whilst this case was suggestive of prion disease it is important that the presentation had features more in keeping with sCJD, which has a lower post-mortem rate compared to vCJD (60% compared to 69% respectively) and different potential public health implications.

The number of vCJD cases peaked in 2000 and has been falling since, reflecting exposure to BSE (Figure 5). There are currently no known living cases of vCJD in the world, however, a prevalence of subclinical prion infection has been reported in the UK, with significant implications for public health. In 2013, the 'Appendix II Study' was published. This demonstrated a prevalence of clinically silent abnormal prion protein amongst those exposed to BSE during the 1980s and 1990s, of 1 in 2000 of the UK population [52]. In 2017 the 'Appendix III Study' was published, demonstrating a prevalence of

abnormal prion protein in approximately 1 in 4,200 in those who had their appendix removed prior to 1980 (that is, prior to the time when BSE was first thought to be circulating) and in those born after 1996 (that is, after the final restrictions were put in place to remove BSE from the human food chain) [53]. Whilst the prevalence in Appendix III is lower compared to the previous Appendix study, the difference was not statistically significant. It may therefore be that the period of BSE infection exposure was longer than originally estimated or that, in fact, the presence of abnormal prion protein does not necessarily equate to previous dietary exposure to BSE. At present, this is unresolved.

Whilst the two heterozygote cases do not amount to a 'second wave' of vCJD, and it is not clear the significance of subclinical infection, they both highlight the important role of on-going disease surveillance and post-mortem confirmation of cases with disease sub-typing.

Figure 5: Number of cases of BSE and vCJD in the UK (1987 – 2004): As taken from the NCJDRSU 23rd Annual report (2015) [7]



1.6 CJD surveillance in the UK

In 1990, the National CJD Research and Surveillance Unit (NCJDRSU) was established in the UK following the BSE epidemic, to '..monitor the characteristics of all forms of CJD, to identify trends in incidence rates, to study risk factors for the development of disease and to contribute to improving the quality of care for those with CJD' [7]. It was through this surveillance project that the first cases of variant CJD were detected [45].

Integral to the surveillance system is the referral, by clinicians, of suspected CJD cases to the NCJDRSU and their subsequent follow up by the NCJDRSU team. Referral may be via: 1) clinicians directly, on clinical suspicion of CJD; 2) referral for cerebrospinal fluid analysis for markers of CJD; 3) death certificates, where CJD has been included as a cause of death; and 4)

pathology, if evidence of CJD is demonstrated on biopsy or at post-mortem, without a CJD diagnosis in life.

The NCJDRSU also works closely with the National Prion Clinic (NPC) at the National Hospital for Neurology and Neurosurgery (NHNN) with clinicians encouraged to refer suspected cases to both institutes. This dual referral system ensures support is available for the clinical team as well as the patient and their family, and facilitates research into prion diseases by both centres.

1.7 Under-ascertainment of CJD

The above approach allows comprehensive case ascertainment, however no case ascertainment system is perfect and it is likely that some cases will be missed. In the UK, evidence for this, comes from the following:

1) For sCJD, an increase in mortality over time, particularly in older age groups has been reported across all European and other international surveillance centres, including the UK (Figure 3). This is thought to reflect increased awareness of CJD amongst clinicians and better diagnostic methods reflecting improved case ascertainment (as opposed to a true increase in incidence). It is likely that at least part of this rise may reflect a move towards distinguishing CJD from other forms of dementia and therefore is unmasking longstanding under-ascertainment, particularly in older patients.

2) Missed cases (i.e. cases of prion disease diagnosed at post-mortem and not suspected in life) are reported as part of national disease surveillance

systems. In the UK, approximately 7% of cases of sCJD are referred to the NCJDRSU at post-mortem (although it is not clear whether CJD was suspected in such cases).

3) As a truly spontaneous protein-related neurodegenerative condition, the incidence of sCJD should rise with increasing age, in line with other neurodegenerative disorders. As per Figure 3, a fall in age specific mortality is seen over the age of 79 years old. It may be that this fall is in part a true phenomenon, such that after reaching a certain age the likelihood of developing CJD will naturally be less likely due to an innate feature of the disease itself or of how the prion protein interacts with the ageing brain. Given however the previously noted difficulties in differentiating dementia subtypes in older patients (and particularly so with less common dementias) and evidence that cases can be missed, missed cases are likely to be at least partially responsible.

vCJD, on the other hand, is a disease of younger ages. Although there is some evidence of age-related susceptibility to infection [54], the Appendix studies have demonstrated that there is a relatively high prevalence of abnormal prion protein in the lymphoreticular systems of older patients also [43,44]. Again this raises the possibility that some cases in older patients may have been missed.

Quantifying the extent of under-ascertainment in the UK surveillance system is difficult in the absence of a gold standard against which to compare

observed versus expected figures. A number of studies have looked into this. In 2002, Hillier *et al* reviewed all death certificates of those aged 15-45 years old who had died of any cause, other than external injury or poisoning, between 1985 and 1995 in England and Wales [55]. A total of 12091 certificates were reviewed, of which 3322 were assigned neuropsychiatric causes of death compatible with vCJD and for whom brain material was available for review. No cases of CJD were identified. A further similar study identified 1537 people aged 15-44 years old at the time of death from 1979 - 1996 in England. A total of 1473 cases were included. Of these, 705 had medical records available for review. In 91% there was sufficient information in the medical notes to exclude vCJD and sCJD as a likely cause of death. As a result of the review a total of four cases were referred to the NCJDRSU; after assessment, no cases were suggestive of CJD [56].

Whilst both studies were primarily undertaken to determine if vCJD was a novel condition, they provide a method of assessing the completeness of surveillance systems and highlight the inherent difficulties of such studies. Death certificates are commonly completed by the most junior member of the medical team who may enter details only of the terminal event (e.g. respiratory failure) rather than the underlying neurodegenerative condition. Indeed, the Office of National Statistics demonstrated that review of unselected death certificate lowers the diagnosis of death by respiratory disease by 7% [57]. Further to this, until recently most dementia was labelled as ‘senile’ dementia or Alzheimer’s dementia with little phenotyping beyond this making it difficult to retrospectively review cases.

A more recent review of brain donations from 1984 – 2005 to the National Alzheimer's Co-ordinating Center in Washington, USA (Maddox, 2015) identified 6000 patients with a clinical diagnosis of dementia and availability of neuropathological material. Of these, 21 cases had neuropathological data indicating prion disease, of which 19 cases had accompanying clinical data. 7/19 cases (37%) had not been considered in life. Limited clinical details were provided, however cases were at the extremes of age range for sCJD (mean age 66 years, range 47 - 88 years) with long disease durations [58].

In 1995 a neuropathological review was published on the Corsellis Collection; a large neuropathological archive collected prospectively from both psychiatric and general hospitals since 1964. Brain tissue from a total of 6559 patients was available for examination, with over 1000 having been diagnosed in life with dementia. 19 cases of CJD were identified. Eight cases (42%) were not suspected in life; 6 of which had protracted histories and who would not have fulfilled diagnostic criteria based on paucity of clinical features on examination [59]. Such cases again were at the extremes of age for sCJD (mean age: 64 years, range: 40 years to 79 years).

Finally, in 1989, Jellinger undertook a neuropathological review of 675 consecutive autopsy cases of patients with dementia from three hospitals in Vienna over a seven-year period. Nine cases of CJD were identified; six were suspected in life. However, it is not clear whether this six were of the nine confirmed at post-mortem [58, 60].

The above studies provide insight into missed cases amongst specialist in-patient settings, where even in such settings cases of CJD may be missed. In practice however generalisability is limited; the majority of older patients with dementia reside in the community and, as previously noted, post-mortem rates in the elderly are low (and a particular rarity in those with a diagnosis of dementia) [28, 61]. The presentation of patients included must therefore have been unusual enough to warrant admission to specialist units and for post-mortem to be undertaken, even if prion disease had not specifically been raised in life.

Reasons for under ascertainment

Surveillance sources are limited and neuropathological series have demonstrated that cases of CJD can be missed, but it is important to review why this might occur. When compared to other, more common, forms of dementia in the elderly (as in Appendix A), the rapidity of decline and associated neurological features as detailed in section 1.5 should set CJD apart easily. One reason is that dementia is not considered as a diagnosis, with resons outlined in section 1.2. Even if it were considered, however, misclassification due to either lack of familiarity with CJD or because the presentation is in some way atypical may be important. A review of these factors follows:

1) The clinical features that together comprise the CJD diagnostic criteria and distinguish CJD from other more common forms of dementia (i.e. rapid

progression and focal neurological features) are not in themselves unique to prion diseases.

a) Rapid progression - a number of studies in the united States and Europe have reviewed rapidly progressive dementias (RPDs) [62-66]. Whilst there is no universal definition of RPD and it is difficult in some to be clear about the timing or nature of initial symptoms, most studies have accepted a definition of 1-2 years from symptom onset to a diagnosis of dementia as fulfilling this concept.

As prion disease is the archetypal form of rapid dementia, the majority of studies are based on cohorts of patients referred to national CJD surveillance units who were subsequently diagnosed with an alternative underlying pathology. Between 12 - 54% of all referrals where CJD has been considered are diagnosed with an alternative diagnosis (dependent on the nature of the referral patterns and whether referrals include CSF-only referrals in addition to clinically suspected cases). A review of non-prion diagnoses from these cohorts, in addition to patients with RPD presenting to tertiary referral dementia centres [67-70], are presented in Table 2. A total of 13606 neuropathologically confirmed cases are included.

It is difficult to draw general conclusions due to the heterogeneity of cohorts. It is also possible that within these cohorts cases of CJD may have been missed by older generation immunohistochemistry techniques with a lower specificity for PrP^{Sc} detection. General conclusions, however can be drawn; Alzheimer's Disease was the single most common non-prion

neurodegenerative condition, likely reflective of the high prevalence of AD in the population. A number however presented with RPD secondary to a non-neurodegenerative condition, most commonly inflammatory disorders, highlighting the importance of investigation for treatable neurodegenerative-mimics.

Table 2: Non-prion diagnoses in cohort of rapid onset dementias referred to national CJD units (Percentages of non-prion diagnoses)

Diagnosis	**Geschwind 2008 (n = 67) [71]**	**Geschwind 2016 (n = 104) [62]**	**Chitravas 2011 (n = 304) [63]**	**Poser 1999 (n= 124) [64]**	**Heinemann 2007 (n = 98) [66]**	**Papageorgiou 2009 (n = 68) [70]**	**Sala 2012 (n = 49) [68]**	**Jansen 2012 (n = 156) [72]**	**Stoeck 2012 (n = 29022) [65]**	**Staekenborg *et al* 2015 (n = 129) [69]**	**Josephs *et al* 2009 (n = 22) [67]**
Neurodegen (non-prion)	**39**	**31**	**77**	**n/a**	**63**	**60**	**37**	**36**	**43**	**95**	**64**
AD	8	5	51	27	40	18	6	21	13	43	9
FTLD	10	7	3			16	12	4	2	18	
VaD		2	12	9	11	13		12	2	13	
'Parkinson's plus'	9	11	2	7	5	15	10	10	10	10	14
HD			0.3	2					0.4		
MND / MND-FTD				2	2			1	0.1		23
Mixed / other / unknown			7		5		6	9	4.5		18
Secondary dementias	**n/a**	**n/a**	**23**	**n/a**	**n/a**	**24**	**26**	**n/a**	**40**	**n/a**	**n/a**
Inflammatory	22	16	6	1.1	5	9	2		11		
Neoplastic	6	8	8	4	7	12	2	8	5		
Infectious	6		5				2	5			
Metabolic/toxic	4		2	6	6	6	8	1	7		
Vascular	4				1			8	8		
Psychiatric	6	12		5		2			6		
Other / unknown	13	32	2	4	15	6	11	11	20.2		

b) Focal neurological features – A sub-selection of RPD reviews have also examined the presence of focal neurological features (common to both vCJD and sCJD) in non-prion pathologies. As demonstrated in Table 3, focal neurological features were commonly seen in other forms of dementia. No studies however provide meaningful comparison between prion and non-prion cohorts to determine significant differences between groups.

Table 3: Clinical features of patients with non-prion pathologies (percentage of all those with non-prion pathologies: clinical features present during illness)

Clinical features	**Chitravas *et al* 2011 (n = 71) [63]**	**Poser *et al* 1999 (n = 109) [64]**	**Sala *et al* 2012 (n = 49) [68]**	**Scarmeas *et al* 2015 (n = 32) [73]**
Dementia	42	63	100	
Myoclonus	12	43	65	75
Pyramidal	20			66
Extrapyramidal	12	41	65	
Cerebellar dysfunction	14	46	31	
Visual disturbance	9	23		
Akinetic mutism	5	14		
Gait disturbance				66

Both reviews demonstrate, that whilst the data are highly selected, the majority of patients who presented with RPD with or without focal neurological features did not have CJD as a cause for their presentation and instead had underlying commonly encountered dementia pathologies (that is AD, FTLD, DLB, and VaD). Such features are therefore not unique to CJD and it could be that cases of CJD are missed amongst these other common neurodegenerative conditions.

2) In some cases, CJD may have an atypical presentation or phenotype, with evidence to suggest this may be more common in older patients.

a) Missed cases of CJD are generally older

There is very little available literature regarding risk factors for missed cases of CJD. As above, however, the Corsellis collection found that missed cases were older (although it is unclear whether they were significantly so) [59] and Maddox *et al* [58] found that missed cases were more likely at the extremes of ages for sCJD. A review undertaken by el Tawil *et al* (2015) of older patients with vCJD referred to the NCJDRSU found that 4 out of 6 patients aged ≥55 years old at time of symptom onset were not diagnosed in life [23].

b) Older cases of dementia are associated with rapid progression

Staekenborg *et al* (2015) reviewed risk factors for RPD in 1623 patients referred to the Amsterdam Dementia cohort; older age was found to a risk factor for rapid progression of non-prion pathologies [69], potentially contributing to diagnostic difficulty in differentiating non-prion RPD from cases of CJD in older ages. With age, cognitive reserves reduce, this may also be an important factor in the rapidity of progression of older cases [74].

c) Older cases of CJD may potentially have different features to younger cases

There is little published description of the clinical features of older patients with vCJD or sCJD. A summary of available literature follows:

sCJD

In sCJD, there are few reviews of the elderly. Karch *et al* (2015) recently reviewed the clinical presentation of patients aged ≥ 75 years old with probable or definite sCJD referred to the German CJD Surveillance Programme between 2001 and 2012 (n = 73) and compared such presentations to those aged <75 years old (n=73). In the older group, patients had a shorter duration of illness and were more likely to present with dementia and less likely to have visual symptoms compared to younger patients. Cerebral MRI was less likely to be typical with isolated cortical lesions more frequently seen in those ≥75 years [75].

A previous review by Brandel *et al* (2008) [76] reviewed cases of probable or definite sCJD referred to the French CJD surveillance programme. The presentation of patients aged ≥80 years old (n = 136) was compared to those <80 years (n = 1171). Similar to Karch, the disease duration in those aged ≥80 years was significantly shorter compared to younger patients. Clinical features were comparable, however cerebellar features and myoclonus were seen less frequently in older patients. In the French group CSF, EEG, and MRI findings were comparable between groups. Both the codon-129 polymorphism and protein subtype were also comparable, potentially suggesting that disease subtype is not responsible for differing phenotypes in the elderly or indeed for reduced incidence in older patients.

Lastly, a previous review undertaken at the NCJDRSU in Edinburgh identified all patients aged ≥80 years with probable or definite sCJD; 12 cases were

identified and described. The authors observed that their clinical presentation and disease duration was typical of sCJD [77], however the study did not compare cases to those <80 years old. It is therefore difficult to conclude if any significant differences were present.

vCJD

In vCJD, until recently only a single case report [78] existed reviewing the presentation of vCJD in older patients. A recent review of all cases aged ≥55 years old in the UK identified six patients, all of whom had neuropathological confirmation of diagnosis. Two of these patients fulfilled the clinical diagnostic criteria for probable vCJD and two for possible vCJD. Five patients underwent MRI imaging with only one demonstrating diagnostic changes of the medio-dorsal thalamus. Alternative diagnoses given in life were VaD (n = 1), FTD (n = 2), and Wernicke's encephalopathy (n = 1). Of the two diagnosed in life one was a known recipient of a blood transfusion from a case of vCJD. No comparison was made of these cases to younger cases (and therefore the presence of differences is unknown), however all cases did have clinical features that would be unusual for the more commonly encountered dementias (for example: ataxic gait, additional movements and sensory disturbance) [23].

The literature base is sparse, however, in general, it would appear that older patients with variant and sporadic CJD are less likely to have positive features on MRI brain imaging and possibly fewer neurological features. This may

contribute towards missed diagnoses, however conclusions cannot be drawn as this association has not been specifically reviewed.

Overall, it is difficult to draw conclusions, however it would appear that older age is a possible risk factor for missed diagnosis in CJD. This is important as, although surveillance is important in all ages it is particularly so in older patients because, as a group, older patients are more likely than the young to require surgical interventions (including blood transfusions) putting themselves and subsequent patients at risk of iCJD (indeed one of the only three blood transfusion associated cases was ≥65 years old).

1.8 Discussion

CJD disease surveillance continues to be a relevant measure to protect public health and the elderly are an important group who require particular consideration.

This section has demonstrated that cases of CJD may be missed, and whilst CJD has a distinct and rapid multifocal neuropsychiatric decline, these features are not unique. Missed cases may be seen in older patients, possibly due to atypical presentation, however a robust review of risk factors for missed diagnosis is lacking. Missed cases have implications not only for appropriate clinical management but also for public health.

The aim of this thesis is to review the ascertainment of CJD in the older population, to investigate age as a risk factor for missed diagnosis in CJD, to

describe the characteristics of CJD in older patients, and to detail and trial methods for prospective study of enhanced surveillance of CJD in older patients. It will do this by first investigating age as a risk factor for missed diagnosis in CJD and describing the clinical and referral characteristics of older patients, separately for variant CJD (chapter 2) and sporadic CJD (chapter 3). A case definition tool for screening patients in whom CJD may be missed will be developed with a protocol for the feasibility stage of an enhanced surveillance project detailed in chapter 4. This will also include a description of the first 10 patients referred to the enhanced surveillance project between 19th January 2016 and 31st September 2016.

CHAPTER 2: FACTORS ASSOCIATED WITH LATE REFERRAL OF VARIANT CJD

2.1 Introduction

Chapter 1 discussed the possibility that diagnoses of CJD may be missed, particularly in older patients. Literature review demonstrated that missed cases do occur, with age appearing to be a possible risk factor for this. Further evidence comes from the epidemiological characteristics of vCJD and sCJD: a) in sCJD, there has been an increase in observed cases over time, particularly in older ages; b) late diagnoses (i.e. those not diagnosed in life) do occur; and c) the association between age and age specific mortality is not linear with a fall in age specific mortality seen in vCJD and sCJD after 29 years and 79 years old respectively.

The reasons for these epidemiological characteristics are not clear but, as previously explored, may include: a) missed cases are in some way atypical for CJD (e.g. in the way they present, progress or in their investigation findings); b) cases of CJD are typical but are overlooked; or c) cases of sCJD are genuinely rising (although as previously discussed, this would seem less likely).

In this chapter cases of vCJD will be reviewed to provide some understanding of the clinical and referral characteristics that may be associated with timing of referral. This will be done by comparing cases recognised as CJD diagnosed

late in the disease process or after death and comparing them with cases diagnosed earlier.

2.2 Background

Between 1995 and 1996, the National CJD Research and Surveillance Unit (NCJDRSU) reviewed 10 cases of CJD with a younger age of onset, atypical but stereotyped clinical features and a longer duration of illness. Neuropathological changes were unusual for sCJD and, similar to clinical features, were strikingly similar between cases. The condition was termed 'new variant CJD' (now 'variant CJD') [45], and a causal link to the BSE agent in cattle was later established.

2.21 Clinical features of variant CJD

Variant CJD (vCJD) presents in the majority of cases with early isolated behavioural change or psychiatric symptoms (predominantly mood changes and social withdrawal, although psychosis can occur). In approximately 20% however, cognitive disturbance or pain may also be seen as early / presenting features. Intellectual decline, ataxia, and slurred speech follow in the majority within 6 months, with persistent painful sensory disturbance seen in up to half of patients. In the later stages, pyramidal features, abnormal movements (inclusive of myoclonus, dystonia and chorea), and agitation are seen. As per all forms of CJD, akinetic mutism heralds the terminal phase [79-81].

2.22 Biomarkers of vCJD

Cerebral MRI demonstrates high signal of the dorsomedial thalamus (the 'pulvinar sign') on fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) sequences. This feature is not specific for vCJD, however, in the correct clinical context it is extremely helpful with 91% of patients with vCJD demonstrating this sign [80]. Non-specific markers of neuronal damage may be seen on CSF (14-3-3 is present in approximately 50% [7]) and EEG (slow waves but, in the vast majority, without the typical changes of sCJD). CSF and EEG do not have the same diagnostic role in vCJD as they do in sCJD and are generally more helpful in excluding other conditions. As PrP^{Sc} is also seen within the lymphoreticular system, biopsies of lymphoid tissue (that is, tonsil biopsy) offer a definitive means of diagnosis in life.

Patients are classified as possible, probable, or definite according to internationally agreed diagnostic criteria (Box 4). Overall, the specificity of the clinical diagnostic criteria is 100% with sensitivity of 83% within the UK [80].

2.23 Epidemiology of vCJD: UK and worldwide

vCJD is a disease of the young and although has a longer duration of illness compared to the classical/sporadic form of CJD it is still a rapidly progressive condition. There is a slight excess of cases in males [82]. Cases of vCJD have been reported in a number of countries, however the majority of vCJD cases reported world-wide were UK residents at the time of illness onset (77% of cases, including 3 cases of secondary transmissions via blood transfusion).

One additional case was a temporary resident during the BSE outbreak in the U.K [38, 39]. Almost all (99.4%) of UK cases have been homozygous for methionine at codon-129, with all tested cases outwith the UK also homozygotes.

2.24 NCJDRSU referral system

As per chapter 1, the NCJDRSU was established in the UK to monitor for changes in epidemiological and clinical trends, which may suggest cross-species transmission of BSE to humans. It continues to monitor incidence rates, study risk factors for disease, and assist local care providers to improve the quality of care for those with CJD.

The NCJDRSU receives referrals of suspected cases from various sources (as detailed in section 1.6). When patients are referred, an NCJDRSU clinician collects details over the telephone on the patient's illness including risk factors for CJD (e.g. family history / known iatrogenic exposure). Advice is provided regarding investigations to improve the diagnostic certainty (generally speaking cerebral MRI with DWI/FLAIR sequences, CSF for 14-3-3 and RT-QuIC, and EEG). Contact continues with the clinicians until either an alternative diagnosis is reached or CJD becomes the most likely diagnosis, in which case a visit is arranged to meet with the patient and their next of kin within 5 working days of referral.

During the visit the NCJDRSU clinician, who is usually accompanied by a member of the NCJDRSU nursing care team, collects data from the family

(and occasionally the patient if able) on clinical and epidemiological features using a standardised format questionnaire (inclusive of details such as first symptom/sign, and the development of specific features during the illness). A description is also taken of the evolution of illness. The patient is examined, using a standardised protocol for neurological examination. The medical notes are reviewed by the NCJDRSU clinician and details such as the onset of objective signs, and results of cognitive / neurological examinations and investigations are documented to supplement the history provided by the family / patient. Cerebral MRI is reviewed if available.

After the visit, all details collected are then entered manually onto a secure electronic database held at the University of Edinburgh. Correspondence files are also retained in paper format for future reference. Requests are sent for copies of medical notes, cerebral MRI scans (with subsequent review and coding by Dr David Summers, NCJDRSU consultant neuroradiologist), and a representative page from the patient's EEG (coded by Professors Will and Knight, NCJDRSU consultant neurologists). After a patient's death, a request is sent to access GP notes. Data entries are updated where information is available to include any subsequent clinical features documented in GP / hospital notes that occurred after the NCJDRSU visit.

Occasionally a patient is not seen during life, either because CJD was not suspected in life (and only diagnosed at post-mortem) or the patient died prior to review. In such instances the patient's next of kin is contacted to invite them for later review during which the same clinical and epidemiological data

are documented with supplementation of the clinical features from review of contemporaneous GP and hospital medical records.

2.3 Methods

2.31 Population and setting

A retrospective review of vCJD diagnoses in the UK was undertaken. All work was undertaken by the author, unless stated otherwise. All patients referred to the NCJDRSU between 1st May 1990 and 31st December 2015, resident in the UK at time of onset and classified as probable or definite (according to the above mentioned criteria, as of 31st December 2015) were included (n = 177).

Data were extracted from the NCJDRSU database with this first pass of data collection undertaken by Ms Jan Mackenzie (NCJDRSU surveillance co-ordinator) and Mr Nick Attwood (NCJDRSU database manager). A database was created in Excel (version 14.7.7). All data were then transferred to SPSS (version 22) (the 'thesis database') and analysed with the aim of looking for factors associated with missed diagnoses of CJD.

2.32 Data processing

Cases of vCJD have been referred over an extended period of time and therefore the clinical and epidemiological review questionnaire used for assessing cases of vCJD has evolved. The iteration with features common to all versions was therefore used as the standardised form (in use from 2002 – 2009). For data collected prior to and after this time (approximately 70% of

case notes) all correspondence and medical notes were individually reviewed and entered onto this common format if this had not already occurred.

The following data were recorded:

1) Basic characteristics and demographic details. Sex and age at time of onset of illness were documented and an index of multiple deprivation (IMD) was calculated based on the patient's postcode of residence at the time of referral. This was then grouped into quintiles.

The IMD is the most widely used socioeconomic scale. It is derived nationally for all four nations, however, with limitations, can be applied UK wide. Scales are updated after each census; the data used for the purposes of this study was calculated from the 2001 census in Scotland and in England and the 2003 census in Wales and in Northern Ireland. These years are the closest to the peak of vCJD cases in 2000.

2) Referral characteristics

a) Source of referral. The speciality of the clinician referring the patient to the NCJDRSU was categorised as neurology, psychiatry, pathology, general medicine, other

b) Type of referring hospital. Hospitals were classified as regional neurosciences centre or other based on data from www.nhs.uk (extracted 01.04.16); where neuroscience services had migrated in an area or a hospital had since closed, the status of the hospital at the time of referral was used

c) Time to review by neurology / psychiatry and time to referral to the NCJDRSU. Timings were calculated from onset of first symptom

d) Region of referral. The UK was divided into North UK (Scotland, North East, North West, Yorkshire and Humberside) and South UK (Wales, East Midlands, West Midlands, South West, South East, London, East of England) according to the patient's area of residency at the time of referral to the NCJDRSU.

3) Clinical features

The following clinical features were extracted:

a) Presenting features. Presenting symptoms were grouped into the following themes: i) behaviour / personality change (consisting of any change which was not attributable to mood change), ii) sensory disturbance (consisting of all sensory modalities including pain), iii) mood disturbance or psychiatric features (consisting of delusions, anxiety, and depression), iv) rapid cognitive decline (any change in cognition), and v) unsteadiness (consisting of gait change or incoordination). These features were enquired about from a family member (i.e. what was the first symptom the patient complained of or the first sign they noticed). Where this was not possible, GP or hospital records were used to determine first symptom the patient sought medical attention for.

b) Signs and symptoms occurring during the course of a patient's illness. Where available, the presence of specific signs and symptoms occurring after initial symptom onset were extracted.

c) Time to onset of clinical features: Timing of symptoms was calculated using time from first symptom to time to development of each subsequent symptom / sign. Where symptoms were present prior to the date of illness onset these symptom dates were excluded (e.g. some patients had long-standing mood disturbance), unless there was clear worsening or evolution of these clinical features during the patient's illness. If deterioration was documented, the point of change was taken as the 'time of onset'. If the exact date of onset was unavailable, the date was standardised to the 15th of the month.

Some features were grouped: depression, anxiety, aggression, and delusions were grouped under one symptom heading of 'psychiatric symptoms'; chorea and dystonia were grouped under 'other movements'; ataxia, nystagmus and cerebellar signs were grouped under 'cerebellar'. The earliest feature that developed after the onset of the illness was used in these variables.

d) Duration of illness: This was calculated from first symptom to time of death.

4) Investigation results were documented:

a) Cerebral MRI was documented as either positive (the presence of medio-dorsal thalamic restricted diffusion: the 'pulvinar sign') or negative (all other changes including normal)

b) CSF was documented as either positive (the presence of 14-3-3) or negative. Equivocal results were excluded from analysis

c) EEG was documented as typical (the presence of periodic generalised synchronised triphasic sharp wave complexes at 1-1.5Hz), atypical (all other changes), or normal

d) Codon-129 polymorphism was documented

5) Diagnostic criteria

Whilst it is important to consider whether specific signs and symptoms are associated with timing of referral outcomes, it is also important to consider the overall clinical picture and whether missed referrals were missed because they perhaps did not fulfil clinical diagnostic criteria in life. All patients were therefore categorised as either 'fulfils diagnostic clinical criteria' or 'does not fulfil diagnostic clinical criteria' based on their clinical features alone. The presence of signs / symptoms documented throughout the patient's illness was reviewed for each case, and, if they had sufficient features (that is a >6 month history of a progressive neuropsychiatric disorder with ≥4 out of 5 associated clinical features – as detailed in Box 4, page 16) to fulfil the diagnostic criteria for 'possible vCJD', they were coded as 'fulfils diagnostic clinical criteria'.

6) Diagnosis in life

Case notes (inclusive of death certificates) from all patients referred on or after the date of death were reviewed to determine a) the referring clinician's working diagnosis at time of death and b) whether CJD (and the subtype

thereof) had been considered in life. All notes of those referred later in the disease process (see page 45) were also reviewed for the working diagnosis prior to the patient's eventual diagnosis of vCJD.

2.33 Data review

Once data were entered onto the thesis database, variables were checked for completeness to ensure cases had not been overlooked during the first pass of case review (that is, that no cases had missing information) Variables were checked for validity and consistency (e.g. there were no variables with negative time to onset of symptoms etc.). If data were missing, notes were re-reviewed and any further available variables were entered at this stage.

Missing data.

Where data were not available, it was not possible to make data assumptions and missing entries were therefore classified as 'missing' with entry fields left blank on the thesis database to ensure they were not included in statistical analysis.

2.34 Analysis approach

a) Outcome variables

The primary outcome variable was to determine the characteristics of patients not referred to the NCJDRSU in life (referred to from here as 'missed referrals') as a proxy measure of missed cases of CJD. It was however expected that this group would be small with analysis therefore limited. A further subgroup of those referred later in the course of their illness (referred

to from here as ‘later referrals’) was therefore added. The rationale for this later group was to review whether there were any atypical features that might help to inform an understanding of possible risk factors for a missed referral / diagnosis in life.

With regards time cut-off points for later referrals, various time points were considered, trying to provide a balance between adequate numbers and duration. Thirty days prior to death was chosen as this represented approximately the last 10% of illness. It might be expected that patients would be at a palliative phase by this stage with further diagnostic investigation less likely.

b) Explanatory variables included demographic, referral and clinical characteristics, and investigation results listed above and described in Table 4.

Table 4: Explanatory variables (vCJD)

Variable	How recorded	Range of values	Completeness: n (%)
Age	Median years + IQR	n/a	177 (100)
Sex	% male	n/a	177 (100)
IMD	n/a	1-5	174 (98)
Duration of illness (time from 1st symptom to time of death)	Median months + IQR	n/a	177 (100)
Time to diagnosis (time from 1st symptom to time of diagnosis)	Median months + IQR	n/a	177 (100)
Time to diagnosis excluding those referred after death	Median months + IQR	n/a	177 (100)
Source of referral	Neurology, psychiatry, pathology, general medicine, other	n/a	177 (100)
Fulfilled diagnostic criteria in life	Yes/no	n/a	177 (100)
Reviewed by neurology	Yes/no	n/a	176 (99.4)
Time to neurology review	Median months + IQR		174 (98.3)
Reviewed by psychiatry	Yes/no	n/a	171 (96.6)
Time to psychiatry review	Median months + IQR	n/a	80 (45.2)
Referred from neurosciences centre	Yes/no	n/a	175 (98.9)
Region of referral	North U.K. / South U.K.	n/a	177 (100)
Presenting feature	Behaviour / personality change, sensory disturbance, mood disturbance or psychiatric features, rapid cognitive decline, and unsteadiness	n/a	177 (100)
Signs / symptoms occurring during illness	Feature present since onset of illness	Yes/no	See Tables 8 and 13
Cerebral MRI	Presence of pulvinar sign	Positive/negative	170 (96)
CSF	Presence of 14-3-3	Positive/negative	129 (72.9)
EEG	Periodic generalised slow synchronised triphasic sharp wave complexes	Positive/negative	168 (94.9)
Codon-129	Polymorphism recorded	MM / MV / VV	160 (90.4)

c) Analysis

Later and missed referrals were identified and described.

Results of explanatory variables for later and missed referrals are as compared to those referred before (referred to as 'early') and after these respective cut-offs. A univariable comparison was initially undertaken. For continuous variables (i.e. age, duration of illness, time to onset of clinical features and time to review by neurology / psychiatry) due to small numbers with a non-parametric spread of data the Mann-Whitney test for association was used. For all, time to onset is stated in median months with interquartile range (IQR) provided.

Pearson's χ^2 exact test (2-sided) was used to cross-tabulate categorical data (i.e. sex, IMD, source of referral, presenting feature, region of referral, presence of specific clinical features / positive investigations, review by psychiatry and neurology, and referral from neurosciences centre). This particular test was used due to the potential for small numbers in categories and to minimise data assumptions. Statistical significance was set at $p < 0.05$. Risk was also calculated using odds ratio (using the odds ratio Chi-Square test) with 95% confidence intervals provided.

In order to determine the relationship between factors identified as associated with referral timing a multivariate analysis was undertaken. A binary logistic regression model was built using missed or later referral as the constant variable and all statistically significant factors from the univariate analysis as

the dependent variables. From both univariable and multivariable analysis age was highly significantly associated with late / missed referral. Further analysis was undertaken to determine whether it was age itself that was important (e.g. those who are older are less likely to have clinical features documented or be investigated as thoroughly) or was it due to a confounding factor (such as investigation findings, presenting complaint, or source of referral, etc.). Ideally, a multivariable analysis would have been undertaken of all explanatory variables, however, due to small numbers, this was not possible and therefore, a separate analysis was undertaken, re-defining age as the outcome.

For the purposes of this analysis, patients were classified as 'older adults' if they were aged ≥65 years old at the time of onset of first symptoms. 65 years old separates young-onset dementia from late-onset dementia; this age separation reflects not only a difference in the probability of the underlying causative pathology but also reflects typical referral pathways for those with dementia (with services generally divided into those <65 years old and ≥65 years old). vCJD, however, as previously stated, is a disease of the young and therefore expected numbers ≥65 years old would be small. A further sub-group analysis was undertaken on the oldest 10% of cases (those aged ≥45 years old); this, similar to timing of referral was chosen as a balance between clinical significance and adequate numbers to undertake statistical analyses. Explanatory variables were then run against those aged ≥ 65 years old compared to those <65 and similarly, ≥45 years old compared to those <45 years old using the same statistical tests stated above.

Data were coded and analysed in SPSS (version 22).

2.4 Results

2.41 All cases vCJD

Overall, 177 patients were included who fulfilled internationally accepted surveillance criteria for probable or definite vCJD. Of these, 122 patients (69%) were definite cases.

a) Basic characteristics (all patients)

101 patients were male (57%). The median age of onset of 26 years (IQR: 21 – 33 years). The median IMD quintile was 3 (1 – 5). Patients had a long median time to diagnosis of 11 months (8 – 13 months, excluding those referred after death) compared to a median disease duration of 14 months (11 – 18 months). 169 patients (96%) fulfilled the clinical diagnostic criteria for vCJD. In all the rest, the reason for failure to fulfil criteria was a lack of documented psychiatric features.

b) Referral characteristics (all patients)

The majority of patients were referred from a clinician in neurology (155 (87.6%) patients). All but one patient (99.4%) were reviewed by neurology during their illness with a smaller number reviewed by psychiatry (91 (51.4%) patients). Over half (103 (58.2%) patients) were under the care of a tertiary neurosciences centre at the point of referral.

c) Clinical characteristics (all patients)

Almost 75% of patients presented with either mood disturbance / psychiatric features or sensory disturbance, although the most frequently encountered clinical features during the illness were cognitive or cerebellar, present in almost all patients. Cerebral MRI (when reviewed by the NCJDRSU research neuroradiologist) was the most useful investigation to detect the changes of vCJD (positive in 91%).

When reviewing the time to onset of symptoms, as expected, given the presenting symptoms, pain and sensory disturbance occurred early at 1 and 2 months respectively. Cognitive, cerebellar and psychiatric features all occurred around the same time after at 3 months. Myoclonus occurred last at 5 months, which, as a late sign in all forms of CJD, was to be expected.

2.42 Late / missed referrals

a) Basic characteristics (late / missed referrals)

A total of 13 patients were referred within 30 days of death or after (7.3% of all cases of definite / probable vCJD) with six patients referred on or after the date of death (3.4% of cases). A description of cases can be found in Table 5. In 4/5 missed referrals in whom information was available, CJD was considered in life, however, in all cases sCJD was considered the most likely subtype.

Later / missed referrals were significantly older compared to earlier referrals ($p = 0.002$ for later referrals and 0.004 for missed referrals). All missed referrals were male ($p = 0.03$). The duration of illness was shorter, however, as expected, the time to diagnosis significantly longer (Table 6).

Table 5: Description of later and missed referrals (vCJD)

Case	Onset year[1]	Age of onset (years)	Duration of illness (months)	Presenting features	Classification in life	MRI	Other investigations to support a diagnosis of CJD	Working diagnosis at death	CJD considered prior to death
1		18	8	Behaviour / personality change	Probable	Positive	EEG – atypical	Insufficient information	Yes – type not mentioned
2*		19	13	Mood / psychiatric symptoms	Probable	Positive	EEG – atypical	Rapid onset dementia	Yes – type not mentioned
3		34	14	Mood / psychiatric symptoms	Probable	Positive	CSF 14-3-3 positive, EEG – atypical	vCJD	Yes – sporadic (prior to brain biopsy result)
4*		41	7	Rapid cognitive decline	Probable	Positive	EEG – atypical	Encephalopathy	Yes - sporadic
5		50	11	Unsteady	Possible	Negative	CSF 14-3-3 negative, EEG – normal	sCJD	Yes - sporadic
6		37	12	Behaviour / personality change	Probable	Positive	CSF 14-3-3 negative, EEG – atypical	vCJD	Yes - variant
7*		74	18	Rapid cognitive decline	Possible	n/a	Insufficient information	Multi-infarct dementia	Insufficient information
8		21	16	Mood / psychiatric symptoms	Probable	Positive	EEG – normal, CSF negative 14-3-3	vCJD	Insufficient information
9		47	11	Mood / psychiatric symptoms	Probable	Positive	EEG – atypical, 14-3-3 positive	vCJD	Insufficient information
10		35	15	Mood / psychiatric symptoms	Probable	Positive	EEG – normal	vCJD	Unclear (vCJD after brain biopsy result)
11*		68	13	Mood / psychiatric symptoms	Possible	Negative	EEG – atypical. MRI negative.	FTLD with Parkinsonism	Yes – sporadic
12*		59	33	Rapid cognitive decline	Possible	Negative	EEG – atypical. CSF no info	Korsakoff's	Yes - sporadic
13*		56	40	Rapid cognitive decline	Did not fulfil criteria	Negative	Insufficient information	FTD	Yes - sporadic

[1]Year removed to protect patient confidentiality *Referred after death; n/a = not available

Table 6: Basic demographics - later / missed referrals (vCJD)

Patient characteristics	Later (referred ≤ 30 days of death)	Early (referred > 30 days of death or after)	p-value	O.R. (95% CI)	Missed (referred on or after date of death)	Referred in life	p-value	O.R. (95% CI)
Median age: years^	41 (28 - 58)	26 (20 – 33)	0.002**	n/a	58 (36 - 70)	26 (21 – 33)	0.004**	n/a
Male: n of N documented (%)	9/13 (69%)	93/164 (56.7%)	0.41	0.82 (0.56-1.2)	6/6 (100%)	96/171 (56.1%)	0.03*	0.56 (0.49-0.64)
Median Index of Multiple Deprivation	3	3	0.61	n/a	3	3	0.94	n/a
Median duration of illness: months^	11 (11 - 15)	14 (11 – 18)	0.22	n/a	13 (7 - 35)	14 (11 – 18)	0.82	n/a
Time to diagnosis: months^	8.4 (6.5 – 10.0)	6.2 (4.8 – 7.9)	0.008**	n/a	9.7 (7.7 – 28.3)	6.3 (4.8 – 7.9)	0.007**	
Fulfilled diagnostic criteria in life	12/13 (92%)	157/164 (96%)	0.46	0.5 (0.06-4.7)	5/6 (83%)	164/171 (96%)	0.15	0.2 (0.02-2.1)

*Significant p <0.05 **Highly significant p <0.01 ^Median + IQR

b) Referral characteristics (late / missed referrals)

As expected in this group, there was an excess of patients referred from pathology with fewer referred by neurology. There was no difference however in the number seen by a neurologist in life (Table 7).

Table 7: Referral characteristics - later / missed referrals (vCJD)

Referral characteristic	later referrals (≤30 days prior to death or after)		Early referrals (>30 days prior to death)				Missed referrals (referred on or after date of death)		Early referrals (referred before date of death)			
		%		%	p-value	O.R. (95% CI)		%		%	p-value	O.R. (95% CI)
Source of referral:												
Neurology	6	46.2	149	90.9			1	16.7	154	90.1		
Psychiatry	0	0	4	2.4			0	00	6	2.3		
General	0	0	4	2.4			0	66.7	4	1.8		
Pathology	6	7.7	6	3.7			4	16.7	3	3.5		
Other	1	46.2	1	0.6	<0.001**	n/a	1		4	2.3	<0.001**	n/a
Reviewed by Neurology: n /N	13/13	100	163/164	99.4	1	n/a	6/6	100	170/170	100	1	n/a
Time to neurology review (months)^	4 (4-6)		4 (0-16)		0.08	n/a	4 (4-7)		4 (3-5)		0.61	n/a
Reviewed by Psychiatry: n /N	9/12	75	82/159	51.6	0.14	2.8 (0.7-10.8)	4/5	80	87/166	52.4	0.37	3.7 (0.4-33.6)
Time to psychiatry review (months)^	4 (4-5)		4 (0-15)		0.69	n/a	4 (2-13)		4 (3-6)		0.96	n/a
Neurosciences centre (at point of referral): n /N	5/13	38.5	98/164	59.8	0.15	0.4 (0.1-1.3)	0/6[2]	0	103/171	60.2	0.07	n/a
Region:												
North	7	53.8	71	44.9			4	66.7	74	44.8		
South	6	46.2	87	55.1	0.6	0.7 (0.2-2.2)[1]	2	33.3	91	55.2	0.4	0.4 (0.07–2.3)[1]

n = number with feature N = number documented *Significant p <0.05 **Highly significant p <0.01 ^Median + IQR [1] For North region [2]If referral at PM, neurosciences centre determined by hospital referring for PM

c) Clinical characteristics (later / missed referrals)

When compared to earlier referrals, there was a strongly significant association with presenting feature and whether referrals were late in the disease process ($p = 0.02$) or missed ($p < 0.001$). In both this was due to an excess of patients presenting with rapid cognitive decline and none presenting with sensory disturbance (Table 8). With regards clinical features developing during illness in both later and missed referrals, there was an excess of features associated with end stage vCJD (myoclonus and akinetic mutism) with fewer complaining of sensory disturbance. The type of psychiatric features also differed between later and earlier referrals; delusions and hallucinations were more likely in later and missed referrals with mood disturbance described more frequently in earlier referrals.

As expected, given the presenting features in Table 8, there was a shorter time to onset of forgetfulness with a longer time to onset of sensory symptoms. MRI, which as above, is the most sensitive investigation in vCJD, was less likely to be positive in both groups, particularly in missed referrals ($p = 0.004$) (Table 9).

Table 8: Clinical characteristics - later / missed referrals (vCJD)

Presenting features	**Later referrals (≤ 30 days prior to death or after)**		**Early referrals (>30 days prior to death)**				**Missed referrals (referred on or after date of death)**		**Referred in life**			
	n (of N[1])	**%**	**n (of N[1])**	**%**	**p-value**	**O.R. (95% CI)**	**n (of N[1])**	**%**	**n (of N[1])**	**%**	**p-value**	**O.R (95% CI)**
Mood disturbance or psychiatric features	7/13	54	82/164	50	1	0.57 (0.1 – 4.6)	2/6	33	87171	51	1	0.9 (0.8-0.9)
Sensory disturbance	0/13	0	38/164	23	0.07	0.8 (0.7 – 0.8)	0/6	0	38/171	22	0.3	0.8 (0.7 – 0.8)
Behaviour / personality change	1/13	8	21/164	13	1	1.2 (0.4 – 3.6)	0/6	0	22/171	13	0.4	0.5 (0.09 - 2.7)
Rapid cognitive decline	4/13	31	11/164	7	0.02*	6.2 (1.7 – 23.3)	4/6	67	11/171	6	<0.001**	29 (4.8 – 177)
Unsteadiness	1/13	8	12/164	7	1	1.1 (0.1 – 8.8)	0/6	0	13/171	8	1	1 (0.9 – 1)
Overall					0.02*						<0.001**	
Presence of sign												
Rapidly progressive dementia	13/13	100	151/156	96.8	1	0.97 (0.94-1)	6/6	100	158/163	96.9	1	n/a
Cerebellar	12/12	100	154/157	98.1	1	0.98 (0.96-1)	6/6	100	160/163	98.2	1	n/a
Visual signs	1/13	7.7	20/147	13.6	0.70	0.53 (0.07-4.3)	0/6	0	21/154	13.6	0.60	n/a
Oculomotor	4/12	33.3	61/146	41.8	0.76	0.7 (0.2-2.4)	1/5	20	64/153	41.8	0.41	0.3 (0.04-3.2)
Pyramidal	9/12	75	106/153	69.3	1	1.3 (0.3-5.1)	3/5	60	112/160	70	1	0.6 (0.1-4.0)
Extrapyramidal	1/12	8.3	18/143	12.6	1	0.6 (0.08-5.2)	0/5	0	19/150	12.7	0.63	n/a
Primitive reflexes	7/10	70	67/139	48.2	0.21	2.5 (0.6-10.1)	2/5	40	72/144	50	1	0.7 (0.1-4.1)
Seizures	1/11	9.1	8/157	5.1	0.47	1.9 (0.2-16.4)	0/6	0	9/162	5.6	1	n/a
Myoclonus	10/11	90.9	98/148	66.2	0.11	5.1 (0.6-41.0)	4/4	100	104/155	67.1	0.21	n/a
Other involuntary movements	8/13	61.5	97/146	66.4	0.76	0.8 (0.3-2.6)	4/6	66.7	101/153	66.0	1	1.0 (0.2-5.8)

Presence of symptom												
Pain	5/12	41.7	85/155	54.8	0.55	0.59 (0.18-1.9)	1/5	20	89/162	54.9	0.18	0.2 (0.02-1.9)
Other sensory disturbance	6/13	46.2	89/149	59.7	0.39	0.58 (0.2-1.8)	3/6	50	92/156	59.0	0.69	0.7 (0.1-3.6)
Muscle wasting	1/9	11.1	2/152	1.3	0.16	9.4 (0.8-114.6)	0/4	0	3/157	1.9	1	n/a
Akinetic mutism	4/12	33.3	9/143	6.3	0.01**	7.4 (1.9-29.5)	2/5	40	11/150	7.3	0.06	8.4 (1.2-55.9)
Gait disturbance	13/13	100	160/164	97.6	1	1 (1-1)	6/6	100	167/171	97.7	1	n/a
Speech disturbance	11/13	84.6	129/156	82.7	1	1.2 (0.2-5.5)	5/6	83.3	135/163	82.8	1	1.0 (0.1-9.2)
Visual disturbance	3/11	27.3	46/148	31.1	1	0.83 (0.2-3.3)	2/6	33.3	47/153	30.7	1	1.1 (0.2-6.4)
Forgetfulness	13/13	100	159/163	97.5	1	1 (1-1)	6/6	100	166/170	97.6	1	n/a
Clinical depression	7/12	58.3	85/132	64.4	0.76	0.77 (0.2-2.6)	3/5	60	89/139	64.0	1	0.8 (0.1-5.2)
Social withdrawal	9/10	90	102/130	78.5	0.69	2.5 (0.3-20.3)	4/5	80	107/135	79.3	1	1.0 (0.1-9.7)
Apathy	7/11	63.6	90/137	65.7	1	0.91 (0.3-3.3)	2/4	50	95/144	66.0	0.61	0.5 (0.07-3.8)
Anxiety	6/10	60	80/139	57.6	1	1.1 (0.3-4.1)	1/3	33.3	85/146	58.2	0.57	0.4 (0.03-4.0)
Delusions	7/11	63.6	50/143	35.0	0.1	3.3 (0.9-11.7)	3/4	75	54/150	36	0.14	5.3 (0.54-52.5)
Hallucinations	7/13	53.8	51/142	35.9	0.24	2.1 (0.7-6.5)	4/6	66.7	54/149	36.2	0.20	3.5 (0.6-19.8)
Aggression	7/12	58.3	66/146	45.2	0.55	1.7 (0.5-5.6)	2/5	40	71/153	46.4	1	0.7 (0.1-4.7)
Time to onset of clinical features: median months (+ IQR)												
Rapidly progressive dementia	3 (1-5)	n/a	3 (2-5)	n/a	0.65	n/a	3 (0-10)	n/a	3 (2-5)	n/a	0.42	n/a
Forgetful	2 (0-3)	n/a	3 (1-4)	n/a	0.21	n/a	1.5 (0-5)	n/a	3 (1-4)	n/a	0.20	n/a
Cerebellar	4 (4-6)	n/a	4 (2-6)	n/a	0.16	n/a	5 (3-16)	n/a	4 (2-6)	n/a	0.22	n/a
Unsteadiness	3.5 (2-5)	n/a	3 (2-4)	n/a	0.37	n/a	2 (2-17)	n/a	3 (2-4)	n/a	0.59	n/a
Sensory disturbance	4 (1-9)	n/a	2 (1-4)	n/a	0.28	n/a	5 (0-n/a)	n/a	2 (1-4)	n/a	0.43	n/a
Pain	4 (3-4)	n/a	1 (0-4)	n/a	0.09	n/a	3 (3-3)	n/a	1 (0-4)	n/a	0.66	n/a
Myoclonus	6 (5-7)	n/a	5 (3-6)	n/a	0.15	n/a	6 (2-n/a)	n/a	5 (4-6)	n/a	0.51	n/a
Other movement	5 (3-12)	n/a	4 (2-6)	n/a	0.25	n/a	8.5 (2-18)	n/a	4 (2-6)	n/a	0.45	n/a
Psychiatric symptoms	4 (2-7)	n/a	3 (1-7)	n/a	0.71	n/a	4 (3-n/a)	n/a	3 (1-7)	n/a	0.33	n/a

[1]N = Number documented *Significant p <0.05 **Highly significant p <0.01 ^Median months + IQR

Table 9: Investigation results - later referrals (vCJD)

Investigation	**Later referrals (≤30 days prior to death or after)**		**Early referrals (>30 days prior to death)**				**Missed (referred on or after date of death)**		**Referred in life**			
	n (of N patients)	**%**	**n (of N patients)**	**%**	**p-value**	**O.R. (95% CI)**	**n (of N patients)**	**%**	**n (of N patients)**	**%**	**p-value**	**O.R. (95% CI)**
Positive MRI[2]	9/12	75	147/158	93.0	0.06	0.2 (0.05-1)	2/5	40	154/165	93.3	0.004**	0.05 (0.007-0.3)
Typical EEG[2]	0/11	0	0/157	0	n/a	n/a	0/4	0	0/164	0	n/a	n/a
Positive CSF 14-3-3[2]	3/5	60	51/124	41.1	0.65	2.1 (0.3-13.3)	Nil done	n/a	107/135	79.3	n/a	n/a
Codon-129 genotype	MM – 12/12 MV – 0/12 VV – 0/12	100 0 0	MM – 148/148 MV – 0/148 VV – 0/148	100 0 0	1	n/a	MM – 6/6 MV – 0/6 VV – 0/6	100 0 0	MM – 154/154 MV – 0/154 VV – 0/154	100 0 0	1	n/a

[1]N = of number documented [2]As defined in table 4

d) Multivariate analysis (later / missed referrals)

An independent association in those referred later was retained only for akinetic mutism (p = 0.004, O.R. 7.4 (1.9 – 29.5)). All other findings were due to the confounding effect of age. Due to the small numbers in missed referrals, a multivariate analysis could not be undertaken.

2.43 Older adults

a) Basic characteristics (older adults)

Three patients aged ≥65 years old were identified (2% of all cases of definite / probable vCJD). One case was linked to a blood transfusion. 18 patients aged ≥45 years old were identified (10% of all included cases). A description of patient characteristics is detailed in Table 10.

Those over 65 years old were more likely to be male (Table 11). In both older groups there was a shorter duration of illness but a longer time to diagnosis. Older patients were less likely to fulfil diagnostic criteria.

Table 10: Description of older cases (vCJD)

Case	Onset year[1]	Age of onset	Duration of illness (months)	Presenting features	Classification in life[2]	MRI	Other investigations to support a diagnosis of CJD	Working diagnosis at death
1		48	29	Rapid cognitive decline	Probable	Positive	EEG negative	vCJD
2		52	11	Mood / psychiatric symptoms	Probable	Positive	14-3-3 positive, EEG negative	vCJD
3		51	11	Behaviour / personality change	Possible	Negative	14-3-3 / EEG negative	Insufficient info
4		53	15	Mood / psychiatric symptoms	Probable	Positive	14-3-3 / EEG negative	vCJD
5		50	11	Unsteadiness	Probable	Positive	14-3-3 / EEG negative	Insufficient info
6		74	7	Rapid cognitive decline	Possible	N/A	N/A	vCJD (blood transfusion)
7		47	11	Mood / psychiatric symptoms	Probable	Positive	14-3-3 positive, EEG – negative	Insufficient info
8		51	13	Rapid cognitive decline	Probable	Positive	14-3-3 / EEG negative	vCJD
9		49	17	Mood / psychiatric symptoms	Probable	Positive	14-3-3 / EEG negative	vCJD
10		62	8	Mood / psychiatric symptoms	Probable	Positive	14-3-3 / EEG negative	vCJD
11		68	13	Mood / psychiatric symptoms	Possible	Negative	EEG negative	Insufficient info
12		54	15	Mood / psychiatric symptoms	Probable	Positive	14-3-3 positive, EEG negative	vCJD
13		74	11	Rapid cognitive decline	Did not fulfil criteria	Negative	EEG negative	vCJD
14		47	45	Sensory disturbance	Possible	Positive	EEG negative	vCJD
15		53	10	Rapid cognitive decline	Possible	Negative	14-3-3 positive, EEG negative	vCJD
16		59	33	Rapid cognitive decline	Possible	Negative	EEG negative	Insufficient info
17		56	40	Rapid cognitive decline	Did not fulfil criteria	Negative	No details	Insufficient info
18		46	12	Behaviour / personality change	Probable	Positive	14-3-3 + EEG negative	vCJD

[1]Year removed to protect patient confidentiality [2] As defined on page 43

Table 11: Basic demographics – older adults (vCJD)

Patient characteristics	**≥ 65 years old (n = 3)**	**<65 years old (n = 174)**	**p-value**	**O.R (95% CI)**	**≥45 years old (n = 18)**	**<45 years old (n = 159)**	**p-value**	**O.R (95% CI)**
Median age: years (median, IQR)	74 (68-74)	26 (21-33)	n/a	n/a	53 (49-60)	25 (20-31)	n/a	n/a
Male: n of N documented (%)	3 (100%)	99 (57%)	0.26	n/a	10 (56%)	92 (58%)	1	n/a
Median Index of Multiple Deprivation	3	3	0.5	n/a	3	3	0.1	n/a
Median duration of illness: months^	11 (7-11)	14 (11-18)	0.019*	n/a	13 (11-20)	14 (11-18)	0.71	n/a
Time to diagnosis (months)^	8.7 (4.6 – n/a)	6.3 (4.8 – 8)	0.42	n/a	7.7 (6.1 – 10.6)	6.2 (4.8 – 7.9)	0.025*	n/a
Fulfilled diagnostic criteria in life	2/3 (67%)	167/174 (96%)	0.13	0.08 (0.07-1.04)	16/18 (89%)	153/159 (96%)	0.19	0.31 (0.07-1.6)

^Median months + IQR *Significant p <0.05 **Highly significant p <0.01

Table 12: Referral characteristics – older adults (vCJD)

Referral characteristic	≥65 years old		<65 years old				≥45 years old		<45 years old			
		%		%	p-value	O.R.		%		%	p-value	O.R.
Source of referral (n)	Neuro – 2 Path - 1	66.7 33.3	Neuro– 153 Path – 6 Psych – 6 General – 4 Other – 5	87.9 3.4 3.4 2.3 2.9	0.13	n/a	Neuro–15 Path – 3	83.3 16.7	Neuro– 140 Psych – 6 Path – 4 General – 4 Other – 5	88.1 3.8 2.5 2.5 3.1	0.04*	n/a
Reviewed by Neurology: n/N	3/3	100	173/174	99	1	n/a	18/18	100	158/159	99	1	n/a
Time to neurology review (months)^	4 (1 – n/a)	n/a	4 (3 – 6)	n/a	0.4	n/a	4.5 (3 – 6)	n/a	4 (3 – 5)	n/a	0.69	n/a
Reviewed by Psychiatry: n/N	1/2	50	90/169	53	1	0.9 (0.05-14.3)	10/17	59	81/154	53	0.80	1.3 (0.47-3.6)
Time to psychiatry review (months)^	1 (1 – 1)	n/a	4 (3 – 5)	n/a	0.1	n/a	4 (3 – 10)	n/a	4 (3 – 6)	n/a	0.17	n/a
Neurosciences centre (at point of referral): n of N documented	1/3	33	102/174	59	0.32	0.3 (0.03-3.9)	11/18	61	92/159	58	0.35	1.1 (0.4 – 3)
Region of residence North South	2 1	66.7 33.3	76 92	45.2 54.8	0.6	0.4 (0.03-4.6)[1]	9 9	50 50	69 84	45.1 54.9	0.8	0.3 (0.8-2.2)[1]
Later referral: n /N	2/3	67	11/174	6	<0.001**	29.6 (2.5-352.8)	6/18	33	7/159	4	<0.001**	10.9 (3.1-37.5)
Missed referral: n /N	2/3	67	4/174	2	<0.001**	85 (6.3-1141.1)	4/18	22	2/159	1	<0.001**	22.4 (3.8-133.4)

n = number with feature N = number documented *Significant p <0.05 **Highly significant p <0.01 ^Median + IQR [1] For North region

b) Referral characteristics (older adults)

Although the majority of older patients were referred from a neurologist there was an excess compared to younger patients of those referred from pathology. A strong association with later referral was demonstrated for both older age groups (Table 12).

c) Clinical characteristics (older adults)

When compared to younger referrals, there was a strongly significant association between age and presenting feature. In both older age groups this was due to an excess of patients presenting with rapid cognitive decline and fewer presenting with sensory disturbance (Table 13).

There were no significant differences between groups and the presence of any clinical features. There was however an earlier onset of forgetfulness (and cognitive impairment) and a non-significant later time to onset of sensory disturbance in the older groups; both these findings in keeping with the presenting features described. In both older groups, cerebral MRI scan was significantly less likely to demonstrate typical changes (Table 14).

Table 13: Clinical characteristics – older adults (vCJD)

	≥65 years old		<65 years old				≥45 years old (n = 18)		<45 years old (n = 159)			
Presenting feature	**n (of N[1])**	**%**	**N (of N[1])**	**%**	**p-value**	**O.R (95% C.I.)**	**n (of N[1])**	**%**	**n (of N[1])**	**%**	**p-value**	**O.R (95% C.I.)**
Mood disturbance or psychiatric features	1	33	88	51	1	0.9 (0.8 – 0.9)	7	39	82	52	1	0.9 (0.2 – 4.1)
Sensory disturbance	0	0	38	22	1	0.8 (0.7 – 0.8	1	6	37	23	0.1	0.2 (0.03 – 1.5)
Behaviour / personality change	0	0	22	13	0.6	0.5 (0.04 – 5.5)	2	11	20	13	0.3	0.6 (0.2 – 1.6)
Rapid cognitive decline	2	67	13	7	0.02*	24.8 (2.1 – 291)	7	39	8	5	<0.001**	12 (3.4 – 39)
Unsteadiness	0	0	13	7	1	0.9 (0.9 – 1)	1	6	12	8	1	0.7 (0.09 – 5.9)
Overall					0.025*	n/a					<0.001**	n/a
Presence of sign												
Rapidly progressive dementia	3/3	100	161/166	97	1	n/a	18/18	100	146/151	97	0.65	n/a
Cerebellar	3/3	100	163/166	98	1	n/a	17/17	100	149/152	98	1	n/a
Visual signs	0/3	0	21/157		1	n/a	2/17	12	19/143	13	1	0.9 (0.2-4.1)
Oculomotor	0/3	0	65/155	42	0.27	n/a	6/17	35	59/141	42	0.80	0.8 (0.3-2.2)
Pyramidal	2/3	67	113/162	70	1	0.9 (0.08-9.8)	9/18	50	106/147	72	0.06	0.4 (0.1-1.0)
Extrapyramidal	0/3	0	19/152	13	1	n/a	1/15	7	18/140	13	0.70	0.5 (0.06-3.9)
Primitive reflexes	1/3	33	73/146	50	1	0.5 (0.04-5.6)	6/14	43	68/135	50	0.78	0.7 (0.2-2.2)
Seizures	0/3	0	9/165	6	1	n/a	0/17	0	9/151	6	0.60	n/a
Myoclonus	2/3	67	106/156	68	1	0.9 (0.08-10.7)	15/18	83	93/141	66	0.18	2.6 (0.7-9.4)
Other involuntary movements	1/3	33	104/156	67	0.55	0.3 (0.02-2.8)	10/17	59	95/142	67	0.34	0.7 (0.3-2.0)
Presence of symptom												
Headache	0/2	0	36/160	23	1	n/a	4/15	27	32/147	22	0.75	1.3 (0.4-4.4)
Pain	1/3	33	89/164	54	0.60	0.4 (0.04-4.7)	9/16	56	81/151	54	0.53	1.1 (0.4-3.1)

Other sensory disturbance	2/3	67	93/159	59	1	1.4 (0.1-16.0)	12/18	67	83/144	58	0.32	1.5 (0.5-4.1)
Dizziness	0/3	0	23/163	14	1	n/a	3/18	17	20/148	14	0.47	1.3 (0.3-4.8)
Pseudobulbar palsy	0/2	0	16/121	13	1	n/a	1/10	10	15/113	13	1	0.7 (0.09-6.1)
Muscle wasting	0/3	0	3/158	2	1	n/a	0/16	0	3/145	2	1	n/a
Akinetic mutism	1/2	50	12/153	8	0.16	11.8 (0.7-199.9)	1/17	6	12/138	9	1	0.7 (0.08-5.4)
Gait disturbance	3/3	100	170/174	98	1	n/a	18/18	100	155/159	98	1	n/a
Speech disturbance	2/3	67	138/166	83	1	0.4 (0.04-4.6)	14/17	82	126/152	83	1	1.0 (0.3-3.6)
Visual disturbance	1/3	33	48/156	31	1	1.1 (0.1-12.7)	6/18	33	43/141	31	1	1.1 (0.4-3.2)
Forgetfulness	3/3	100	169/173	98	1	n/a	18/18	100	154/158	98	1	n/a
Clinical depression	1/3	33	91/141	65	0.55	0.3 (0.02-3.1)	9/17	53	83/127	65	0.42	0.6 (0.2-1.7)
Social withdrawal	2/3	67	109/137	80	1	0.5 (0.05-5.9)	12/15	80	99/125	79	1	1.1 (0.3-4.0)
Apathy	0/2	0	97/146	66	0.12	n/a	7/15	47	90/133	68	0.11	0.4 (0.1-1.2)
Anxiety	0/2	0	86/147	59	0.18	n/a	6/14	43	80/135	59	0.27	0.5 (0.2-1.6)
Delusions	1/2	50	56/152	37	1	1.7 (0.1-27.9)	8/15	53	49/139	35	0.26	2.1 (0.7-6.1)
Hallucinations	2/3	67	56/152	37	0.60	3.4 (0.3-38.7)	9/17	53	49/138	36	0.19	2.0 (0.7-5.6)
Aggression	1/3	33	72/155	47	1	0.6 (0.05-6.5)	5/18	28	68/140	49	0.13	0.4 (0.1-1.2)
Time to onset of clinical features: median months (+ IQR)												
Rapidly progressive dementia	1 (1-n/a)	n/a	3 (2-5)	n/a	0.38	n/a	2 (0-5)	n/a	3 (2-5)	n/a	0.11	n/a
Forgetful	1 (1-n/a)	n/a	2.5 (1-4)	n/a	0.15	n/a	1 (0-2)	n/a	3 (2-4)	n/a	0.007**	n/a
Cerebellar	4 (2-n/a)	n/a	4 (2-6)	n/a	1.00	n/a	5 (2-7)	n/a	4 (2-5)	n/a	0.24	n/a
Unsteadiness	2 (1-n/a)	n/a	3 (2-4)	n/a	0.54	n/a	2.5 (1-5)	n/a	3 (2-4)	n/a	0.78	n/a
Sensory disturbance	2.5 (0-n/a)	n/a	2 (1-4)	n/a	0.86	n/a	4 (1-5)	n/a	2 (1-4)	n/a	0.29	n/a
Pain	3 (3-3)	n/a	1 (0-4)	n/a	0.66	n/a	2 (1-5)	n/a	1 (0-4)	n/a	0.31	n/a
Myoclonus	4 (2-n/a)	n/a	5 (4-6)	n/a	0.72	n/a	5 (4-6)	n/a	5 (4-6)	n/a	0.38	n/a
Other movement	3 (3-3)	n/a	4 (2-6)	n/a	0.63	n/a	6 (3-14)	n/a	4 (2-6)	n/a	0.076	n/a
Psychiatric symptoms	3 (3-3)	n/a	3 (1-7)	n/a	0.93	n/a	4 (0-7)	n/a	4 (3-6)	n/a	0.81	n/a

[1]Where N = number documented with clinical feature *Significant p <0.05 **Highly significant p <0.01

Table 14: Investigation results - older patients (vCJD)

Investigation	**≥65 years old**		**<65 years old**				**≥45 years old (n = 18)**		**<45 years old (n = 159)**			
	n (of N[1])	**%**	**n (of N[1])**	**%**	**p-value**	**O.R (95% C.I.)**	**n (of N[1])**	**%**	**n (of N[1])**	**%**	**p-value**	**O.R (95% C.I.)**
MRI	0/2	0	156/168	93	0.006**	n/a	11/17	65	145/153	95	0.001**	0.1 (0.03-0.3)
EEG	0/2	0	0/166	0	n/a	n/a	0/16	0	0/152	0	n/a	0
CSF 14-3-3	Nil done	n/a	54/129	42	n/a	n/a	4/11	36	50/118	42	0.76	0.8 (0.2-2.8)
Codon-129 genotype	MM – 3/3 MV – 0/3 VV – 0/3	100 0 0	MM – 157/157 MV – 0/157 VV – 0/ 157	100 0 0	1	n/a	MM – 17/17 MV – 0/17 VV – 0/17	100 0 0	MM – 143/143 MV – 0/143 VV – 0/143	100 0 0	1	n/a

[1]N = number documented with clinical feature

2.5 Discussion

This review of vCJD provides an update to previously published series [80, 82]. It is the first to review characterisation of later and missed referrals versus early referrals and the first to provide comparative review of older versus younger patients.

Factors associated with later / missed referral include older age, male sex, rapid cognitive decline as a presenting feature, the presence of myoclonus and akinetic mutism and the relative absence of sensory disturbance. A negative cerebral MRI and referral from a non-neurosciences centre were also associated.

Further review of older patients demonstrated a phenotype that overlapped with later referrals (with multivariate analysis demonstrating the confounding effect of age). A discrepancy between a shorter duration of illness with a longer time to diagnosis in older age groups was seen - an expected finding given the association with later diagnoses in these groups.

Whilst this retrospective review has provided valuable insight into the referral and clinical characteristics of late and older referrals there are limitations to consider. The accuracy and full documentation of all clinical features that develop after the NCJDRSU neurologist's review is likely to be incomplete. This is most notable for the over-representation of akinetic mutism in those referred later / missed with time for such patients to develop the full clinical spectrum of signs compared to earlier referrals. Conversely whilst those

referred later may be more likely to have a complete dataset, their data on clinical features was often collected retrospectively and although features are cross-checked / supplemented with contemporaneous medical records, recall bias cannot be excluded.

Factors associated with the difficulties of a diagnosis of dementia in older patients, as discussed in section 1.2, may be important here; specifically, older patients may be less likely to have collateral histories. Similarly, the excess of male patients may be due to spousal survival with women less likely to have a surviving spouse to report concerns over new cognitive decline. It may also be that the shorter disease duration may lead to delayed referral in older patients with initial symptoms potentially attributed to age or another dementing condition, relatively more common in these older ages. However, as similar findings were seen in those ≥ 45 years old (i.e. young, particularly with respect to a diagnosis of dementia) this is unlikely to fully explain these observations.

Included in this cohort are both probable cases and definite cases. Whilst the diagnostic criteria have been demonstrated to have a high specificity it is impossible to exclude CJD mimics (i.e. other forms of RPD) without neuropathological confirmation. It is unlikely however that if present such mimics would be in sufficient numbers to influence results in an important way.

Interpretation of retrospective review of missed cases is also limited by confirmatory and selection bias; later referrals had features recognisable for vCJD and those who reached post-mortem (which is, as per section 1.5, unusual in older patients with dementia) must have displayed features unusual enough to warrant pathological examination. Indeed, from review of medical notes it appeared post-mortem in some missed referrals was only undertaken as CJD was still under consideration.

It may also be considered that there would be a longer time to diagnosis in early cases due to the novel nature of vCJD at this time. A post-hoc analysis of year of referral and time to diagnosis did not however demonstrate this association ($p = 0.17$), suggesting this is unlikely to be a significant confounding factor.

Later and missed referrals were combined in order to improve statistical power. In order to exclusively review risk factors for missed cases it would have been more accurate to analyse those referred after death separately, as before, however this was not possible due to small numbers. Further to this, there may have been possible error introduced by using those referred after death as a surrogate marker of missed cases. Some may not have been referred in life due to family wishes / clinician choice despite a working diagnosis of CJD by the local team; analysis is therefore of later referral to the NCJDRSU rather than delayed diagnosis per se.

With regards investigation results, patients were dichotomously coded as cerebral MRI undertaken or not and MRI positive or not. If the MRI sequences most sensitive for the detection of prion disease (that is, DWI and FLAIR sequences) were not undertaken as part of a patient's MRI protocol, changes would be missed with such scans documented as negative. It may be that those referred later or older were less likely to have full MRI protocols undertaken introducing a confounder not accounted for here. Indeed, a post-hoc review demonstrated that of the 18 probable / definite cases of vCJD who had a negative MRI (and in whom sequences undertaken were known), only five (27.8%) had DWI and FLAIR sequences performed and a further two (11.1%) had FLAIR only sequences performed (data provided by Ms Jan Mackenzie).

Despite these limitations the analysis provides evidence of differences, largely associated with age. There are no comparative studies of later / missed referrals in vCJD, however it is important to note that most patients presented with a rapidly progressive dementia (which, as demonstrated in chapter 1, is a relatively non-specific presentation of a number of neurodegenerative (and non-neurodegenerative) pathologies) with symptoms more suggestive of vCJD (i.e. sensory disturbance) not present until later in the disease course. Further to this, there was an excess of features unusual for vCJD (e.g. muscle wasting and, in later referrals, seizures). These factors, when combined with a lower sensitivity of MRI in the later groups, means it is perhaps not surprising that patients were less likely to be managed in a non-neurosciences centre and referred later / missed.

Results from review of older patients is consistent with el Tawil *et al* (2015) [23] description of older cases of vCJD. This is to be expected as patients reviewed here overlap with those previously described. Similar to above, however, as dementia is associated with increasing age it is not unexpected that diagnosis may be later / missed if older patients with vCJD have a non-specific presentation of a rapid dementia, a negative MRI, and a later time to onset of features that normally help to distinguish CJD from more common forms of dementia.

Whilst it is important to consider whether later / missed and older referrals look different to vCJD it is also important to review whether their illness could in fact be recognised as CJD, and specifically, as vCJD. Such review will allow for a greater understanding of where diagnostic confusion may lie prior to considering measures to identify later / missed referrals earlier.

1) Fulfilment of diagnostic criteria. The vast majority of patients fulfilled internationally agreed diagnostic clinical criteria for vCJD, however there was a slight excess of cases who did not in both older ages and later diagnoses (although this did not reach statistical significance). In general, therefore patients did eventually look like vCJD, although as demonstrated the time to onset of diagnostic features in the later and missed referrals was longer, likely contributing to later diagnosis.

2) Consideration of CJD in life: In 4/5 missed referrals in whom information was available CJD was considered in life. In all cases however sCJD was considered the most likely form (with a diagnosis of CJD eventually considered less likely in most due to a lack of supportive investigation results for sCJD). A post-hoc analysis reviewed whether this diagnostic confusion was because later and older cases of vCJD presented in a sCJD-like manner (Appendix B).

When comparing all cases, the criteria separate forms of CJD well with a significant difference in the presenting feature and presence of clinical features (that contribute towards respective diagnostic criteria) throughout illness. This was also seen in missed referrals. In those ≥65 years old, however, whilst sensory features and pain were more likely in vCJD, there was no difference when compared to sCJD for any other features and no difference in the presenting symptom between groups. Interestingly, at the other end of the age spectrum there were common features seen between young onset cases of sCJD and vCJD (Table D1). This suggests that the differences in age at onset between variant and sporadic CJD may be partially responsible for the phenotypic differences seen; this will be further discussed in chapter 3.

Older patients may therefore present in a manner suggestive of sCJD. Sensory disturbances are less likely in older groups however their presence is an important marker of vCJD in older ages.

Direct comparison of the clinical features of vCJD with other forms of dementia has not been undertaken here. A comparative review of pathologically proven cases of vCJD and vCJD mimics (i.e. cases considered to be vCJD in life but subsequently diagnosed with an alternative pathology at post mortem) was undertaken by Heath *et al* (2010) [80]. This demonstrated that, consistent with findings here, pain was the least commonly documented symptom in other forms of dementia.

2.6 Conclusion

This review has demonstrated that whilst later referrals could be recognised as vCJD there are key atypical features, which may limit case recognition. The most significant 'atypical' feature was older age. Older age presents unique challenges given the relative frequency of other more common forms of dementia.

Evidence has therefore been provided here which is consistent with the possibility that the epidemiological characteristics of vCJD, and specifically the absence of cases in older ages, may be in part due to case under-recognition and under-ascertainment of vCJD in older ages.

CHAPTER 3: FACTORS ASSOCIATED WITH LATE REFERRAL OF SPORADIC CJD

3.1 Introduction

Section 2.1 discussed that age may be a risk factor for late diagnosis of sCJD. An association between age and later / missed referral in vCJD was demonstrated in chapter 2 with clinical and referral characteristics potentially influential in this. The aim of the current chapter is to review whether such an association is also seen in sCJD.

3.2 Background

3.21 Clinical features of sCJD

sCJD is the most common form of CJD. It may present initially with non-specific symptoms such as weight loss, sleep disturbance and mood changes [84, 85]. In the majority, a rapidly progressive dementia then follows associated with multifocal neurological decline.

sCJD is clinically and pathologically heterogeneous and can be sub-classified into 6 categories according to clinical, biochemical, and pathological parameters [34, 35], mediated by the expression of either methionine or valine at codon 129 on *PRNP* and the subtype of the abnormal prion protein isoform (type 1 or 2). The most common subtype, however, representing 57% of those cases for which information is available is MM1 [36, 86] (see Table 15 [86, 87]).

In general, ataxia and myoclonus are seen in almost all patients, with visual / oculomotor disturbance, pyramidal and extrapyramidal features seen in most. As per all forms of CJD, patients typically converge on a terminal akinetic mute state.

Table 15: sCJD subtypes (data from surveillance cohorts in Germany [66] and USA [87])

Subtype	Median age of onset - years (range)	Median duration - years (range)	Most frequently observed presenting features	Clinical features seen throughout illness (% of patients experiencing features) [87]	Predominant hyperintensity changes on MRI (DWI sequences) [66]
MM1	65.5 (42-91)	3.9 (1-18)	Cognitive, ataxia, psychiatric, visual	>50%: Early myoclonus, cognitive, pyramidal, ataxia >25%: visual, psychiatric	Basal ganglia, frontal, temporal, and parietal
MM2	64.3 (49-77)	15.7 (9-36)	Cognitive, ataxia, psychiatric	>50%: Cognitive, aphasia, pyramidal, late myoclonus, ataxia >25%: oculomotor	Basal ganglia and widespread cortical
MV1	62.1 (51-72)	4.9 (2.5-9)	Ataxia, cognitive, sensory, aphasia	>50%: Early myoclonus, ataxia, cognitive, pyramidal >25%: sensory, dysarthria	Frontal and parietal
MV2	59.4 (40-81)	17.1 (5-72)	Ataxia Cognitive	>50%: Ataxia, late myoclonus, pyramidal >25%: psychiatric, apraxia, dysarthria	Basal ganglia and thalamus
VV1	39.3 (24-49)	15.3 (14-16)	Cognitive	>50%: Cognitive, aphasia, apraxia, pyramidal, later myoclonus >25%: oculomotor, extrapyramidal	Cingulate gyrus, insular cortex, and hippocampus
VV2	61.3 (41-80)	6.5 (3-18)	Ataxia, oculomotor	>50%: Ataxia, cognitive, pyramidal, myoclonus >25%: dysarthria, oculomotor	Basal ganglia and cingulate

3.22 Biomarkers of sCJD

Unlike vCJD, CSF is the most sensitive and specific marker in sCJD. The presence of 14-3-3 is a marker of neuronal damage, which, in the correct context, is supportive of a diagnosis of sCJD with a sensitivity of 93% and a specificity of 80% [88, 89]. RT-QuIC is the most useful ante-mortem investigation with sensitivity in the UK of approximately 95% and a very favourable specificity approaching 100% [90]; it has recently been incorporated into the internationally agreed diagnostic criteria for sCJD (Box 3). Cerebral MRI demonstrates high signal of the basal ganglia and cerebral cortex on DWI and FLAIR sequences. Overall specificity of basal ganglia restricted diffusion is unknown and dependent on local reporting variation, however previous reports have demonstrated this to be 93% within specialist units [91]. EEG typically evolves from slow changes into disorganised generalised triphasic periodic complexes at a slow rate of 1-1.5Hz, a feature seen in 64% of patients with sCJD [92].

3.23 Epidemiology of sCJD: UK and worldwide

As detailed in chapter 1, sCJD is a disorder of retirement ages, however, and at odds with other sporadic neurodegenerative conditions, the association between age and age specific mortality in older patients is not linear with a decline seen after the age of 79 years. There is a slight excess of cases in females. Similar to all forms of CJD, there is a significant excess, compared to the general population, of patients homozygous for methionine at codon-129 on *PRNP* [7].

3.3 Methods

3.31 Study design/subjects/setting

A retrospective review of sCJD diagnoses was undertaken. All work was undertaken by the author, unless stated otherwise All patients referred to the NCJDRSU between 1st January 2010 and 31st December 2015, resident in the UK at the time of onset and classified as either probable or definite sCJD according to internationally agreed diagnostic criteria by 30th April 2016 were included (n = 584). The time period chosen for sCJD was to define a contemporary period that incorporated recent changes in the diagnostic criteria in January 2010. This allowed for inclusion of MRI basal ganglia changes and therefore afforded a greater number of probable cases to be included.

As per chapter 2, for the purposes of this thesis, data was extracted from the NCJDRSU database with this first pass of data collection undertaken by Ms Jan Mackenzie and Mr Nick Attwood.

Data collection methods are as per those detailed in chapter 2. All data were collected on the same standardised form over this shorter period of time and are therefore comparable. However, if questionnaires were missing (approximately 10% of cases), correspondence and medical notes were reviewed, the questionnaire retrospectively completed and data entered onto both the NCJDRSU and thesis database. In a small number of cases,

hospitals were re-contacted for medical notes if none had previously been made available.

If, on database review, a patient had been referred late but contact had not yet been made with the patient's relatives an invitation to participate in the NCJDRSU surveillance project was sent. Two invitations were sent; if no response was received no further contact was made. Only patients referred ≤2 years of database review were included. In those referred prior to this time, it was considered too late for unsolicited contact to be made and entries were listed as missing.

3.32 Data processing

1) Basic demographics and referral characteristics

Data fields are described in chapter 2.

2) Clinical features

Presenting feature, signs and symptoms occurring during the patient's illness, time to onset of clinical features, investigation results, and diagnostic criteria were collected as detailed in chapter 2. Further detail specific for sCJD is provided in Table 16

5) Diagnosis in life

Case notes and death certificates from all missed referrals (as defined on page 83) were reviewed to determine the working diagnosis in life. As medical notes from later referrals of vCJD (as defined on page 45) were largely

unrewarding a sample of sCJD later referrals (as defined on page 83) were reviewed. These were also unrevealing of the initial working diagnosis and therefore data searching was limited to only those referred on or after the date of death.

3.33 Data review

Once data had been entered onto the thesis database, as per chapter 2, variables were checked for validity and consistency. Missing entries were entered as 'missing' and not included in analysis.

3.34 Analysis approach

a) Outcome variables

As per chapter 2, the primary outcome variable was to determine the characteristics of patients not diagnosed in life. Here, again, patients were classified as 'missed referral' if they were referred on the day of their death of after or 'later referral' if they had been referred later in the disease course. In sCJD, later referrals included all patients referred within 14 days of their death or after. The shorter period was chosen here to reflect the shorter disease duration of sCJD and, specifically, approximately the last 10% of illness. Results are as compared to those referred before these respective cut-offs.

b) Explanatory variables

Explanatory variables are as described in chapter 2 and detailed in Table 16.

c) Analysis

Statistical methods are described in chapter 2.

Similar to vCJD, age was associated with timing of referral with multivariate analysis highlighting it as a confounding factor. A separate analysis was undertaken re-defining age as the outcome. Patients were classified as 'older adults' if they were aged ≥65 years old at time of onset of first symptoms. Reasons for using 65 years old are as detailed in section 2.33. A further sub-group analysis was undertaken on the oldest 10% of cases; in sCJD this equated to patients aged ≥80 years old.

A database was created in Excel (version 14.7.7). All data was then transferred to SPSS (version 22) and analysed with the aim of looking for factors associated with missed diagnoses of CJD.

Table 16: Explanatory variables (sCJD)

Variable	How recorded	Range of values	Completeness: n (%)
Age	Median years + IQR	n/a	584 (100)
Sex	% male	n/a	584 (100)
IMD	n/a	1-5	578 (99)
Duration of illness	Median months + IQR	n/a	567 (97.1)
Time to diagnosis	Median months + IQR	n/a	581 (99.5)
Source of referral	Neurology, psychiatry, pathology, general medicine, other	n/a	584 (100)
Fulfilled diagnostic criteria in life	Yes/no	n/a	538 (86.1)
Reviewed by neurology	Yes/no	n/a	507 (86.8)
Time to neurology review	Median months + IQR	n/a	380 (65.0)
Reviewed by psychiatry	Yes/no	n/a	544 (93.0)
Time to psychiatry review	Median months + IQR	n/a	89 (15.2)
Referred from neurosciences centre	Yes/no	n/a	584 (100)
Region of referral	North U.K. / South U.K.	n/a	569 (97.4)
Presenting feature	Behaviour / personality change, sensory disturbance, mood disturbance or psychiatric features, rapid cognitive decline, unsteadiness, visual disturbance, and other)	n/a	484 (82.9)
Presence of signs / symptoms during illness	Feature present since onset of illness	Yes/no	See Tables 19 and 23
Cerebral MRI	Presence of basal ganglia restricted diffusion (DWI) or high signal (FLAIR)	Positive/negative	284 (51.2)
CSF 14-3-3	Presence of 14-3-3	Positive/negative	414 (70.9)
CSF RT-QuIC	Presence of RT-QuIC	Positive / negative	309 (57.2)
EEG	Periodic generalised slow synchronised triphasic sharp wave complexes	Positive/negative	45 (7.7)
Codon 129 + protein isoform	Polymorphism / isoform recorded	MM1 / MM2 MV1 / MV2 VV1 / VV2	250 (42.8)

3.4 Results

3.41 All cases sCJD

a) Basic characteristics (all cases)

584 patients were included who fulfilled internationally accepted surveillance criteria for probable or definite sCJD. Of these, 356 patients were definite cases (61%).

283 patients were male (48.5%). The median age of onset was 68 years (50 – 86 years). The median IMD was 3 (1 – 5). There was a long median time to diagnosis of 6 months (0 – 19 months; excluding those referred after death) compared to disease duration of 7 months (0 – 22 months).

b) Referral characteristics (all patients)

All patients were reviewed by a neurologist during their illness (n = 507). The majority of patients were referred by neurology (n = 341, 62.2%). Approximately 20% (n = 111) were referred by psychiatry specialities. 65.7% of patients (n = 360) were managed in a non-neurosciences centre (of which 29% were from hospitals with in-house neurologists).

c) Clinical characteristics (all patients)

The majority of patients (approximately 60%) presented with either cognitive or cerebellar features and cognitive and cerebellar were the most frequently reported clinical features seen during illness. Involuntary movements were also commonly seen. CSF 14-3-3 was positive in 84% (n = 348), RT-QuIC

was positive in 90% (n = 278) and MRI demonstrated typical changes in 78% (n = 223).

When reviewing the time to onset of symptoms, as expected, given the presenting symptoms, forgetfulness and gait change were early features. Although sensory and visual disturbances were uncommon features if they did occur they occurred early in the disease process.

3.42 Later / missed referrals

a) Basic characteristics (later / missed referrals)

A total of 190 patients were referred within 14 days of death or after (32.5% of all referred cases of definite / probable sCJD). Of these, 42 patients were referred on or after the date of death (7.2% of referrals), however in almost all of these 42, sCJD had been considered in life. The most frequent diagnoses in life were CJD, a rapidly progressive dementia, or an encephalitis / encephalopathy. In those with a non-prion disease-specific working diagnosis, Alzheimer's disease and vascular dementia were diagnosed most frequently (Table 17).

Those referred later were significantly older ($p < 0.001$ for later and 0.01 for missed referrals). In those referred in the later stages of their illness patients were more likely to be male and had a shorter duration of illness (Table 18).

Table 17: Missed referrals: diagnoses in life / CJD considered in life (sCJD)

Rapidly progressive dementia	13	31.0
CJD	6	14.3
Encephalitis / encephalopathy	6	14.3
Vascular dementia	3	7.1
Alzheimer's dementia	3	7.1
Parkinson's plus	1	2.4
Delirium	1	2.4
Not clear	9	21.4
CJD considered	Yes: 35 No: 3	Yes: 83.3 No: 7.1

Table 18: Basic demographics - later referrals (sCJD)

Patient characteristics	**Later (referred ≤14 days of death or after)**	**Early (referred > 14 days of death)**	**p-value**	**O.R. (95% CI)**	**Missed (referred on or after date of death)**	**Referred in life**	**p-value**	**O.R. (95% CI)**
Median age: years^	72 (66-78)	67 (62-73)	<0.001**	n/a	71 (66-79)	68 (63-74)	0.012*	n/a
Male: n of N documented (%)	110/ 190 (57.9)	173/394 (43.9)	0.002*	1.2 (1.1-1.3)	22/42 (52.4)	261/542 (48.2)	0.63	1.0 (1-1.1)
Median Index of Multiple Deprivation	3 (2-4)	3 (1-5)	0.8	n/a	2 (1-4)	3 (2-4)	0.75	n/a
Median duration of illness: months^	4 (2-7)	5 (3-10)	<0.001**	n/a	5 (2-11)	5 (3-9)	1.0	n/a
Time to diagnosis: months^	4.4 (2.2-9)	3.9 (2.4-8)	0.82	n/a	9.2 (4.8-18.2)	3.8 (2.3-7.8)	<0.01**	n/a
Fulfilled diagnostic criteria in life	115/141 (81.5%)	275/362 (76.0%)	0.19	1.4 (0.9-2.3)	13/23 (56.5%)	377/480 (78.5%)	0.02*	0.36 (0.15-0.83)

*Significant p <0.05 **Highly significant p <0.01 ^Median + IQR

b) Referral characteristics (later / missed referrals)

Later / missed referrals were less likely to be referred from neurology (although all were reviewed by a neurologist during their illness), and, as expected, there was an excess of patients referred from pathology. In general those referred later were less likely to be managed in a neurosciences centre and were more likely to be reviewed by psychiatry with a strong association seen with missed referrals ($p = 0.005$) (Table 19).

Table 19: Referral characteristics - later referrals (sCJD)

Referral characteristic	Later referrals (≤14 days prior to death or after)		Early referrals (>14 days prior to death)				Missed referrals (referred ≥date of death)		Early referrals (referred before date of death)			
		%		%	p-value	O.R.		%		%	p-value	O.R.
Source of referral:	(N = 190)		(N = 394)				(N = 42)		(N = 542)			
Neurology	85	44.7	278	70.6			7	16.7	356	65.7		
Psychiatry	1	0.5	4	1			1	2.4	4	0.7		
General	56	29.5	85	21.6			3	7.1	138	25.5		
Pathology	33	17.4	2	0.5			30	71.4	5	0.9		
Other	15	7.9	25	6.3	<0.001**	n/a	1	2.4	39	7.2	<0.001**	n/a
Reviewed by Neurology: n / N	144/144	100	363/363	100	n/a	n/a	21/21	100	486/486	100	n/a	n/a
Time to neurology review (months)^	2 (1-4.5)	n/a	2 (1-5)	n/a	0.6	n/a	3 (1-8)	n/a	2 (1-5)	n/a	0.6	n/a
Reviewed by Psychiatry: n / N	37/157	23.4	71/387	18.3	0.2	1.1 (1-1.3)	12/28	42.9	96/516	18.6	0.005*	1.1 (1-1.16)
Time to psychiatry review (months)^	3 (2-6)	n/a	2 (1-5)	n/a	0.8	n/a	3.5 (1.5-7.25)	n/a	3 (2-7)	n/a	0.8	n/a
Neurosciences centre (at point of referral): n / N	259/584	44.3	198/394	50.3	<0.001**	0.8 (0.7-0.9)	10/42	23.8	249/542	45.9	0.006*	0.9 (0.9-1)
Region of residence: North	52/184	28.3	123/385	31.9	0.38	1.2 (0.8-1.8)[1]	13/41	31.7	162/528	30.7		1 (0.5-1.9)[1]
South	132/184	71.7	262/385	68.1			28/41	68.3	366/528	69.3	0.86	

*Significant p <0.05 **Highly significant p <0.01 ^Median + IQR [1] For North region n = number with feature N = number documented

c) Clinical characteristics (later referrals)

When compared to earlier referrals, later referrals demonstrated an association with presenting feature; this was due to an excess of patients presenting with rapid cognitive decline, visual disturbance, and behavioural changes and fewer than expected presenting with sensory disturbance and unsteadiness (Table 20).

Cerebellar features were consistently less likely in both later and missed referrals. In missed referrals there was a general paucity of signs and symptoms other than delusions and hallucinations, which were seen more frequently (although not significantly so).

In later referrals, again clinical features were less likely to be described compared to earlier referrals, although features associated with end stage CJD (akinetic mutism and cortical blindness) were significantly more likely. Forgetfulness and behavioural disturbance occurred earlier in later referrals, however no differences were seen with missed referrals.

MRI was less likely to be positive in later and missed referrals; CSF was more likely to be positive with a significant association demonstrated with later referral. In later referrals there was a significant difference in the codon-129 polymorphism / isoform subtype, with an excess of MM1 seen.

Table 20: Clinical characteristics - later and missed referrals (sCJD)

Presenting features	**Later referrals (≤14 days prior to death or after)**		**Early referrals (>14 days prior to death)**				**Referred on or after date of death**		**Referred before date of death**			
	n (of N[1])	**%**	**n (of N[1])**	**%**	**p-value**	**O.R. (95% CI)**	**n (of N[1])**	**%**		**%**	**p-value**	**O.R. (95% CI)**
Mood disturbance or psychiatric features	13/134	9.7	27/350	7.7	0.16	1.5 (0.9 – 2.7)	3/24	12.5	37/460	8.0	0.2	2 (0.7 – 5.5)
Sensory disturbance	1/134	0.7	19/350	5.4	0.02*	0.1 (0.02 – 1)	0/24	0	20/460	4.3	0.6	1 (0.9 – 1)
Behaviour / personality change	21/134	15.7	38/350	10.9	0.5	1.3 (0.6 – 2.6)	5/24	20.8	54/460	11.7	0.4	1.6 (0.5 – 5.7)
Rapid cognitive decline	49/134	36.6	111/350	31.7	0.3	1.2 (0.8 – 2.9)	7/24	29.2	153/460	33.3	0.8	0.8 (0.3 – 2)
Unsteadiness / motor	28/134	20.9	100/350	28.6	0.1	0.7 (0.4 – 1.1)	5/24	20.8	123/460	26.7	0.6	0.7 (0.3 – 2)
Visual disturbance	16/134	11.9	29/350	8.3	0.2	1.5 (0.8 – 2.9)	3/24	12.5	42/460	9.1	0.5	1.4 (0.4 – 5)
Other	6/134	4.5	26/350	7.4	0.3	0.6 (0.2 – 1.5)	1/24	4.2	31/460	6.7	1	0.6 (0.08 – 4.6)
Overall					0.04*	n/a					0.67	n/a
Presence of sign												
Cognitive impairment	123/152	80.9	322/375	85.9	0.16	0.9 (0.8-1.1)	17/27	63.0	428/500	85.6	0.002**	0.9 (0.8-1)
Apraxia	33/87	37.9	126/245	51.4	0.03*	0.9 (0.8-1)	6/19	31.6	153/313	48.9	0.14	1 (0.9-1)
Dysphasia	67/118	56.8	192/336	57.1	0.95	1 (0.9-1.1)	3/20	15.0	256/434	59.0	<0.001**	0.9 (0.9-1)
Grasp reflex	54/121	44.6	180/364	49.5	0.36	1 (0.9-1.1)	1/21	4.8	233/464	50.2	<0.001**	0.9 (0.9-1)
Cerebellar gait ataxia	65/108	60.2	221/336	65.8	0.29	0.9 (0.8-1.1)	10/23	43.5	276/421	65.6	0.031	1 (0.9-1)

Cerebellar signs	84/187	44.9	266/394	67.5	<0.001**	0.7 (0.6-0.8)	11/41	26.8	339/540	62.8	<0.001**	0.9 (0.9-1)
Lower motor neurone	13/148	8.8	53/383	13.8	0.11	0.9 (0.8-1)	0/23	0	66/508	13.0	0.07	1 (0.9-1)
Akinetic mute	80/146	54.8	103/384	26.8	<0.001**	1.4 (1.3-1.7)	8/24	33.3	175/506	34.6	0.90	1 (1-1)
Pyramidal features	79/148	53.4	217/381	57	0.46	1 (0.9-1.1)	5/24	20.8	291/505	57.6	<0.001**	0.9 (0.9-1)
Extrapyramidal features	69/146	47.3	178/375	47.5	0.97	1 (0.9-1.1)	7/24	29.2	240/497	48.3	0.07	1 (0.9-1)
Cortical blindness	40/132	30.3	52/374	13.9	<0.001**	1.4 (1.1-1.7)	3/24	12.5	89/482	18.5	0.46	1 (0.9-1)
Oculomotor palsy	15/143	10.5	43/374	11.5	0.75	1 (0.8-1.1)	1/26	3.8	57/491	11.6	0.22	1 (0.9-1)
Dysarthria	39/132	29.5	108/357	30.3	0.88	1 (0.9-1.1)	2/24	8.3	145/465	31.2	0.02*	0.9 (0.9-1)
Myoclonus	114/151	75.5	296/384	77.1	0.70	1 (0.9-1.1)	11/24	45.8	399/511	78.1	<0.001**	0.9 (0.9-1)
Chorea	6/146	4.1	14/381	3.7	0.82	1 (0.8-1.4)	0/21	0	20/506	4	0.35	1 (0.9-1)
Dystonia	33/147	22.4	82/380	21.6	0.83	1 (0.9-1.2)	0/21	0	115/506	22.7	0.01**	0.9 (0.9-1)
Sensory signs	3/146	2.1	28/379	7.4	0.02*	0.8 (0.7-0.9)	0/23	0	31/502	6.2	0.22	1 (0.9-1)
Presence of symptom												
Forgetfulness	133/152	87.5	334/386	86.5	0.76	1 (0.9-1.2)	22/27	81.5	445/511	87.1	0.40	1 (0.9-1)
Other higher function (eg apraxia / disorientation)	71/148	48	188/372	50.5	0.60	1 (0.9-1.1)	10/27	37.0	249/493	50.5	0.17	1 (0.9-1)
Language disturbance	86/152	56.6	230/383	60.1	0.46	1 (0.9-1.1)	10/25	40	306/510	60	0.05*	1 (0.9-1)
Psychiatric symptoms	59/156	37.8	137/383	35.8	0.65	1 (0.9-1.1)	9/28	32.1	187/511	36.6	0.63	1 (1-1)
Depression	36/154	23.4	85/379	22.4	0.81	1 (0.9-1.2)	6/28	21.4	115/505	22.8	0.87	1 (1-1)
Anxiety	71/152	46.7	150/380	39.5	0.12	1.1 (1-1.2)	9/28	32.1	212/505	42	0.30	1 (0.9-1)
Behavioural disturbance	93/155	60	207/383	54	0.21	1.1 (1-1.2)	16/28	57.1	284/510	55.7	0.88	1 (1-1)
Apathy / withdrawal	61/151	40.4	160/378	42.3	0.68	1 (0.9-1.1)	11/26	42.3	210/503	41.7	0.96	1 (1-1)
Delusions	33/149	22.1	98/384	25.5	0.42	1 (0.9-1.1)	9/26	34.6	122/507	24.1	0.22	1 (1-1.1)
Hallucinations - visual	88/155	56.8	205/384	53.4	0.48	1 (0.9-1.2)	17/28	60.7	276/511	54	0.49	1 (1-1.1)
Hallucinations -	4/154	2.6	10/385	2.6	1.00	1 (0.7-2.3)	2/27	7.4	12/512	2.3	0.11	1.1 (0.9-1.4)

auditory												
Other psychiatric symptoms	7/152	4.6	21/384	5.5	0.69	1 (0.8-1.2)	1/27	3.7	27/509	5.3	0.72	1 (0.9-1.1)
Disturbance of gait	135/157	86	337/383	88	0.52	0.9 (0.8-1.1)	22/28	78.6	450/512	87.9	0.15	1 (0.9-1)
Bed-bound	135/156	86.5	221/385	57.4	<0.001**	1.4 (1.3-1.6)	21/27	77.8	335/514	65.2	0.18	1 (1-1.1)
Speech disturbance	104/153	68	256/381	67.2	0.86	1 (0.9-1.1)	12/27	44.4	348/507	68.6	0.009**	0.9 (0.9-1)
Diplopia	27/153	17.6	53/384	13.8	0.26	1.1 (0.9-1.3)	0/27	0	80/510	15.7	0.026*	0.9 (0.9-1)
Visual impairment	65/153	42.5	150/380	39.5	0.52	1 (0.9-1.2)	10/27	37.0	205/506	40.5	0.72	1 (1-1)
Involuntary movements	114/156	73.1	261/383	68.1	0.26	1.1 (1-1.2)	20/27	74.1	355/512	69.3	0.60	1 (1-1.1)
Sensory symptoms (pain / numbness etc)	20/153	13.1	73/382	19.1	0.1	0.9 (0.8-1)	2/27	7.4	91/508	17.9	0.16	1 (0.9-1)
Seizures	17/153	11.1	25/384	6.5	0.07	1.2 (0.9-1.6)	4/28	14.3	38/509	7.5	0.19	1 (1-1.2)
Time to onset of clinical feature												
Forgetful	1 (0-2)	n/a	1 (0-3)	n/a	0.03*	n/a	1 (0-2)	n/a	1 (0-3)	n/a	0.2	n/a
Rapid Cognitive Decline	2 (1-4)	n/a	3 (1-5)	n/a	0.13	n/a	4 (1-11)	n/a	2 (1-5)	n/a	0.22	n/a
Gait disturbance	1 (0-3)	n/a	1 (0-4)	n/a	0.37	n/a	2 (1-6)	n/a	1 (0-3)	n/a	0.16	n/a
Cerebellar signs	2 (1-5)	n/a	3 (1-5)	n/a	0.23	n/a	4 (1-11)	n/a	2 (1-5)	n/a	0.12	n/a
Visual symptoms	1 (0-4)	n/a	2 (0-4)	n/a	0.2	n/a	1 (0-6)	n/a	1 (0-4)	n/a	0.94	n/a
Extrapyramidal signs	3 (2-6)	n/a	3 (2-6)	n/a	0.62	n/a	4 (1-11)	n/a	3 (2-6)	n/a	0.56	n/a
Pyramidal signs	3 (1-7)	n/a	3 (2-7)	n/a	0.13	n/a	7 (2-26)	n/a	3 (2-7)	n/a	0.22	n/a
Myoclonus	2 (1-6)	n/a	3 (2-6)	n/a	0.19	n/a	4 (2-14)	n/a	3 (2-6)	n/a	0.21	n/a
Akinetic mutism	3 (2-6)	n/a	3 (2-5)	n/a	0.95	n/a	5 (2-21)	n/a	3 (2-5)	n/a	0.18	n/a
Behavioural and mood disturbance	0 (0-2)	n/a	1 (0-3)	n/a	0.04*	n/a	1 (0-5)	n/a	1 (0-3)	n/a	0.27	n/a
Psychiatric symptoms	1 (0-3)	n/a	4 (1-8)	n/a	0.28	n/a	0.5 (0-11)	n/a	1 (0-3)	n/a	0.92	n/a
Sensory symptoms	4 (1-7)	n/a	1 (0-5)	n/a	0.17	n/a	3 (3-3)	n/a	1 (0-6)	n/a	0.81	n/a

[1]N = number documented with clinical feature *Significant p <0.05 **Highly significant p <0.01 ^Median months + IQR

Table 21: Investigation findings - later and missed referrals (sCJD)

	Later referrals (≤14 days prior to death or after)		**Early referrals (>14 days prior to death)**				**Referred ≥date of death**		**Referred before date of death**			
	n (of N patients)	**%**	**n (of N patients)**	**%**	**p-value**	**O.R. (95% CI)**	**n (of N patients)**	**%**	**n (of N patients)**	**%**	**p-value**	**O.R. (95% CI)**
Investigation												
MRI	50/67	74.6	172/217	79.3	0.4	0.9 (0.8-1.1)	3/6	50	219/278	78.8	0.09	n/a
EEG	2/10	20.0	12/35	34.3	0.39	n/a	0/1	0	14/44	31.8	0.50	n/a
CSF 14-3-3	97/106	91.5	251/308	81.5	0.04*	1.3 (1.1-1.4)	11/12	91.7	337/402	83.8	1.0	1 (0.9-1.1)
CSF RT-QuIC	84/86	97.7	194/223	87.0	0.02*	1.3 (1.2-1.5)	10/11	90.9	268/298	90	1.0	1 (0.9-1.1)
Codon-129 genotype / isoform	(N = 87) MM1 - 62 MM2 - 4 MV1 - 2 MV2 - 4 VV1 - 1 VV2 - 14	 71.3 4.6 2.3 4.6 1.1 16.1	(N = 163) MM1 - 82 MM2 - 13 MV1 - 13 MV2 - 23 VV1 - 5 VV2 - 27	 50.3 8.0 8.0 14.1 3.1 16.6	0.02*	n/a	(N = 20) MM1 - 11 MM2 - 1 MV1 - 1 MV2 - 2 VV1 - 1 VV2 - 4	 55.0 5.0 5.0 10.0 5.0 20.0	(N = 230) MM1 - 133 MM2 - 16 MV1 - 14 MV2 - 25 VV1 - 5 VV2 - 37	 57.8 7.0 6.1 10.9 2.2 16.1	1.0	n/a

*Significant p <0.05 **Highly significant p <0.01 ^Median + IQR

Multivariate analysis

An independent association with later referral was retained for being-bed-bound (p = 0.001, O.R. 4 (2.4 – 6.6)) / akinetic mutism (p <0.001, O.R. 2.9 (1.9 – 4.4)), cerebellar signs (p <0.001, O.R. 0.6 (0.4 – 0.9)), cortical blindness (p <0.001, O.R. (2.4 (1.5 – 3.8)), and being referred by a regional hospital (p = 0.03, O.R. 1.8 (1.2 – 2.6)). All other findings were due to the confounding effects of age.

In missed referrals, an independent association was retained for language impairment (p = 0.05, O.R. 0.4 (0.2 – 1)), speech disturbance (p = 0.008, O.R. 0.3 (0.2 – 0.8)), cerebellar signs (p <0.001, O.R. 0.1 (0.05 – 0.4)) / ataxia (p = 0.05, O.R 0.4 (0.2 – 1)), grasp reflex (p = 0.003, O.R. 0.05 (0.006 – 0.4)), pyramidal features (p = 0.001, O.R. 0.18 (0.07 – 0.5)), cognitive impairment (p = 0.002, O.R. 0.3 (0.1 – 0.6)), dysphasia (p <0.001, O.R. 0.1 (0.03 – 0.4)), myoclonus (p <0.001, O.R. 0.2 (0.1 – 0.5)), whether they were seen by psychiatry (p = 0.002, O.R. 3.5 (1.6 – 7.8)), and whether they were referred from a neurosciences centre (p = 0.023, O.R. 2.4 (1.1 – 5)). Age was a confounding factor in all other associations.

3.43 Older adults

a) Basic characteristics (older adults)

396 patients aged ≥65 years old were identified (67.8% of all cases of definite / probable sCJD). Of these, 62 patients aged ≥80 years old were identified (10% of all included cases). Older patients were more likely to be male. The duration of illness was shorter in both groups compared to younger patients with no shortening of the time to diagnosis to compensate for this more rapid progression (Table 22).

b) Referral characteristics (older adults)

The source of referral was significantly associated with age. Older patients were less likely to be referred by neurology and were more likely to be referred by general physicians and pathology. All patients were however reviewed by a neurologist during their illness. Older patients were significantly less likely to be managed in a neurosciences centre at the time of referral. There was a strong association between older age and later referral with an excess of missed referrals in older patient groups (Table 23).

Table 22: Basic demographics - older adults (sCJD)

Patient characteristics	**≥65 years old (n = 396)**	**<65 years old (n = 188)**	**p-value**	**O.R (95% CI)**	**≥80 years old (n = 62)**	**<80 years old (n = 522)**	**p-value**	**O.R (95% CI)**
Median age: years (median, IQR)	72 (68-77)	60 (55-63)	n/a	n/a	82 (80-84)	67 (62-73)	n/a	n/a
Male: n of N documented (%)	202 (51%)	81 (43%)	0.07	1.2 (1-1.6)	31 (50%)	252 (48%)	0.8	1 (1-1.1)
Median Index of Multiple Deprivation	2 (2-4)	3 (2-4)	0.4	n/a	3 (1.8-4)	3 (2-4)	0.6	n/a
Median duration of illness: months^	4 (3-8)	6 (3-12)	<0.001**	n/a	4 (3-7)	5 (3-10)	0.02*	n/a
Time to diagnosis (months)^	4 (2.3-7.7)	4.7 (2.4-9.6)	0.08	n/a	4.1 (2.4-6.5)	4.1 (2.3-8.3)	0.7	n/a
Fulfilled diagnostic criteria during life	268/342 (78.6%)	122/161 (75.8%)	0.57	1.15 (0.7-1.8)	42/51 (82.4%)	348/452 (77.0%)	0.48	1.4 (0.67-3.0)

^Median months + IQR *Significant p <0.05 **Highly significant p <0.01 n/a = not applicable

Table 23: Referral characteristics - older adults (sCJD)

Referral characteristic	≥65 years old		<65 years old				≥80 years old		<80 years old			
		%		%	p-value	O.R.		%		%	p-value	O.R.
Source:												
Neurology	230	58.1	133	70.7			23	37.1	340	65.1		
Psychiatry	4	1	1	0.5			0	0	5	1		
General	111	28	30	16			31	50	110	21.1		
Pathology	28	7.1	7	3.7			7	11.3	28	5.4		
Other	23	5.8	17	9	0.004*	n/a	1	1.6	39	7.5	<0.001**	n/a
Reviewed by Neurology: n / N	333/333	100	174/174	100	n/a	n/a	45/45	100	462/462	100	n/a	n/a
Time to neurology review (months)^	2 (1-4)		3 (1-6)		0.02*	n/a	3 (1-6)		2 (1-5)		0.5	n/a
Reviewed by Psychiatry: n / N	69/367	18.8	39/177	22.0	0.4	0.9 (0.7-1.2)	8/56	14.3	100/488	20.5	0.4	1 (0.9-1)
Time to psychiatry review (months)^	3 (2-6)		4 (1.3-8.8)		0.2	n/a	3 (2-8)		3.5 (1.8-7)		0.9	n/a
Neurosciences centre (at point of referral): n / N	150/396	37.9	109/188	58.0	<0.001**	0.6 (0.5-0.7)	11/62	17.7	248/522	47.5	<0.001**	0.9 (0.8-0.9)
Region: North	113/384	29.4	62/185	33.5	0.33	1.2 (0.8-1.8)[1]	15/59	25.4	160/510	31.4	0.38	1.3 (0.7-2.5)[1]
South	271/384	70.6	123/185	66.5			44/59	74.6	350/510	68.6		
Later referral: n /N	150/396	37.9	40/188	21.3	<0.001**	1.8 (1.3-2.4)	36/62	58.1	154/522	29.5	<0.001**	1.2 (1.1-1.2)
Missed referral: n / N	33/396	8.3	9/188	4.8	0.1	1.5 (0.9-2.8)	8/62	12.9	34/522	6.5	0.07	1.1 (1-1.3)

*Significant p <0.05 **Highly significant p <0.01 ^Median + IQR [1] For North region n = number with characteristic N = of number documented

c) Clinical characteristics (older adults)

In both older age groups there was an excess of patients presenting with rapid cognitive decline and an earlier onset of forgetfulness and cognitive impairment in keeping with this (Table 24).

In both older groups, clinical features were less likely to be seen than in earlier groups. In particular, older patients were significantly less likely to have psychiatric features and in those ≥80 years old, cerebellar features. Older patients were however more likely to be bed-bound, akinetic and mute, and be cortically blind. Seizures were also significantly more likely in those ≥80 years old.

There was a shorter time to onset of forgetfulness in both older groups. A shorter time to onset was also demonstrated for a number of other clinical features in those ≥65 years old; this may simply reflect the significantly shorter duration of illness in this older group (an association seen to a lesser extent in those ≥80 years old).

MRI was less likely to demonstrate the typical changes of sCJD in both groups (Table 25). In those ≥ 80 years old, EEG was more likely to demonstrate typical changes of sCJD.

Table 24: Clinical characteristics - older adults (sCJD)

	≥65 years old (n of N[1])	%	<65 years old (n of N[1])	%	p-value	O.R.	≥80 years old (n of N[1])	%	<80 years old (n of N[1])	%	p-value	O.R.
Presenting feature												
Mood disturbance or psychiatric features	24/328	7.3	16/156	10.3	0.5	0.8 (0.4 – 1.4)	2/49	4.1	38/435	8.7	0.8	0.8 (0.3 – 2.1)
Sensory disturbance	8/328	2.4	12/156	7.7	0.01	0.3 (0.1 – 0.8)	2/49	4.1	18/435	4.1	1	1 (0.2 – 4.4)
Behaviour / personality change	37/328	11.3	22/156	14.1	0.3	0.7 (0.4 – 1.3)	5/49	10.2	54/435	12.4	0.4	0.4 (0.1 – 1.9)
Rapid cognitive decline	116/328	35.4	44/156	28.2	0.1	1.4 (0.9 – 2.1)	24/49	49.0	136/435	31.3	0.02*	2.1 (1.2 – 3.8)
Unsteadiness	94/328	28.7	34/156	21.8	0.1	1.4 (0.9 – 2.3)	9/49	18.4	119/435	27.4	0.2	0.6 (0.3 – 1.3)
Visual	32/328	9.8	13/156	8.3	0.7	1.2 (0.6 – 2.3)	5/49	10.2	40/435	9.2	0.8	1.1 (0.4 – 3)
Other	17/328	5.2	15/156	9.6	0.08	0.5 (0.3 – 1.1)	2/49	4.1	30/435	6.9	0.8	0.6 (0.1 – 2.5)
Overall					0.02*	n/a					0.28	n/a
Presence of sign												
Cognitive impairment	299/354	84.5	146/173	84.4	0.98	1 (0.7-1.4)	42/52	80.8	403/475	84.8	0.44	1 (0.9-1.1)
Apraxia	111/215	51.6	48/117	41.0	0.07	1.3 (1-1.8)	10/28	35.7	149/304	49.0	0.18	1 (0.9-1)
Dysphasia	187/304	61.5	72/150	48.0	0.006**	1.4 (1.1-1.9)	27/47	57.4	232/407	57.0	0.95	1 (0.9-1.1)
Grasp reflex	169/325	52.0	65/160	40.6	0.02*	1.4 (1-1.8)	19/46	41.3	215/439	50.0	0.32	1 (0.9-1)
Cerebellar gait ataxia	189/293	64.5	97/151	64.2	0.96	1 (0.8-1.3)	19/38	50.0	267/406	65.8	0.05*	0.9 (0.9-1)
Cerebellar signs	234/394	59.4	116/187	62.0	0.54	1 (0.8-1.3)	19/50	38	280/449	62.4	0.001**	0.9 (0.8-1)
Lower motor neurone	47/357	13.2	19/174	10.9	0.46	1.2 (0.8-1.7)	7/55	12.7	59/476	12.4	0.94	1 (0.9-1.1)
Akinetic mute	138/356	38.8	45/174	25.9	0.003**	1.5 (1.1-2)	27/54	50.0	156/476	32.7	0.01**	1.1 (1-1.2)

Pyramidal features	197/357	55.2	99/172	57.6	0.61	0.9 (0.7-1.2)	33/52	63.5	263/477	55.1	0.25	1 (1-1.1)
Extrapyramidal features	166/351	47.3	81/170	47.6	0.94	1 (0.8-1.3)	30/54	55.6	217/467	46.5	0.21	1 (1-1.1)
Hemianopia	33/340	9.7	14/166	8.4	0.64	1.1 (0.7-1.8)	2/49	4.1	45/457	9.8	0.19	0.9 (0.9-1)
Cortical blindness	70/339	20.6	22/167	13.2	0.04*	1.5 (1-2.2)	14/50	28	78/456	17.1	0.06	1 (1-1.2)
Oculomotor palsy	37/345	10.7	21/172	12.2	0.61	0.9 (0.3-1.3)	3/50	6.0	55/467	11.8	0.22	0.9 (0.9-1)
Dysarthria	103/324	31.8	44/165	26.7	0.24	1.2 (0.9-1.6)	12/44	27.3	135/445	30.3	0.67	1 (0.9-1)
Myoclonus	283/360	78.6	127/175	72.6	0.12	1.2 (1-1.6)	41/56	73.2	369/479	77.0	0.52	1 (0.9-1.1)
Chorea	14/353	4.0	6/174	3.4	0.77	1.1 (0.6-2.2)	3/54	5.6	17/473	3.6	0.48	1.1 (0.9-1.3)
Dystonia	38/174	21.8	77/353	21.8	1.00	1 (0.7-1.3)	7/55	12.7	108/472	22.9	0.08	0.9 (0.9-1)
Sensory signs	22/353	6.2	9/172	5.2	0.65	1.1 (0.7-2)	1/53	1.9	30/472	6.4	0.19	0.9 (0.9-1)
Presence of symptom												
Forgetfulness	316/362	87.3	151/176	85.8	0.63	1.1 (0.8-1.5)	45/55	81.8	422/483	87.4	0.25	1 (0.9-1)
Other higher function	170/350	48.6	89/170	52.4	0.42	0.9 (0.7-1.2)	24/54	44.4	235/466	50.4	0.41	1 (0.9-1)
Language disturbance	215/360	59.7	101/175	57.7	0.66	1.1 (0.8-1.4)	33/55	60.0	283/480	59.0	0.88	1 (0.9-1.1)
Psychiatric symptoms	121/363	33.3	75/176	42.6	0.04*	0.8 (0.6-1)	12/56	21.4	184/483	38.1	0.01**	0.9 (0.9-1)
Depression	68/358	19.0	53/175	30.3	0.003**	0.7 (0.5-0.9)	6/56	10.7	115/477	24.1	0.02*	0.9 (0.9-1)
Anxiety	135/357	37.8	86/176	48.9	0.02*	0.7 (0.6-0.9)	15/56	26.8	206/477	43.2	0.02*	0.9 (0.9-1)
Behavioural disturbance	189/362	52.2	111/176	63.1	0.02*	0.7 (0.6-1)	27/56	48.2	273/482	56.6	0.23	1 (0.9-1)
Apathy / withdrawal	143/353	40.5	78/176	44.3	0.40	0.9 (0.7-1.1)	15/56	26.8	206/473	43.6	0.02*	0.9 (0.9-1)
Delusions	85/358	23.7	46/175	26.3	0.52	0.9 (0.7-1.2)	6/56	10.7	125/477	26.2	0.01**	0.9 (0.9-1)
Hallucinations - visual	201/363	55.4	92/176	52.3	0.50	1.1 (0.9-1.4)	29/55	52.7	264/484	54.5	0.80	1 (0.9-1)
Hallucinations - auditory	8/364	2.2	6/175	3.4	0.40	0.8 (0.4-1.4)	0/56	0	14/483	2.9	0.20	0.9 (0.9-0.9)
Other psychiatric	15/361	4.2	13/175	7.4	0.11	0.7 (0.5-1)	1/56	1.8	27/480	5.6	0.22	0.9 (0.9-1)

symptoms												
Disturbance of gait	320/363	88.2	152/177	85.9	0.45	1.1 (0.8-1.6)	44/56	78.6	428/484	88.4	0.04*	0.9 (0.8-1)
Bed-bound	259/364	71.2	97/177	54.8	<0.001**	1.6 (1.3-2)	49/56	87.5	307/485	63.3	<0.001**	1.1 (1-1.2)
Speech disturbance	248/360	68.9	112/174	64.4	0.30	1.1 (0.9-1.5)	37/56	66.1	323/478	67.6	0.82	1 (0.9-1.1)
Diplopia	54/361	15.0	26/176	14.8	0.96	1 (0.7-1.4)	5/55	9.1	75/482	15.6	0.20	1 (0.9-1)
Visual impairment	150/358	41.9	65/175	37.1	0.29	1.1 (0.9-1.5)	16/55	29.1	199/478	41.6	0.07	0.9 (0.9-1)
Involuntary movements	261/363	71.9	114/176	64.8	0.09	1.2 (1-1.6)	39/55	70.9	336/484	69.4	0.82	1 (0.9-1.1)
Sensory symptoms	53/359	14.7	40/176	22.7	0.02*	0.7 (0.5-0.9)	7/55	12.7	86/480	17.9	0.34	1 (0.9-1)
Seizures	27/361	7.5	15/176	8.5	0.67	0.9 (0.6-1.4)	13/56	23.2	29/481	6.0	<0.001**	1.3 (1.1-1.6)
Time to onset of clinical features^												
Forgetful	1 (0-2)		1 (0-4)		0.01*		0 (0-1)		1 (0-3)		0.001**	
Rapid Cognitive Decline	2 (1-4)		3 (1-7)		0.04*		2 (1-5)		2 (1-5)		0.40	
Gait disturbance	1 (0-3)		2 (1-5)		0.001**		1 (0-3)		1 (0-3)		0.39	
Cerebellar signs	2 (1-4.5)		3 (1-7)		0.003**		3 (1-6)		2 (1-5)		0.52	
Visual symptoms	1 (0-4)		1.5 (0-5)		0.30		1 (0-7)		1 (0-4)		0.88	
Extrapyramidal	3 (2-5)		4 (2-8)		0.024*		2.5 (2-5.5)		3 (2-6)		0.38	
Pyramidal signs	3 (2-6)		4 (2-9)		0.08		3 (2-6)		3 (2-7)		0.28	
Myoclonus	2 (1-5)		4 (2-8)		0.003**		2 (1-5)		3 (2-6)		0.36	
Akinetic mutism	2 (2-4)		4 (2-9)		0.008**		3 (2-5)		3 (2-5)		0.59	
Behavioural and mood disturbance	1 (0-2)		1 (0-4)		0.15		1 (1-2)		1 (0-3)		0.92	
Psychiatric symptoms	1 (0-3)		2 (0-4)		0.40		1 (0-8)		1 (0-3)		0.52	
Sensory symptoms	2 (0.5-5)		1 (0-7)		0.79		2 (0-8)		1 (0-5)		0.95	

*Significant p <0.05 **Highly significant p <0.01 ^Median months (+ IQR)

Table 25: Investigation findings - older adults (sCJD)

Investigation Results	**≥65 years old (N = 328)**	**%**	**<65 years old (N = 156)**	**%**	**p-value**	**O.R.**	**≥80 years old (N = 49)**	**%**	**<80 years old (N = 435)**	**%**	**p-value**	**O.R.**
MRI	141/191	73.8	81/93	87.1	0.01**	0.5 (0.3-0.9)	17/29	58.6	205/255	80.4	0.01*	0.9 (0.8-1)
EEG	10/33	30.3	4/12	75.0	0.8	0.9 (0.3-2.5)	5/6	83.3	9/39	23.1	0.008**	1.5 (1-2.2)
CSF 14-3-3	231/250	92.4	117/131	89.3	0.3	1.3 (0.8-1.9)	30/33	90.9	318/348	91.4	1.00	1 (0.9-1.1)
RT-QuIC	189/201	94.0	89/107	83.2	0.004**	1.9 (1.3 -2.6)	27/28	96.4	251/279	90.0	0.34	1.1 (1-1.2)
Codon-129 genotype / isoform	(N = 170) MM1 - 104 MM2 - 9 MV1 - 9 MV2 - 15 VV1 - 1 VV2 - 32	 61.2 5.3 5.3 8.8 0.6 18.8	(N = 80) MM1 - 40 MM2 - 8 MV1 - 6 MV2 - 12 VV1 - 5 VV2 - 9	 50 10 7.5 15 6.3 11.3	 0.01**	 n/a	(N = 31) MM1 - 25 MM2 - 1 MV1 - 0 MV2 - 2 VV1 - 0 VV2 - 3	 80.6 3.2 0 6.4 0 9.7	(N = 219) MM1 - 119 MM2 - 16 MV1 - 15 MV2 - 25 VV1 - 16 VV2 – 38	 54.3 7.3 6.8 11.4 7.3 17.4	 0.13	 n/a

3.5 Discussion

This is one of the largest reviews of sCJD and provides an update to previously published series [34, 80]. It provides the first comparative review of late referrals and provides a further understanding of the clinical features, including their timing in older patients.

Factors associated with later / missed referral were older age and male sex. In general clinical features were less likely to be documented, in particular the absence of cerebellar features was significantly associated with later and missed referrals. Features associated with end stage sCJD however were more likely. The MM1 subtype, a negative cerebral MRI but positive CSF 14-3-3 and RT-QuIC were also associated with later / missed referral.

Findings in older patients were largely consistent with a general paucity of clinical features demonstrated other than those associated with the later stages of sCJD. The MM1 subtype, a negative cerebral MRI but positive CSF RT-QuIC were also similarly associated with older age.

The limitations described in chapter 2 also apply here with spousal survival, and possible later referral for investigation in older patients due to initial symptoms potentially attributed to age or another neurodegenerative condition, relatively more common in these older ages. Again, it would be unusual for older patients with dementia to reach post-mortem, with, similar to vCJD, correspondence suggesting that post-mortem was only undertaken in some missed referrals because CJD was a consideration. Confirmatory bias

is therefore likely a factor here. Recall bias however may be expected to be potentially lower in cases referred in life due to the shorter disease duration as compared vCJD; recall bias in missed referrals however cannot be excluded.

As older patients and those referred after death were more likely to be under the care of general physicians it may also be that documentation of clinical features would be less than if managed in a neurosciences centre. Further to this, as older patients were more likely to be bed-bound, cerebellar signs may be missed. Indeed the discrepancy between the low frequency of signs in missed referrals with a higher frequency of symptoms recalled by family members may be suggestive of differing levels of examination, documentation and review at a more advanced stage in this group. Consistency was however seen in certain features such as cerebellar with fewer older patients having positive signs, symptoms, and a later time to onset of cerebellar dysfunction if present, consistent also with the literature [75, 76].

In general missed referrals were also not investigated as thoroughly as those presenting earlier; MRI was undertaken in 14% of missed referrals compared to 51% presenting earlier (as defined by those coded by the NCJDRSU). This however was not replicated in older patients suggesting that although referral pathways differed in older patients the level of investigation did not.

With regards investigation results, for the purposes of this thesis only those with basal ganglia changes were documented as ‘positive’. MRI findings however are influenced by sCJD subtype, with some subtypes demonstrating

more extensive cortical ribboning (that is cortical high signal on DWI and FLAIR sequences) than basal ganglia changes, such changes would be missed here.

Further to this, data collection did not include the type of MRI sequences performed, and it was therefore not possible to determine whether DWI sequences (i.e. the most sensitive sequences for changes of CJD) had been undertaken in those with negative scans. Further work (Dr Graeme Mackenzie, NCJDRSU research registrar, personal communication [04/12/18]) has since demonstrated that in those with possible, probable or definite sCJD, 9% (of 463 MRIs reviewed) had negative scans; of this number, 21 (65%) did not have DWI sequences performed. Similar to vCJD, it is therefore likely that completeness of MRI sequences performed / available to the NCJDRSU is a confounding factor; it is now known, however, whether this is influenced by age.

In general clinical features present during the course of illness in older patients were consistent with the literature. Similar to Karch *et al* [75], those ≥ 80 years old were more likely to have documented pyramidal and extrapyramidal features and less likely to have cerebellar signs or symptoms. Interestingly, those ≥80 years old were more likely to have seizures; a feature demonstrated to be more common in non-prion pathologies [64].

The excess of cases of MM1 subtype in older groups (as compared to younger groups) is to be expected given the known older age of onset of this

subtype (see Table 15). An excess of cases of MM1 was also seen in later and missed referrals (as compared to earlier referrals). As sCJD subtype influences clinical and investigation findings a post-hoc analysis defining subtype as the outcome measure was undertaken to determine if there were factors beyond this later age of onset that may be relevant to later and missed referrals (Appendix C).

Whilst MM1 were more likely to present with an atypical presentation of visual or behavioural disturbance than other subtypes, no statistically significant factors were noted otherwise - the majority still presented with rapid cognitive decline with no difference in features seen throughout illness. There was no association between subtype and MRI findings, which is at odds with previous observations [86]. This may however be a reflection of data collection methods as previously discussed. Association was demonstrated with CSF findings, in keeping with previous observations [93].

CSF was more likely to be positive in later and older cases with both 14-3-3 and RT-QuIC demonstrating a more favourable sensitivity in older patients. The association between older age and RT-QuIC is contrary to previous studies where no association has been demonstrated. Association has however been demonstrated with disease duration, and those with a more rapid course (here, older patients) were more likely to have a positive result [93].

MRI was less likely to be positive in older cases, this is in keeping with findings by Karch *et al* (2014) who demonstrated that both cortical and basal ganglia changes were less commonly seen in patients with sCJD aged ≥75 years. Isolated cortical changes were however more frequently seen in such older patients, which, contrary to previous reviews, was independent of sCJD subtype (although numbers were limited). Here, MRI findings were associated with age but not with sCJD subtype providing some support to Karch's findings. Further review incorporating cortical changes would be helpful to further clarify this association.

EEG, although undertaken regularly unfortunately was missing in the majority of cases from the NCJDRSU database with resultant small numbers and associations difficult to conclude. Despite this, the results are worth comment; in those ≥80 years old, EEG was more likely to demonstrate typical changes of sCJD. This finding however may be a reflection of the less specific nature of EEG, with similar findings seen in other dementias common in this older group. Further to this, as older patients were reviewed later in their illness they would be more likely to have developed the typical EEG changes of sCJD (which are known to be a relatively late finding). The potential confounding effect of EEG timing has not been reviewed due to small numbers.

Similar to chapter 2, it is important not only to look for differences in later and older cases but also to consider whether cases were recognisable as sCJD:

1) Fulfilment of diagnostic criteria

Missed referrals were less likely to fulfil diagnostic criteria. Older patients were however more likely to fulfil the internationally agreed diagnostic criteria for sCJD, predominantly due to an excess of late features (i.e. akinetic mutism, and to a lesser extent, myoclonus). This suggests that whilst patients eventually fulfilled the diagnostic criteria they are less helpful in the early stages of illness in older and missed referrals.

2) Consideration of CJD in life

In the vast majority of cases CJD was considered in life. When documented, sCJD was the considered form in all. Due to lack of detail in medical notes it is difficult to be certain of the reasons cases were not referred to the NCJDRSU prior to death. Some notes commented on mis-interpretation of MRI changes (e.g. restricted diffusion not initially recognised), lack of supportive investigations, or the patient dying prior to receipt of investigation results.

As per chapter 2, it is important to have diagnostic criteria that separate CJD subtypes due to the differing public health implications. Although different forms of CJD were not confused here, during analysis of older patients it was demonstrated that there was an excess of younger patients presenting with psychiatric and behavioural disturbance, and in those <65 years old an excess presenting with sensory features (Table 24). A post-hoc analysis of younger cases of sCJD was undertaken to determine whether the merging of phenotypes in older vCJD cases and sCJD described in chapter 2 was also seen here in younger ages (Appendix D).

As demonstrated in Appendix D, sensory disturbance was still more likely in vCJD compared to sCJD however there was no difference in psychiatric features seen between groups. An association of younger age with psychiatric features has been previously noted [94]. Such presenting features are reminiscent of vCJD, which, as per chapters 1 and 2 is a disease of younger patients. This further raises the possibility that the phenotype of different forms of CJD is, in part, a product of the differing age of onset of cases.

3.6 Conclusions

The aim of this study was to review risk factors associated with later referral. Findings are similar to vCJD and although the majority of cases can be recognised as sCJD, atypical clinical and referral characteristics were seen and again older age was a significant factor associated.

Further to the associations described in chapter 2, evidence is provided here for older age as a risk factor for later diagnosis of sCJD and therefore possible case under-ascertainment in older patients.

CHAPTER 4: 'THE +65 STUDY' – A PROSPECTIVE STUDY OF ENHANCED SURVEILLANCE OF OLDER ADULTS WITH CJD

4.1 Introduction

Chapter 1 discussed the possibility that cases of CJD are missed and that age may be a risk factor for this. Chapters 2 and 3 have demonstrated that cases of CJD diagnosed later in the disease process / after death are older. Differences were demonstrated in the clinical and referral characteristics of older patients although the majority eventually looked like CJD.

It is important for public health protection to ensure comprehensive CJD surveillance systems exist. It follows from previous chapters that in order to look for 'missed' cases (that is, those not registered by the current surveillance systems), the older population is the most suitable group to consider.

Whilst chapters 2 and 3 have provided insight into why age may influence timing of referral, conclusions are limited by selection bias. Unanswered questions still remain as to why and to what extent, older patients are missed. Possibilities include: 1) Cases are present and recognisable as CJD but they are not labelled as such, possibly in part due to a lack of differentiation of different sub-types of dementia within elderly services, 2) Cases of CJD in the elderly differ from younger cases and present with clinical features more in keeping with common forms of dementia (for example Alzheimer's dementia),

or 3) Cases of CJD in the older population are very different and do not present like a dementia (that is unlike CJD or common forms of dementia).

In order to address this and look for missed cases (that is, otherwise unrecognised CJD) there are different approaches dependent on the mechanism by which cases are missed:

1) Cases of CJD are recognisable as CJD but not labelled as such

A means of addressing this is to ask clinicians to refer all older patients with dementia but features which would be atypical for the more common forms of dementia to a project of 'enhanced surveillance'. As will be further expanded on below, this was the clinical approach adopted here and the subject of this chapter.

2) Cases of CJD in older patients present like common forms of dementia

This is difficult to investigate with clinical surveillance due to the volume of cases required to be screened and followed up. The only feasible approach to this would be to screen for evidence of prionopathy amongst banked brain donations representing the more common forms of dementia.

A separate study was established in 2015 screening all brain material received at the Edinburgh Brain Bank with referrals received via Alzheimer Scotland, the Scottish Motor Neuron Disease Register, the Lothian Intracerebral Haemorrhage Pathology, Imaging and Neurological outcome

study and the Fiscal Sudden Death Register. The details of this study are outwith this thesis and therefore will not be further considered here.

3) Cases of CJD in the older population are very different and do not present like a dementia

This is impossible to address in a systematic manner. It is unlikely this is the case and therefore efforts have been focused on the above 2 interventions.

This chapter will provide an overview of the development of a protocol for enhanced surveillance of CJD in older patients ('The +65 study'). Details of the first patients referred to the study will also be presented. Finally the chapter will conclude with a review of feasibility issues arising during this initial phase.

4.2 Background

4.21 Case definition

As above, three possibilities for the case definition were reviewed: patients were typical of CJD but not labelled as such; patients were typical for other common forms of dementia; or patients were atypical for CJD and common forms of dementia. For the reasons stated above, the basis of the case definition for this study was patients who could be identified as CJD (that is, patients with dementia but with features considered atypical for the more common forms of dementia), with a separate neuropathology study to investigate patients with dementia who may not be recognised as CJD.

Chapters 1 – 3 were used to inform the case definition (see Box 5). Four specific parameters were included: older age, cognitive decline, neurological features, and speed of progression.

1) Older age

Older age was defined as ≥65 years old. As per chapters 2 and 3, 65 years classically separates unusual young onset dementias from the more common late onset dementias. It is also the age above which patients with dementia are generally seen by non-neurology services; such services are easily identified and, as highlighted from retrospective review, were more likely to be involved in later referrals.

2) Cognitive decline

Literature review demonstrated that, where clinical details were available, all patients who were diagnosed later had cognitive decline [59]. This was also demonstrated in chapters 2 and 3 with cognitive decline described in all later and older cases, and indeed dementia as a presenting feature was seen in excess in both groups. The presence of cognitive decline (and specifically a diagnosis of dementia) was therefore a pre-requisite for study inclusion.

3) Neurological features

Literature review highlighted that although older patients with sCJD were less likely to have focal neurological features the majority did still exhibit signs and symptoms that would be unusual in the more common forms of dementia [75,

76]. No comparative studies were available for vCJD, however a description of cases detailed that focal neurological features were seen [23].

Retrospective review of the NCJDRSU databases demonstrated similar findings. Although features associated with both forms of CJD (e.g. cerebellar dysfunction) were less likely, in the majority focal neurological features were seen.

It therefore followed that any focal neurological features (the presence of which would be considered less typical for the common forms of dementia) were included.

4) Speed of progression

CJD is a rapidly progressive condition. Those who were older or referred later / missed had a shorter duration of illness. A history of rapid progression was therefore included in the case definition. After discussion with the +65 management group (a group of key stakeholders in neuropathology, clinical neurology, old age psychiatry, medicine for the elderly, and neuroradiology), a slowly progressive illness (beyond what would normally be expected for the common forms of dementia) was also included in order to capture the slowly progressive inherited prion diseases.

As can be seen in Box 5, the inclusion criteria were kept relatively open. Such an all-inclusive approach was adopted: 1) as per section 4.1, selection bias of referrals to the NCJDRSU limits the understanding of the possible full clinical

spectrum of CJD in the older population. It is impossible to exclude the possibility that older patients with CJD may have a more atypical presentation than that seen to date in the NCJDRSU; 2) for ease of referral at the start of the study (the case definition was expected to become more focused after patient recruitment / feedback from clinicians).

In order to be eligible for the study, patients were required to fulfil the inclusion criteria. An information sheet detailing these criteria was designed, listing the salient clinical features of the more common forms of dementia to aid identification of cases (Appendix E).

Box 5: The +65 study - case definition

Inclusion criteria

Aged 65 years or older *and*

Have a new or established diagnosis of dementia *and*

Have features considered to be atypical for the recognised forms of dementia (features considered to be atypical include a time course which is either rapid (over weeks to months) or slow (over a period greater than 10 years), or focal neurological signs) *and*

Have accessed secondary or tertiary care services for dementia (inclusive of medicine for the elderly (MFE), old age psychiatry (OAP), and neurology), or tertiary referral memory services, within Lothian (residents outwith Lothian will be eligible for the study, however will be excluded from statistical analyses).

Exclusion criteria

A non-progressive disorder *or*

A very clear alternative explanation for their cognitive decline (inclusive of head injury, a clear / stable psychiatric disorder, demonstrable vascular insult which was temporally related to the cognitive deficit, significant and on-going alcohol / drug use as a cause, space occupying lesion, neuro-inflammatory or neuro-infectious conditions) *or*

A positive genetic result (including prion), which again could explain the features.

4.22 Size of population

Lothian health board was selected as a discrete and local area serving a population of approximately 800 000 from which patients could be recruited. The health board local to this study was also chosen for practical reasons

(such as travel distance, and familiarity of target clinicians to the study team and vice versa) [95].

Having identified the target population, estimates of potentially eligible patients were required for study planning purposes:

1) Establishing a denominator

There are two sources of data from which to calculate a denominator of eligible patients in Lothian: i) Alzheimer Scotland data (using EuroCoDe data projected onto 2016 estimates from the 2012 census [96]) or ii) general practice quality and outcomes framework (QOF) registers for dementia (and other QOF compatible registers for dementia) [97].

a) Prevalence

Using Alzheimer Scotland data, the prevalence of dementia in patients aged ≥65 years in Scotland in 2016 is estimated to be 87,510. Lothian NHS health board covers approximately 16% of people residing in Scotland [98], and therefore c.14,000 patients with dementia would be expected in Lothian. Only 50% of such patients are likely to be registered with dementia (and therefore eligible for this study) [2]; indeed using GP registers, the number of patients aged ≥65 years registered with a diagnosis of dementia in Lothian was c.7000. The figure from GP registers was therefore used as the most realistic denominator.

b) Incidence

Using actual numbers of new diagnoses of dementia from health boards within Scotland and projected population demographics, in 2015, an estimated 2400 patients aged ≥65 years old in Lothian were diagnosed with dementia [99].

2) Establishing predicted numbers

The literature base regarding patients with dementia with less typical features, i.e. the group from which eligible patients for this study would most likely be referred, is limited. Surrogate estimates include those with 'dementia due to unknown aetiology' (i.e. those with atypical features precluding a diagnosis of a specific dementia type in life). Studies are small and include poorly phenotyped patients, however overall approximately 25% of patients would be expected to present with atypical features, with this number rising with age [100].

Other studies have reviewed patients presenting with specific atypical features. These include a) rapidity of onset: Staekenborg *et al* (2015) found that 8.6% (of 4,500 patients with Alzheimer's dementia (AD) referred to the Amsterdam Dementia Cohort) died within 2 years of 1st reported symptom [69], or b) focal motor features: Scarmeas *et al* (2005) found that 14% (of 533 patients with AD) had motor features at onset, with 45% developing abnormal signs during their illness [73].

Using the above literature base and local expert opinion, we estimated 10% of patients seen in secondary and tertiary care would fulfil our criteria. This

would provide an incidence of 120 patients per year with a prevalence of 700 patients.

4.23 Source of recruitment

In order to be certain about full ascertainment of all eligible patients, recruiting patients from primary care would be recommended. In 2006 the NCJDRSU proposed a prospective study of enhanced surveillance of older adults. This was a feasibility study in Lothian to determine if older patients presenting to their general practitioner with cognitive decline may be missed cases of prion disease. Discussions with stakeholders in general practice in NHS Lothian highlighted that due to other time commitments and constraints recruitment from primary care would not be possible. The project was therefore closed as it was considered not feasible.

A different approach was therefore considered here. Both the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Clinical Excellence (NICE) recommend that all patients with dementia should be assessed in a memory clinic [101, 102]. Secondary / tertiary care services were therefore selected as the most feasible option. The limitation that not all patients would fulfil this standard was acknowledged, however the benefit of discrete and easily identifiable clinical pathways as described below was considered to outweigh this limitation.

Patients aged ≥65 years with dementia are generally diagnosed, admitted under and managed in the community by old age psychiatry, medicine for the

elderly (MFE), or less commonly, neurology [101, 103]. Chapters 2 and 3 demonstrated that this is the experience also of those with CJD. Indeed, there was a trend towards earlier psychiatry input in older patients with vCJD, with a similar but non-significant association in the same age group in sCJD (despite older patients being less likely to have psychiatric features documented). Further to this, older patients with sCJD were less likely to be referred from tertiary neuroscience centres and more likely to be managed by general physicians, with medicine for the elderly expected to be the main providers of care in such circumstances. Focus was therefore placed on old age psychiatry and medicine for the elderly in addition to neurology as recruitment sources.

4.3 Methods

4.31 Study population and setting

All consultants covering memory clinics and clinical leads in each speciality were contacted to discuss how best to approach their colleagues. Meetings were then arranged to disseminate information about the study. In order to ensure high ascertainment, patients were recruited from both inpatient and outpatient settings.

1) Old age psychiatry (OAP)

Within Lothian there is one hospital with in-patient beds for OAP (Royal Edinburgh Hospital), with a further six sites of outpatient clinics (Leith Community Treatment Centre, St John's Hospital, Midlothian Community

Hospital, Herdmanflat Hospital, Royal Edinburgh Hospital, and the Memory Assessment and Treatment Service (MATS) Centre).

Meetings were arranged at individual sites with consultant and trainee OAPs and community psychiatric nursing staff. Continuing Professional Development (CPD) sessions on CJD were provided with information disseminated on the +65 project. Separate meetings were also arranged with key consultants with active involvement in research with additional attendance at regional OAP research sessions to gain OAP input into the project prior to launching and to allow promotion of the project once started.

ii) Medicine for the Elderly (MFE)

Four hospitals within Lothian have MFE consultants based on-site; Liberton Hospital, Western General Hospital, Royal Infirmary of Edinburgh and St John's Hospital. Meetings were arranged at individual sites. Similar to OAP, CPD sessions on CJD were provided along with promotional sessions on the study. Key consultants were also targeted separately.

iii) Neurology

Three hospitals within Lothian have neurologists based on site (Western General Hospital, Royal Infirmary of Edinburgh, and St John's Hospital). All consultant and trainee neurologists in Lothian attend a weekly neurosciences meeting; this platform was used to present study information and updates.

The cognitive disorders clinic at the ARRNC (tertiary referral centre for cognitive disorders) was approached separately. Weekly attendance at this clinic ensured on-going study visibility with clinicians and research managerial staff.

4.32 Patient recruitment

Clinicians and community psychiatric nurses (CPNs) were encouraged to discuss any patient they considered may be eligible. Leaflets containing study information and contact details were provided to all key consultants and recruitment sites (Appendix F). A monthly e-mail was also sent out to all consultant and trainee old age psychiatrists, medicine for the elderly physicians and neurologists reminding them of the study and contact details for referral / discussion. Email reminders were generated by a research nurse, appointed to the study.

An established research database of patients with dementia willing to participate in research was also available to the +65 study via the ARRNC. This database was regularly reviewed with study patient information leaflets and accompanying invitation to participate in the study sent out to eligible patients.

For all referrals, basic details were documented on a standardised form. Patients (or their representatives: as defined below) were then contacted, and, if the patient / representative agreed, study information was sent (Appendix F) and a study visit arranged.

4.33 Study design / approach

Assessing capacity

Before recruiting any study participant, capacity was assessed and appropriate consent obtained. Capacity was defined, using the Adults with Incapacity (Scotland) Act 2000, as the ability to understand and retain the information relevant to the decision in question and to weigh that information in the balance to arrive at a choice [104]. Capacity was assessed at the beginning of all meetings by assessing the participant's understanding of the project and their voluntary role within this. For adults who lacked capacity, consent was taken from a representative (either the patient's legal representative [welfare attorney or welfare guardian] or, if none, their nearest relative) in accordance with the Adults with Incapacity (Scotland) Act 2000.

If the participant lost capacity to consent during the study, their wishes whilst able to consent were respected in line with Scottish law.

Ethics approval

Ethics approval was granted by the local Scotland A Research and Ethics Committee on 19th January 2016.

Clinical / epidemiology assessments

The following assessment tools were developed:

1) Clinical review

a) History

A detailed history of the dementia syndrome was taken. Specific illness details were taken for all in order to complete a symptom questionnaire encompassing disturbances of mood, cognitive domains, focal neurological disturbance and psychiatric features. Other details including initial prominent symptoms and evolution of symptoms were taken in order to phenotype the patient in as much detail as possible.

b) Cognitive examination

Formal neuropsychology is the gold standard in cognitive assessment. It is however time-consuming and arduous for patients to undertake and therefore a shorter screening test was sought. Multiple screening tests exist ranging from very brief tests (e.g. abbreviated mental test), brief tests (e.g. mini mental state examination and Montreal Cognitive Assessment), longer assessments which can still be undertaken in clinical practice (e.g. Addenbrooke's cognitive examination-III), and longer / detailed assessments primarily reserved for research studies (e.g. clinical dementia rating scale).

It was expected that participants may be at a more advanced stage of their dementia and as other assessments were to be undertaken it was considered that longer research orientated assessments would not be feasible. The mini mental state examination (MMSE), Montreal Cognitive Assessment (MoCA), and Addenbrooke's cognitive examination-III (ACE-III) were considered to be the most appropriate; they are of an acceptable length for patients and are

commonly used end points in dementia research studies. A summary of these tests is provided in Table 26.

Table 26: An overview of cognitive tests considered

Test	Overview	Pros	Cons	Refs
MMSE	Scored out of 30 (lower scores indicating greater impairment). Rapid assessment of orientation, registration, attention, recall, language and constructional praxis	<10 minutes to administer. No special equipment required. Commonly reported in studies. High sensitivity for detecting dementia in general population. High test-retest reliability (range 0.79-0.99)	Over-reliance on verbal assessment of attention / memory. Poor assessment of frontal / visuospatial function Poor specificity. Performs poorly in longitudinal studies	54, 55, 32 [105]
MOCA	Scored out of 30 (lower scores indicating greater impairment). Rapid assessment of orientation, registration, attention, recall, language and constructional praxis. Additional tests of executive function	10-12 minutes to administer. Superior sensitivity compared to MMSE particularly early in disease course.	Less commonly encountered in research trials. Lower specificity compared to MMSE.	[106]
ACE-III	Scored out of 100 (lower scores indicating greater impairment). Quick assessment of orientation, attention, recall, language, executive and visuospatial function.	No special equipment required. Well tolerated. High sensitivity (94%) to a favourable specificity (89%) (on well characterised patients). Addresses executive and visuospatial short falls of MMSE.	Up to 30 minutes to administer.	56, 57, [105, 106]

Overall, the ACE-III was considered to be the most appropriate assessment; it is validated, short enough to be acceptable to patients whilst detailed enough to provide a level of phenotyping, and was a familiar tool to the research team.

Although the ACE-III incorporates tests of executive function it still lacks comprehensive assessment of frontal lobe functions. Such assessment was desired to ensure patients had global cognitive testing and were phenotyped in detail; the frontal assessment battery (FAB) was therefore added to the protocol. The FAB is the most commonly cited assessment of frontal lobe functions. It is quick and easy to administer. It is scored out of 18 (with lower scores reflecting increasing impairment), and includes assessment of mental flexibility and inhibitory control [107].

c) Neurological examination

The neurological examination consisted of the Edinburgh Motor Assessment Scale (EMAS).

It has become increasingly recognised that there are motor manifestations of the dementias, however, no standardised generic (i.e. non disease specific) scales exist for documenting motor scores in dementia. The EMAS was devised for this role in research. It is scored out of 99, with a higher score representing a greater level of impairment. The validity of the EMAS is currently under assessment but thus far has been demonstrated to be a quick

and easy test to administer with high inter-tester reliability (personal communication from Dr T Bak), and good test-retest reliability [108].

d) Mood assessment

Due to the association between mood and cognition and the presence of mood disturbance in (particularly variant) CJD, an assessment of mood was incorporated. The hospital anxiety and depression scale (HADS) [109] was selected due to its established validity in secondary care [110], with established validity in older patients [111, 112]. The HADS is a 14-item questionnaire scored out of 42, with higher scores representing more significant mood disturbance.

e) Functional assessment

In order to provide an overall assessment of impact of illness a functional assessment was incorporated. The Barthel Index (BI) is a 10-item questionnaire scored out of 20, with higher scores indicating lower disability [113]. Although the BI was originally devised to assess disability post-stroke, it has been widely adopted as a generic scale of functional ability.

2) Ancillary investigations

a) Codon-129 sampling

All patients were asked to donate a 2ml blood sample for codon-129 polymorphism typing. As discussed in previous chapters, allele expression at codon-129 has a modulating effect on population risk and phenotype of CJD. Due to this effect it is important to ensure codon-129 polymorphism was not a

significant factor in referrals of positive cases, particularly in vCJD where experience of the phenotype of cases beyond methionine homozygotes is very limited.

b) Cerebral MRI scan

As previously detailed, cerebral MRI is a highly sensitive investigation in CJD, and in particular in vCJD. If a cerebral MRI scan had not been performed during the patient's illness then a research MRI scan was organised. Imaging protocol included sequences with the highest sensitivity for CJD (i.e. axial diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR)) in addition to standard T1 and T2 sequences. All images were reviewed by the NCJDRSU consultant neuroradiologist. A full MRI report was made available for the referring clinician on the standard Lothian radiology reporting service.

If an MRI had been undertaken, a repeat was not organised unless there had been a ≥6 month period since the previous MRI or there had been significant decline since previous imaging.

c) Neuropathology

In the event of a study participant's death a limited, head only post-mortem was organised. The details of this procedure are beyond the scope of this thesis.

Excluded investigations

CSF and EEG were discussed and excluded from the protocol. CSF, which as demonstrated in chapter 3 is particularly sensitive to the changes of sCJD in older patients, was discussed on a number of occasions within the management group and with referring clinicians in old age psychiatry and neurology. The decision not to pursue CSF testing at this stage in the study was agreed due to the invasive nature of the investigation which may limit referral and an inability to ensure on-going availability of a neurologist / facilities to undertake the procedure consistently and safely.

EEG has been demonstrated to have a lower clinical utility in sCJD compared to other biomarkers and with no EEG marker of vCJD, EEG was not pursued.

3) Epidemiology questionnaire

An epidemiological questionnaire was designed to help generate hypotheses as to risk factors for disease, and, in the event of a positive case, to help identify the most likely route of infection and to inform any related public health actions. The questionnaire was based on the current iteration of the NCJDRSU questionnaire; additional questions on known risk factors for neurodegenerative conditions were included (e.g. vascular risk factors) and other questions removed to reflect an evolving understanding of the risk factors for CJD (e.g. details about dentist, occupation (beyond high risk jobs), and place of historic residence).

4.34 Analysis approach

1) Study design / subjects / setting

This was a feasibility study to assess enhanced surveillance approaches to ascertaining 'missed' cases of CJD.

All patients referred to the study between 1st April 2016 and 31st September 2016 (when data gathering undertaken for this thesis ended) were included (n = 62). All patients who were eligible for inclusion with assessments completed during this time period (n = 10) were included in this analysis.

Methods are as described in the previous section with all patients undertaking an epidemiology / clinical questionnaire and clinical assessments (ACE-III, FAB, HADS, BI, and EMAS). Blood was taken for codon-129 polymorphisms, MRI was discussed and arranged as appropriate, and post-mortem provisional consent obtained (with consent for authorisation organised at time of post-mortem).

Telephone contact was then scheduled at 3 monthly intervals thereafter to assess patient progression.

In patients whose illness was consistent, or became consistent, with CJD (for example ataxia / involuntary movements and/or a more rapid course or acute terminal deterioration) a further visit was arranged for repeat clinical assessment and MRI. If there was sufficient suspicion of CJD, then the

treating clinician was informed with recommendation to refer the patient to the NCJDRSU / National Prion Clinic for assessment.

Follow up continued for the duration of the patient's illness (either until improvement or death) with post-mortem confirmation of diagnosis.

All details collected were entered manually onto a secure electronic database. Correspondence files were also retained in paper format and filed securely.

2) Data processing

A) Data collection

As above, all data was manually entered onto the study database and extracted for the purposes of this initial review.

B) Basic variables

Basic demographic variables included sex and age at time of onset of illness.

C) Referral characteristics

The following referral characteristics were documented:

a) Source of referral. Neurology, old age psychiatry, medicine for the elderly, ARRNC cognitive disorders clinic, and other.

b) Reason for referral. Thematic grouping was undertaken with the following groups emerging during data analysis: i) the presence of focal neurology; ii) the patient did not fulfil diagnostic criteria for recognised forms of dementia; iii)

the patient had an unusual rate of progression; and iv) the presence of psychiatric features.

c) Time to review by neurology / psychiatry were calculated from onset of first symptom

D) Clinical features

The following clinical features were extracted:

a) Presenting features. Presenting symptoms were grouped into similar as chapters 2 and 3, with patients presenting with one of: i) behaviour / personality change (consisting of any change which was not attributable to mood change); ii) sensory disturbance (consisting of pain or any other sensory modality); iii) mood disturbance or psychiatric features (consisting of delusions, anxiety, and depression); iv) cognitive impairment (any change in cognition); and v) unsteadiness (consisting of gait change or incoordination).

b) Signs and symptoms occurring during the course of a patient's illness. The presence of specific signs and symptoms were extracted. Clinical features were grouped into the following themes to improve statistical analysis: i) mood (anxiety and depression); ii) language (receptive and expressive); iii) behaviour (lack of empathy, disinhibited, aggressive); iv) hallucinations (visual and auditory); v) dystonia (inclusive of alien limb); and vi) visual symptoms (impairment and diplopia).

c) Duration of illness was calculated from first symptom to time of death.

d) Working diagnosis (as provided by the referring clinician).

e) Examination findings (ACE-III, FAB, Barthel index, HADS, and EMAS)

E) Investigation results

The following investigation results were documented:

a) Cerebral MRI. MRI was documented as either positive (restricted diffusion of the medio-dorsal thalamus, basal ganglia or cerebral cortex) or negative (all other changes including normal)

b) Codon-129 polymorphism

c) Neuropathology: Histopathological diagnosis of the underlying dementia pathology and whether there was any evidence of prionopathy were documented.

F) Missing data

Where data were not available entries were classified as 'missing' and therefore not included in statistical analysis.

3) Analysis approach

An overview of basic demographic, referral characteristics, and working clinical diagnosis are as described for all patients referred to the study (n = 62). Results are detailed for all patients eligible for inclusion in the study (n =

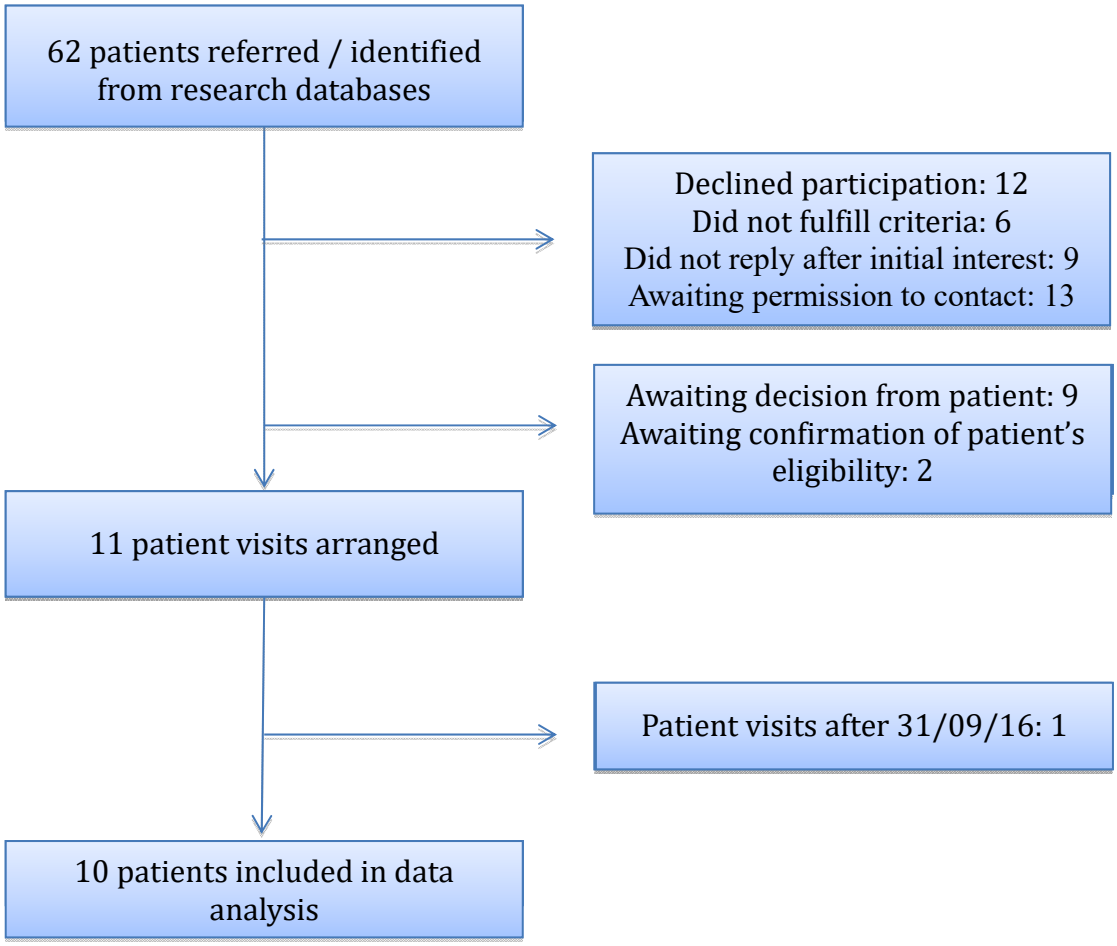
10). Due to the non-parametric spread of data, times are stated in median months / years with interquartile ranges (IQR) provided.

4.4 Results

4.41 All referrals (n = 62)

62 patients were referred or identified from research databases as eligible for inclusion in the study. 11 patients agreed to participate, 10 of whom had completed review by 31st September 2016. Reasons for exclusion are as stated in Figure 6. The age and sex of patients included did not differ significantly from those excluded (Table 27).

Figure 6: Flow diagram of patient numbers



The majority of patients were referred from the cognitive disorders clinic at the ARRNC (CDC). The reason for referral to the study in most was failure to fulfil diagnostic criteria for recognised forms of dementia. Where information was available, all included patients had been reviewed by both neurology and psychiatry with a median time from symptom onset to review of 3 years and 2.5 years respectively (Table 28).

Table 27: The +65 study - patient characteristics (all referrals, n = 62)

Patient characteristics	Referred to study (n = 62)	Included in study (n = 10)	p-value
Age at time of referral (median years + IQR)	71 (67 – 77)	69 (66 – 75)	0.82
Male: n of N documented (%)	43 (69%)	7 (70%)	1
Age at symptom onset (median years + IQR)	u/k	62 (57 – 69)	n/a
Duration of illness (median years + IQR)	u/k	7 (3.5 – 10.5)	n/a
Median time to referral (years)	u/k	1 (0 – 2)	n/a

Table 28: The +65 study - referral characteristics (all referrals, n = 62)

Referral characteristic	Referred to study (n = 62)	Included in study (n = 10)	p-value
Referral source: CDC OAP MFE Neurology	 35 (57%) 16 (29%) 7 (11%) 4 (6%)	 9 (90%) 1 (10%) 0 (0%) 0 (0%)	0.2
Reason for referral: Did not fulfil diagnostic criteria Focal neurology Unusual rate of progression Psychiatric features Other	 21 (35%) 18 (29%) 8 (13%) 4 (7%) 2 (3%)	 6 (60%) 3 (30%) 1 (10%) 0 (0%) 0 (0%)	0.8
Reviewed by neurology (n of N documented)	u/k	8/8	n/a
Time to review by neurology	u/k	3 (3 – 7)	n/a
Reviewed by psychiatry (n of N documented)	u/k	8/8	n/a
Time to review by psychiatry	u/k	2.5 (2 – 7)	n/a

CDC = Cognitive Disorders Clinic, Anne Rowling Regenerative Neurology Centre; OAP = Old age psychiatry; MFE = medicine for the elderly; u/k = unknown; n/a = not applicable

The majority of patients presented with cognitive decline (Table 29). Alzheimer's dementia was the most frequent clinical diagnosis for patients both referred and those included in the study (Table 30), with an excess of patients with less common forms of dementia (as compared to Figure 2) seen also. There was no statistical difference between clinical diagnoses in the 10 patients included in the study and all patients referred (p = 0.71).

Table 29: The +65 study - patient characteristics (patients included in study, n = 10)

Presenting symptom / sign	n (of N = 10)	%
Cognitive impairment	7	70
Behaviour change	1	10
Unsteadiness	1	10
Missing	1	10
Sensory change	0	0
Mood disturbance	0	0

Table 30: The +65 study - clinical diagnoses (all referrals, n = 62)

Diagnosis	**Patients referred**		**Eligible Patients**	
	n (N = 62)	**%**	**n (N = 10)**	**%**
Alzheimer's dementia	14	22.6	5	50
Neurodegenerative condition not otherwise specified (NOS)	7	11.3	1	10
'Parkinson's plus'	5	8.1	1	10
Posterior cortical atrophy	4	6.5	2	20
Frontotemporal dementia	3	4.8	1	10
Frontotemporal dementia + Parkison's disease	3	4.8	0	0
No syndromic diagnosis	3	4.8	0	0
Primary progressive aphasia	2	3.2	0	0
No dementia	2	3.2	0	0
Vascular dementia	1	1.6	0	0
Mixed (AD + VaD)	1	1.6	0	0
Missing	17	27.4	0	0

4.42 Study patients (n = 10)

Table 31 details the clinical features of patients seen. As a group, all patients had language difficulties, with the majority also experiencing mood and behaviour change. Almost all experienced both executive dysfunction and visuospatial difficulties. Almost half experienced sensory symptoms.

Table 31: The +65 study - clinical features (patients included in study, n = 10)

Patient	**n of N**	**%**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Working diagnosis			AD	PCA	FTD	PCA	NOS	PD+	AD	AD	AD	AD
Forgetful / repetitive	9/9	100	Y	Y	Y	Y		Y	Y	Y	Y	Y
Visuospatial / apraxia	8/9	89	Y	Y		Y	Y	Y	Y	Y	N	Y
Executive dysfunction	9/9	100	Y	Y	Y	Y	Y		Y	Y	Y	Y
Language	10/10	100	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mood	8/10	80	Y	Y	N	Y	Y	Y	Y	Y	N	Y
Delusions	1/6	17			N	N		N	Y	N	N	N
Behaviour	7/10	70	Y	N	Y	Y	Y	Y	Y	N	N	Y
Apathy	4/7	57			Y	N	Y	N	N		Y	Y
Hallucinations	2/9	22	Y	N	N	Y	N	N		N	N	N
Gait	3/9	33	Y	Y	Y	N	N		N	N	N	N
Speech change	3/6	50		N	Y	N				N	Y	Y
Visual symptoms	2/10	20	Y	N	N	Y	N	N	N	N	N	N
Tremor	5/8	63	Y	Y	Y		Y		N	Y	N	N
Myoclonus	4/9	44	Y	Y	N	Y	N		Y	N	N	N
Dystonia	2/7	29		N	N		N	Y	Y		N	N
Clumsiness	3/3	100	Y		Y	Y						

Slowness of movement	6/8	75		Y	Y	N	Y		Y	Y	N	Y
Sensory symptoms	4/9	44	N		Y	Y	N	N	Y	N	N	Y
Seizures	2/9	22	Y	N	N	N	N	N		N	Y	N
Akinetic mute	1/10	10	N	N	N	N	N	N	Y	N	N	N
Clinical examination												
ACE-III (/100)			0	5	71	71	11	29	0	45	39	87
FAB (/18)			0	1	13	13	3	Unable	Unable	7	7	17
BI (/20)			4	6	18	19	12	2	0	20	19	16
HADS (/42)			Unable	Unable	6	10	Unable	31	Unable	14	9	11
EMAS (/99)			86	60	15	19	22	77	69	17	15	2
Study MRI undertaken?			N	N	Y	N	Y	N	N	N	Y	Y

Clinical assessments demonstrated that the majority of the group had advanced dementia with a general association seen between the severity of cognitive decline and load of physical signs on EMAS. Additional motor features were common and seen in almost all patients.

Of those undergoing cerebral MRI, no features of prion disease were detected (Figure 7). The majority demonstrated generalised atrophy with areas of focal predominance in keeping with a dementia process. One MRI demonstrated small vessel disease with no specific radiological markers of neurodegeneration (of note, although incidental findings were fed back to the referring clinician, as this is not an uncommon finding in patients with dementia no action was taken).

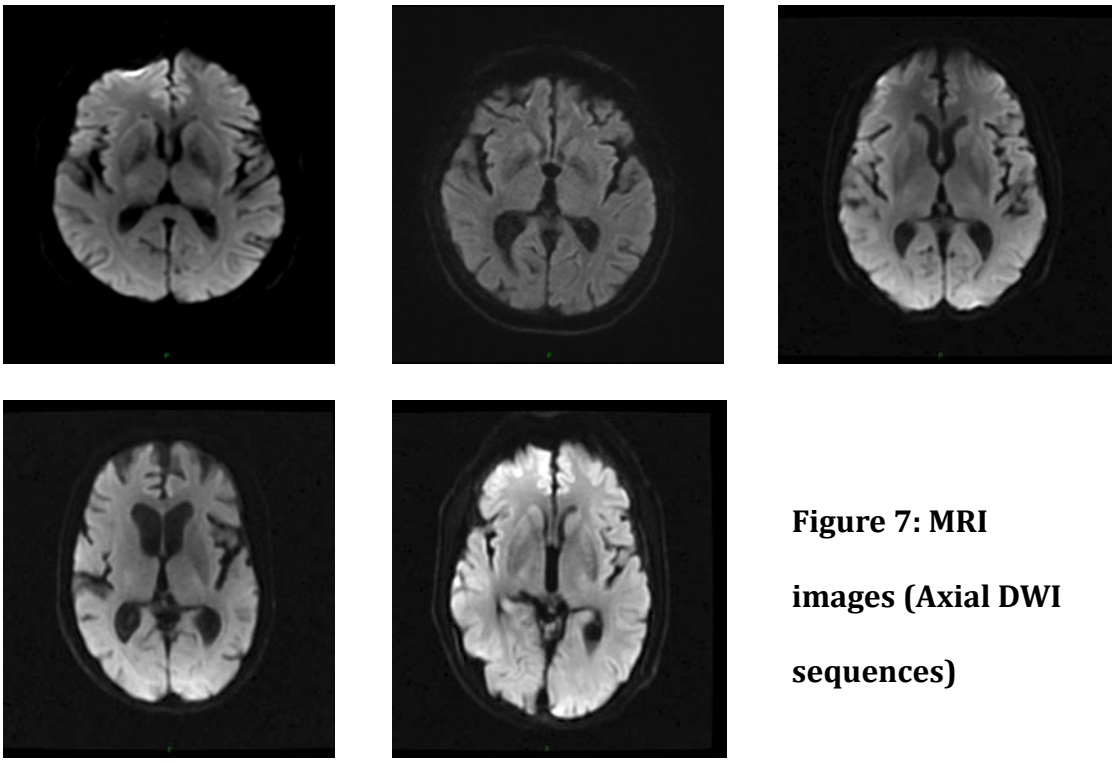


Figure 7: MRI images (Axial DWI sequences)

No patients completed neuropathology assessment during the study period.

4.5 Discussion

The initial results demonstrate that clinical and referral characteristics were heterogenous and whilst patients did have features seen in CJD, overall no patients had a clinical syndrome suggestive of CJD. Critically however no patients died and had a post-mortem performed during this initial study period and therefore confirmation of diagnosis is awaited in all.

There are limitations to address. Due to small numbers of patients included it is not possible to draw robust conclusions about the phenotype or referral patterns of older patients with dementia and atypical features. Four of the ten participants were very impaired and had difficulty undertaking assessments further limiting characterisation. It is also possible that patients are being seen by other specialities not included in this study (e.g. acute medicine / palliative care). However it would be hoped that such patients would still come to the attention of OAP / MFE / neurology if such a relentless neurological presentation were encountered. Lastly whilst efforts have been made to reduce the confirmatory bias common to retrospective studies our case definition is based on knowledge from previous missed cases, thereby introducing an element of bias. The inclusion criterion has however been kept broad and with the additional pathology arm of recruitment it would hope that bias would be limited.

There are no other identified studies of enhanced surveillance to compare the findings to. Of patients referred to the study there was an excess of patients with less common forms of dementia (as compared to Figure 2). This would

be expected, as it is in this group that diagnostic uncertainty would be expected to be greatest. The cognitive profile of patients (with both executive dysfunction and visuospatial difficulties) were consistent with the reasons for referral, with most patients referred to the study due to a mixed cognitive phenotype with features of an anterior and posterior dementia present. It is noteworthy that 5/10 patients seen experienced sensory disturbance; it is uncommon for patients with other (that is, non-vCJD) forms of dementia to experience sensory symptoms; <10% of patients with a diagnosis of a non-CJD dementia who were referred to the NCJDRSU with suspected vCJD described sensory disturbance [80]. Further profiling of the nature of the sensory symptoms would be helpful to review features that distinguish between CJD and other forms of dementia. Additional motor features were seen in almost all patients, this is consistent with previous studies with motor features reported in up to 75% of patients with dementia (Table 3).

4.52 Feasibility issues

One of the most important considerations at this juncture in the study is whether this is a feasible means of enhanced surveillance. It is therefore necessary to review feasibility issues that arose and consider how they might be overcome prior to expanding the study to areas outwith Lothian.

In order to systematically review the difficulties and potential solutions to these issues they have been grouped as ‘patient factors’, ‘clinician factors’ and ‘other’, as described below and as summarised in Table 32.

Table 32: A summary of feasibility issues and solutions

Patient factors	**Problem**	**Solution**
Advanced stage of illness	Unable to complete assessments	Substitute ACE-III for S-SIB, and HADS for informant mood screening questions
Referral bias	Older / more frail patients less likely to be referred	Reassurance to clinicians / participants. New assessments less arduous. Telephone contact of non-responders to reassure.
Other	Lack of awareness of study	Promotional events Involvement of patient groups in protocol development to try to reach as many as possible
Clinician factors		
Case definition	Difficulty applying case definition	Change case definition to all patients without classical AD / DLB / VaD
Work-load	Time / clinical pressures limiting time to discuss research	Remove / reduce onus on clinicians to discuss study (presence of study team on ward / clinic + study information sheets provided)
Lack of confidence discussing research	Clinicians / CPNs felt out of their depth introducing study	CPD sessions provided. Remove / reduce onus on clinicians to discuss study as above. Regular update sessions.
Doctor-patient relationship	Concern discussing CJD may undermine diagnosis made	Reassurance of clinicians. Update sessions. MRI results fed-back
Lack of accountability for referral	Multiple agencies involved in a patient's care; not clear who should take responsibility for referral to study	Regular meetings arranged, particularly in areas of expected referrals (OAP) and sites of low referral. Regular e-mail contact to encourage referrals directly
Other factors		

Accessibility to eligible patients	Lack of research register outwith ARRNC	OAP to integrate research into clinics
Functional rating scales	Lack of specificity of functional rating scales	Barthel Index substituted for MRC Prion Rating Scale
Patient eligibility	Patients seen by memory services <65 years old included	Limited referrals to patients with 1st referral ≥65 years old

1. Patient factors

i) Clinical assessments

After initial recruitment to the study it became apparent that patients who were most readily identified as eligible for the study were at a more advanced stage of their illness. Clinical assessments included in the protocol required a level of cognitive reserve and therefore were not appropriate for all.

Three approaches to address this were considered: a) The use of a separate test in those perceived to be very impaired (with assessment of this by initial interaction with patient / highlighted from referring clinician); b) Change all assessments; or c) Attempt to undertake original assessments in all - if patients were unable to complete initial assessments, additional assessments for those with severe impairment would then be undertaken.

A review of potential solutions, as summarised below, addressed this. Due to the ceiling effect of assessments designed for advanced dementia there is no universally acceptable alternative to use for all patients, and in some other aspects of clinical assessment no appropriate alternative was found. It is therefore proposed that the original assessments should be attempted in all, if

however patients were unable to complete such assessments then an alternative, if available, would be used:

1) Cognitive assessments

A floor effect was seen with the ACE-III in 4/10 participants. Cognitive assessments in those with advanced dementia were therefore sought; these may be either informant-based or involve direct assessment of the patient (Table 33).

Table 33: Overview of cognitive assessments in more severely impaired patients

	Description	Advantages	Disadvantages	Ref
Informant based				
IQCODE	• 26-point screening tool. Compares current functioning to 10 years previously. Combination score out of 5 (1+2 indicate improvement, 3 = no change, 4+5 = deterioration) • Areas covered include learning, recall of recent and remote information and day-to-day functioning • Identifies patients requiring further assessment (not a stand-alone diagnostic tool).	• Most widely cited. • Questions are of 'everyday relevance'. • IQCODE can be administered remotely and is less invasive to the patient. • Performs as well as MMSE	• Significant heterogeneity of effectiveness and potential for investigator bias. • More useful for excluding patients without cognitive decline. • Not validated in longitudinal studies.	[114-116]
Short form IQCODE	• 16-point screening tool. • All other features as per longer version.	• Similar utility as long version. • Quicker to complete.	• Same disadvantages as standard IQCODE	
Direct assessment of the patient				
Severe	• 40-item assessment scored out of 100	• Most widely cited.	• Takes 30 minutes.	[117,

Impairment Battery (SIB)	(with lower scores indicating greater impairment). • Assesses social interaction, memory, orientation, language, attention, praxis, visuospatial, construction, and orientation to name	• Allows a degree of phenotyping • Validated in longitudinal studies. High inter-rater reliability and test-retest reliability. • Sensitive to changes in moderate to severe dementia	• Requires specialist equipment and training	118]
The Hierarchic Dementia Scale (HDS)	• 20-item assessment scored out of 200 (with lower scores indicating greater impairment). • Based on the reverse Piaget's theory	• High test-retest reliability and validity (as compared to the CDRS and MMSE)	• Rarely used. • Takes 40-50 minutes. • Requires specialist training.	[119]
Severe Mini Mental State Examination (S-MMSE)	• 10-item questionnaire, scored out of 30 (with lower scores indicating greater disability)	• Correlates significantly with the CDRS and GDS, with good inter-rater reliability. • Addresses the floor effect of the MMSE. Quick and easy to administer • Acceptable to patients with advanced dementia	• Relies on language (a highlighted area of difficulty for participants in this study). • Not validated in more advanced patients requiring institutional care	[120]
Severe Impairment Rating Scale	• 14-item test scored out of 28. • Assesses memory, motor function, language and recognition	• High inter-rater reliability and test-retest reliability • Lacks a significant floor effect.	• Over-representation of language.	[121, 122]

(SIRS)		• Quick and easy to administer with no specialist equipment required. • Validated in advanced, institutionalised patients.		
Short form of the SIB (S-SIB)	• Developed for those with an MMSE <5 who had difficulty completing the original SIB. • Covers same domains as SIB • Similar to the SIB it incorporates gestural cues to assist those with impaired language	• Modest floor effects • Acceptable to patients • Validated in long-term institutional patients • Compares well to MMSE and the original longer SIB. • Quick to administer (10 minutes)	• Ceiling effect seen in less advanced stages of dementia	[123, 124]

Solution

A direct assessment of the patient is desirable as it provides an element of cognitive phenotyping that is more comparable to assessments undertaken in less advanced patients. The SIB is a validated and reliable form of assessment based on the limited reviews available. The short-form (S-SIB) is a validated form of the SIB and, as it is of a more acceptable length to patients with advanced disease, the S-SIB is proposed if a patient was unable to progress through ACE-III.

2) Mood assessment

Patients with advanced disease had difficulty engaging with the HADS. Alternative scales, which could be employed as informant or observational assessments were therefore explored.

Solution

Few scales exist. The gold standard is the Cornell Scale for Depression in Dementia (CSDD) [125]. The CSDD takes approximately 20 minutes to administer and involves semi-structured interviews with both the patient and informant [126]. The inter-rater reliability is low, and the sensitivity / specificity again low when compared to old age psychiatry diagnosis. The same is true of other, less commonly used tests for depression in dementia (e.g. the Minimum Data Set Depression Rating Scale, and the Hayse and Lohse Non-Verbal Depression Scale [127]).

As mood was not a primary outcome measure in this study and considering the limitations of assessments, it is proposed that mood symptoms, which currently form part of the symptom questionnaire, would be used as a primary informant-based outcome measure if a patient were unable to engage meaningfully with the HADS.

ii) Other patient characteristics / factors

As will be addressed below, the referral numbers to the study were lower than expected. There are general patient factors to consider which may impact referral patterns in any study of dementia in older patients; older age, more advanced stage of condition and the presence of co-morbidities have been demonstrated to negatively influence referral [128, 129], all of which were relevant to the study population here.

Solution

Undertaking additional tests when already at an advanced stage of illness can be a daunting prospect and therefore reassurance to both the referring clinician and participants / their representative is necessary.

At time of initial contact with referring clinicians and during study update sessions, reassurance will be provided regarding the above changes to assessments, which will be more appropriate for the patients' abilities. Further on-going reassurance will also be provided regarding the variable level of involvement each patient may wish to consent to.

2. Clinician factors

ii.i) Case definition

This was arguably the greatest feasibility issue in this study. A number of iterations of the case definition were proposed and developed with the +65 management group but despite this it was raised most consistently as point of confusion. Some clinicians stated almost all their patients would fulfil this definition (a view which was encouraged) and others (with a similar patient load) felt that it was unlikely they would see any eligible patients.

Solution

Feedback suggested that the need to consider study eligibility at each patient encounter was both time-consuming and complex. In order to simplify matters 3 possible options were considered: a) All patients without a typical presentation of a common dementia (defined here as Alzheimer's dementia, dementia with Lewy bodies, and vascular dementia) should be referred; or b) All patients with non-typical Alzheimer's dementia should be referred; or c) All patients with dementia should be referred.

Option a) would increase prevalence figures to c. 2,300 and incidence to c. 70 patients (based on the relative percentage of dementia subtypes in the UK, (Figure 1) [18]). Option b) would increase expected prevalence figures to c.5,000 and incidence to c.150 . Option c) would increase prevalence figures to c14,000 and incidence to c.400. For this option it would be envisaged that all patients fulfilling the inclusion criteria would have illness details taken and clinical assessment completed; if features were highlighted from the duration

of illness, the symptom questionnaire or the EMAS that were atypical then those patients would be followed up. If no unusual features were highlighted then data would be collected, patients signed up for post-mortem and no follow up otherwise arranged.

Whilst options b) and c) are the most vigorous, reduce referring clinician workload the most and permit fewer assumptions about phenotype in older patients they are limited by their sheer number. Option a) was therefore considered the most feasible by the +65 management group with incorporation of this case definition into future protocol changes.

ii.ii) Age eligibility

A number of patients referred during this initial phase were seen in secondary and tertiary referral care clinics prior to turning 65 years old. As before, the prior probability of specific dementia syndromes is different in these groups and referral pathways differ. Insight into referral patterns of those ≥65 years old is therefore limited by their inclusion.

Solution

In conjunction with changes to the clinical eligibility, it is proposed that patient demographics should also be changed to include only patients seen who were aged 65 years and over at the time of referral and diagnosis to memory clinics. This would help to re-focus the study to only late onset dementias.

ii.ii) Workload

It was highlighted, particularly during meetings with OAP, that there was limited time and space in clinic for research to be discussed with patients. Additional workload is a common deterrent for referral to clinical studies [129, 130]. Research is generally not regarded as integral or as important as clinical work [129] and can therefore be seen as an unwelcome extra in addition to an already busy clinical job.

Solution

As before, it would also be hoped that by widening the case definition that clinicians will not have to use time considering whether a patient is eligible and therefore any additional workload would be reduced.

Referral workload was also reduced by the study research nurse attending the ARRNC cognitive disorders clinic with additional attendance on OAP ward rounds (REH) and proposal of attendance at OAP memory clinics (MATS). The presence of a research nurse can improve recruitment [128] and it would be hoped here to further improve study visibility and reduce referral workload for clinicians.

Further efforts to remove responsibility of the clinician to introduce the study were also explored. During contact with referral sites it was emphasised that the role of the referring clinican was to obtain permission to refer the patient to the study rather than discuss the study in detail. Patient information leaflets were provided to clinicians in memory clinics to assist with this.

ii.iii) Clinician confidence in introducing research

During meetings with MFE and OAP it was raised that clinicians had a general lack of confidence in introducing research (a common finding [129]). Specific issues also arose regarding prion disease as an area unfamiliar to many referring clinicians.

Solution

Potential solutions include on-going involvement of clinicians in protocol amendments prior to progressing to a pilot study. Educational incentives have also been shown to improve recruitment [129]. CPD sessions on CJD were organised with consultants and trainees in OAP and MFE. As above, study information sheets were also available with contact details of the study team should patients have questions regarding the study or about CJD.

Monthly meetings were arranged with OAP (at the Marchhall MATS Clinic, where c70% of all patients aged ≥65 years with dementia in Lothian are seen) to present an update on study recruitment and project developments. This was arranged to enable greater involvement of referring clinicians / CPNs / MATS nurses in the study and also enabled any difficulties experienced in the referral process to be addressed.

ii.iv) Doctor-patient relationship

Clinicians have reported an unwillingness to expose patients to study interventions [95], and have reported embarrassment at asking patients to

participate in studies. Discussing uncertainty may also negatively impact on the doctor – patient relationship [128]; raising the issue of another dementia diagnosis here could potentially be felt to undermine the patient's diagnostic process.

Solution

During contact with referral sites it was emphasised that patients could consent to as little or as much as they wished of the study. It was highlighted that there would be potential benefit to the referring clinicians / CPNs with information sharing of cognitive assessments and MRI results, limiting clinician's time and resources and limiting any additional or duplicate assessments of patients. Whilst it was felt important to address this and ensure reciprocal benefit from patient involvement in the study, at odds with the above, studies have highlighted that benefits to the referring clinician have not been shown to influence the likelihood of referral. These methods may therefore realistically only assist those who would likely refer anyway.

ii.v) Lack of accountability for enrolment to study

As it was not initially clear, particularly within community OAP, who would be best placed to refer patients and when (e.g. old age psychiatrist at diagnosis or CPN at follow up), there was a lack of accountability resulting in no referrals to date from community OAP.

Solution

Regular contact was made with all OAP, MFE and neurology clinicians and CPNs to remind them of the study and to give opportunity to refer patients by return of e-mail.

In particular areas where either the majority of patients were seen (MATS), or areas where recruitment of the referral site was slow (e.g. non-MATS community OAP memory clinics), separate meetings were arranged to clarify in each individual area who should refer patients and when in order to improve local accountability for referral.

3. Other

iii.i) Research databases

Other than the ARRNC there were no accessible databases for researchers. Local and national databases of patients interested in participating in research have been found to be the greatest strategy for improving recruitment to studies on dementia [131]. It was also known from the ARRNC database how often information sheets were provided for researcher follow up, thus providing numbers of patients enrolled from those approached (to assess if there were any barriers at this level). There was no such system in other recruitment sites.

Solutions

Separate to this study but using this study as an impetus for change, OAP have committed to a research database, initiating monthly research meetings

to discuss studies and recruitment, and adapting clinic introduction letters to include mention of research to ensure research becomes an integrated part of patient management.

Whilst these solutions will not impact this study it was hoped they might provide benefit to future studies. Realistically however, although they provide an effective means of contacting patients, the recruitment rate from the ARRNC database was low from patients contacted and therefore it is not clear whether such changes would yield significant improvement in numbers recruited.

iii.ii) Miscellaneous - 2

Feedback from the +65 management group highlighted the importance of utilising specific prion rating scales when assessing functional ability.

Solution

The Barthel Index was substituted with the MRC Prion rating scale: a specific and validated scale for the use in CJD [94].

4.6 Conclusions

Comprehensive case ascertainment of CJD is important in older patients. A protocol for enhanced surveillance of CJD in the older population has been designed and piloted here. Of the initial patients recruited there was no evidence of CJD clinically, however, no patients reached post-mortem. Barriers to referral likely impacted numbers recruited and further review of the

feasibility of this study is necessary after protocol changes have been incorporated.

CHAPTER 5: OVERALL DISCUSSION

5.1 Introduction

This thesis has considered CJD with a focus on older patients, specifically on their detection through disease surveillance activities and the possibility that cases may be missed.

CJD continues to be an important concern to public health and disease surveillance remains as relevant now as it has ever been. There is caution that there may potentially be more cases of vCJD to come with the first pathologically confirmed case of a codon-129 heterozygote, and the appendix III study demonstrating a potentially larger at risk population. Further to this, the first case of chronic wasting disease (a prion disease of deer and elk) in Europe has been confirmed; whilst the zoonotic potential is not clear, it further emphasises the importance of on-going surveillance.

The epidemiological characteristics of CJD, and in particular sCJD, are suggestive of possible case under-ascertainment, and specifically in older ages. This thesis has demonstrated that age is a risk factor for later referral to surveillance systems and that clinical and referral characteristics may be influential in this. It has done this by:

1) Literature review

This demonstrated that missed cases do occur with older age a possible risk

for this. It was however unclear whether this was due to a different presentation of CJD in older patients or whether there was a tendency for cases of CJD in the older population to become lost in the more common dementias. Given the rapid neuropsychiatric presentation of CJD it would seem unlikely that many cases would be missed, however as has been demonstrated, the features most suggestive of CJD (that is rapidity of decline and focal neurological features) are not unique markers of CJD.

2) NCJDRSU database retrospective review

In general, for both vCJD and sCJD, older age was significantly associated with later / missed referrals and indeed older age was a confounding factor in most associations seen in cases referred later. It further demonstrated that clinical features and referral characteristics were associated with later referral and older age with the following findings noted:

A) vCJD

In both later and older cases: 1) patients were more likely to present in a relatively non-specific manner with rapid cognitive decline; 2) symptoms more suggestive of vCJD (e.g. sensory symptoms) presented later in the disease course. Sensory symptoms were the only consistent differentiating feature between later / older cases of vCJD and sCJD with late diagnoses confused with sCJD, possibly related to the later onset of such symptoms; and 3) cerebral MRI was a less sensitive investigation.

B) sCJD

In both those ≥80 years old and those referred later: 1) cerebellar features were less likely throughout illness with a later time to onset of such features also; 2) atypical features at onset (e.g. visual disturbance in those referred later in their illness) and during illness (e.g. seizures in those ≥80 years old) were noted; 3) MRI was less sensitive in later referrals; a product of the confounding effect of the older age of such cases (in keeping with previous review [75]); and 4) patients were less likely to be referred by a neurologist or be managed in a neurosciences centre.

Following these findings a protocol for enhanced surveillance was proposed to manage this unmet need. A system of enhanced surveillance in the older population is required as: 1) All cases of CJD have potential implications for public health; 2) The elderly are more likely to require surgery / blood transfusions and are therefore at a greater risk of not only contracting iCJD but also of transmitting to others; and 3) To phenotype in detail cases missed in life who would not have otherwise been referred to the NCJDRSU surveillance system or reached post-mortem. Another potential benefit of this study is to produce the first prospective clinicopathological study of dementia with atypical features in the older population.

5.2 The next steps in 'The +65 Study'

No conclusions can yet be drawn about the characteristics of additional, previously undetected cases from enhanced surveillance. Recruitment is continuing and protocol feasibility issues are being addressed. Further to the necessary protocol changes an area that requires additional consideration is the lower than expected referral numbers. It is difficult to know at this stage whether the low study recruitment is reflective of feasibility issues, or because such numbers are an accurate reflection of eligible patients.

As previously discussed there is limited literature from which to predict accurate patient numbers. Estimates are based on small cases series with larger cohorts focusing specifically on older age groups making generalisability / applicability specifically to this study difficult [26]. In addition to this it has been previously observed that: "The number of patients who are actually available for a trial is about 1/10 to 1/3 of what was originally estimated" ('Lasagna's Law' [132]). Without clear predicted recruitment estimates for the +65 study it is difficult to know whether 'Lasagna's Law' has been a significant factor here.

In order to clarify this, a two part approach is proposed: 1) A survey of potentially eligible patients to determine accurate numbers; and 2) Assuming numbers could be improved, a survey of clinicians to understand in greater detail the barriers to recruitment that may be most important here (and therefore how best to re-focus efforts to improve recruitment).

a) Audit of potentially eligible patients

Ideally an audit would involve a coded outcome measure (e.g. ISD coded diagnosis of dementia, number who had died or had required long-term institutional care within a defined, short period of time). As became apparent when this was further explored, there are no clear outcome codes that could be utilised. The certainty of diagnosis is not coded, and whilst those dying within a short period of time could be coded, a great number of other potentially eligible patients would be missed. The only way to reliably audit this was to review medical notes of all patients seen within a time period over-lapping with the study to determine whether eligible patients were missed. Such an audit is proposed in Appendix G.

Accepting the limitations of this approach (for example, neurological features may not be detailed outwith a neurology appointment), the potential insights into the clinical and referral characteristics of patients seen through, particularly community OAP, would outweigh any such limitations.

b) Survey of referring clinicians

A survey of clinicians / CPNs at recruitment sites should be quick, accessible, and anonymous (beyond job title). An electronic 'doodle poll' is proposed for these reasons. The aim of this survey is to determine how strongly participants feel about certain potential barriers to referral (identified both from literature review and those identified during discussions with local clinicians). Such a survey would not only assist study development but also add to

the literature base, as currently assessment of recruitment of cohort studies are lacking. Such a survey is proposed in Appendix H.

Whilst the clinical arm of this study has been a little slow to recruit, the concurrent pathology arm (to capture additional cases missed through clinical screening) has been successful. During the same first 6 months of the study 49 cases were referred with 36 cases fully analysed during this time (84%); no cases of prion disease were detected.

As a final consideration, whilst measures to improve feasibility are still required, assuming difficulties can be overcome, the next step beyond this is to consider how to roll this study out as a standard add-on enhanced surveillance service in the UK. In order to do this, two areas would require consideration: 1) How to reach all relevant referring clinicians and to ensure on-going study visibility and; 2) How to manage numbers.

1) How to reach all relevant referring clinicians

Possible means of reaching trainee and consultants in OAP / MFE / neurology would be via national societies. All trainee and consultant neurologists are members of the Association of British Neurologists (ABN) - likewise all OAP clinicians and the majority of MFE clinicians are members of the Scottish branches of the Royal College of Psychiatrists and British Geriatrics Society respectively. It is proposed that an e-mail alert could be generated from these societies with later inclusion in society news update emails to maintain study

visibility.

2) How to manage numbers

This will be managed by the case definition. At present the inclusion criteria are too broad. This has been beneficial for this stage of the study in order to minimise any preconceptions / bias about the presentation of older patients with CJD and to ensure confidence that surveillance has been as comprehensive as possible whilst the case definition is developed. It will not however be possible to ensure all patients are seen and followed up adequately if such an all-inclusive case definition is rolled out. Refinement of the inclusion criteria will be required following analysis of the clinicopathological features of the first patients recruited and feedback from referring clinicians.

5.3 Conclusions

This thesis has demonstrated a relationship between age and timing of referral in both variant and sporadic CJD. Further to this it has addressed this association with description of the first study of enhanced surveillance of CJD in the older population. Results are awaited to determine the characteristics of otherwise missed cases and whether this is an on-going feasible means of enhanced surveillance.

APPENDICES

Appendix A: An overview of the most common dementias

Table A1: An overview of the most common dementias

Dementia	Pathological substrate	Age at onset (>65 vs <65)	Disease Duration (years)	Typical presentation	Less typical presentations	Biomarkers	Neuropsychology [133]	Particular features in elderly	Refs
Alzheimer's Disease	Extracellular amyloid deposition and intracellular tau neurofibrillary tangles	> 65	8 – 10	Deficits in episodic memory. Changes in visuospatial abilities also seen	Language difficulties (Logopenic variant) Visuospatial (Posterior cortical atrophy) Executive dysfunction (Frontal variant)	CSF[1]: ↓ amyloid : tau MRI/CT: hippocampal / parietal atrophy SPECT[2]/FDG-PET[3]: posterior hypoperfusion / hypometabolism Amyloid-ligand: ↑ amyloid load	Deficits in episodic memory with involvement of visual perception, visuomotor co-ordination and constructive praxis. Language, behaviour and social cognition relatively	Small studies – more aggressive disease course SPECT – different patterns Amyloid biomarkers – less specific	[14, 134], [135-137]

							preserved in the early stages		
Fronto-temporal Dementia	Tau TDP-43 FUS	< 65	8	Executive dysfunction with relative sparing of episodic memory / visuospatial abilities	Language (Non-fluent aphasia / semantic dementia)	CSF: ↑ tau in c45% MRI[4]/CT[5]: fronto-temporal atrophy SPECT/FDG-PET: anterior hypoperfusion / hypometabolism	Impairment of frontal lobe function (deficits in executive tasks) with relative sparing of episodic memory / visuospatial skills	Lower validity of diagnostic criteria. Majority mis-diagnosed; age greatest influence on clinical presentation. Early amnesia Shorter disease duration. Radiological features compatible with AD	[6, 138], [6, 24, 139, 140]
Dementia with Lewy Bodies	Alpha-synuclein	> 65	8	Fluctuating attention , alertness and recurrent well-formed visual hallucinations	Rapid onset	DaT[6]: ↓ dopamine uptake SPECT: posterior hypoperfusion CSF: presence of alpha-synuclein	Deficits on tests of attention, and visuospatial / visuoperceptual ability. Memory and executive function usually become evident with disease progression	New alpha-synuclein biomarkers likely to be less specific in elderly	[17, 141]

Vascular Dementia	Cerebral hypoperfusion and ischaemia Co-existent AD	> 65	5	Cortical damage - dependent on area affected Sub-cortical – executive dysfunction and slow thought processes	n/a	MRI/CT: vascular changes corresponding to cognitive deficits Presence of superadded amyloid common	Dependent on area of brain affected. Subcortical changes present with slowness of processing.	Lower validity of diagnostic criteria compared to all ages. Radiological features less specific	[15], [142-144]
Parkinson's Associated dementia	Alpha synuclein	> 65	No reliable estimates	Subcortical (fluctuating attention and slow thought processes) and cortical changes (executive and visuospatial dysfunction plus impaired free recall)	As per dementia with Lewy Bodies	As per dementia with Lewy Bodies	Subcortical deficits in attention (may fluctuate) and slowness of processing with cortical deficits in executive and visuospatial functions, and memory (impaired free recall improves with cueing)	Unknown	[16]

[1]CSF – cerebrospinal fluid; [2]SPECT – single photon emission computerized tomography; [3]FDG-PET – fluorodeoxyglucose-positron emission tomography; [4]MRI – magnetic resonance imaging; [5]CT: computed tomography; [6]DaT: Dopamine transporter imaging

APPENDIX B: vCJD VERSUS sCJD

Table B1: Clinical features vCJD compared to sCJD (all cases)

Clinical feature	**vCJD**	**sCJD**	**p-value**
Forgetful	172/176	467/538	<0.001**
Rapid cognitive decline	164/169	503/538	0.08
Gait change	173/177	472/540	<0.001**
Cerebellar features	166/169	350/581	<0.001**
Pyramidal	115/165	296/529	<0.001**
Extrapyramidal	19/155	247/521	<0.001**
Visual symptoms	49/159	268/536	<0.001**
Myoclonus	108/159	410/535	0.027
Sensory	133/169	93/535	<0.001**
Pain	90/167	40/535	<0.001**
Hallucinations	58/155	293/539	<0.001**
Anxiety	86/149	221/533	<0.001**
Depression	92/144	121/533	<0.001**
Social withdrawal + apathy	97/148	221/529	<0.001**
Delusions	57/154	131/533	0.002**
Grasp / primitive reflexes	74/149	234/485	0.76
Seizures	9/168	42/537	0.28
Other movements (chorea / dystonia)	105/159	130/528	<0.001**
Akinetic mutism	13/155	183/530	<0.001**

*Significant (p <0.05) **Highly significant (p <0.01)

Table B2: Clinical features vCJD compared to sCJD (≥65 years old)

Clinical feature	vCJD	sCJD	p-value
Forgetful	3/3	316/362	0.51
Rapid cognitive decline	3/3	342/362	0.68
Gait change	3/3	320/363	0.53
Cerebellar features	3/3	234/394	0.15
Pyramidal	2/3	197/357	0.69
Extrapyramidal	0/3	166/351	0.10
Visual symptoms	1/3	184/361	0.54
Myoclonus	2/3	283/360	0.62
Sensory	2/3	53/359	0.013*
Pain	1/3	22/359	0.054
Hallucinations	2/3	201/363	0.70
Anxiety	0/2	135/357	0.27
Depression	1/3	68/358	0.53
Social withdrawal + apathy	0/2	143/353	0.24
Delusions	1/2	85/358	0.39
Grasp / primitive reflexes	1/3	169/325	0.52
Seizures	0/3	27/361	0.62
Other movements (chorea / dystonia)	1/3	86/354	0.72
Akinetic mutism	1/2	138/356	0.75

*Significant ($p < 0.05$) **Highly significant ($p < 0.01$)

APPENDIX C: POST-HOC ANALYSIS OF sCJD SUBTYPE

Introduction

As per chapter 1, sCJD may be sub-classified into 6 sub-types according to their allele expression at codon-129 (M or V) and the isoform of prion protein (type 1 or type 2).

Methods

A cross tabulation using χ^2 was undertaken of basic demographics with the sCJD subtype.

Results

There was no association with gender (p = 0.78). The age at onset however was significantly associated (p = 0.002) with MM1 and VV2 seen more frequently in older patients. The duration of illness was also strongly associated (p <0.001), with MM1 having the shortest duration at 3 months (1-25), and MV2 with the longest duration at 15 months (3-63) (Table D1)

Table C1: Basic demographics and sCJD subtype

	MM1 (n = 144)	**MM2 (n = 17)**	**MV1 (n = 15)**	**MV2 (n = 27)**	**VV1 (n = 6)**	**VV2 (n = 41)**
Cases (%)	57.6	6.8	2.4	16.4	6.0	10.8
Age (median – years)	70 (64-77)	66 (59-72)	66 (63-70)	67 (61-71)	52 (43-66)	71 (66-76)
Duration (median – months)	3 (2-5)	10 (6.5-15)	5 (3-11)	15 (12-21)	17 (6.5-19)	7 (4-10)

There was a significant association between presenting feature and sub-type (p = 0.02). Those presenting with behavioural / visual symptoms were over-represented

by MM1, those with rapid cognitive decline were over-represented by MM2 and MV2, and those with an ataxic onset were over-represented by VV2 (Table D2).

Table C2: Presenting feature and sCJD subtype

Presenting feature (%)	MM1 (n = 120)	MM2 (n = 15)	MV1 (n = 14)	MV2 (n = 22)	VV1 (n = 5)	VV2 (n = 34)
Behavioural	14.2	20.0	14.3	13.6	20.0	8.8
Sensory	4.2	0	7.1	0	0	0
Mood / psychiatric	5.0	13.3	21.4	4.5	0	0
Rapid cognitive decline	32.5	53.3	28.6	45.5	60.0	29.4
Unsteady / motor	20.8	6.7	21.4	27.3	20.0	50.0
Visual	19.2	6.7	7.1	0	0	0
Other (insomnia, 'dizziness')	4.2	0	0	9.1	0	11.8

When analysed with grouped clinical features, there was no statistically significant association with cognitive decline ($p = 0.76$), psychiatric symptoms ($p = 0.38$), cerebellar (0.09), extrapyramidal ($p = 0.12$), pyramidal ($p = 0.39$), sensory symptoms ($p = 0.17$), and seizures ($p = 0.63$). Furthermore there was no statistically significant association with fulfilment of the diagnostic criteria ($p = 0.69$). There was however a significant association with vision $p < 0.001$ (more likely in MM1 and MV1), and features of lower motor neurone involvement $p = 0.007$ (more likely in MV2 and VV2).

There was no statistically significant difference in MRI findings ($p = 0.70$), and EEG result ($p = 0.31$), however there was a statistically significant association with CSF 14-3-3 results ($p = 0.03$) and RT-QuIC results ($p = 0.001$).

APPENDIX D: YOUNG ONSET sCJD VERSUS vCJD

Table D1: Clinical features vCJD compared to sporadic CJD: <45 years old

Clinical feature	vCJD	sCJD	p-value
Forgetful	154/158	2/4	<0.001**
Rapid cognitive decline	146/151	2/4	<0.001**
Gait change	155/159	2/4	<0.001**
Cerebellar features	149/152	2/4	<0.001**
Pyramidal	106/147	2/4	0.33
Extrapyramidal	18/140	0/4	0.44
Visual symptoms	43/141	0/4	0.19
Myoclonus	93/141	1/4	0.09
Sensory	119/152	1/4	0.013*
Pain	81/151	1/4	0.26
Hallucinations	49/138	1/4	0.66
Anxiety	80/135	1/4	0.17
Depression	83/127	2/4	0.53
Social withdrawal + apathy	90/133	1/3	0.21
Delusions	49/139	1/4	0.67
Grasp / primitive reflexes	68/135	1/4	0.32
Seizures	9/151	0/4	0.62
Other movements (chorea / dystonia)	95/142	0/4	0.006**
Akinetic mutism	12/138	1/4	0.27

*Significant (p <0.05) **Highly significant (p <0.01)

APPENDIX E: THE +65 STUDY CASE DEFINITION TOOL

The 65+ Dementia Study Case Definition Tool

Inclusion Criteria

1. Aged 65+ (at time of contact, not onset)
   AND
2. Progressive cognitive impairment (memory, language, behaviour change)
   AND
3. Atypical features for the known types of dementia (typical features detailed overleaf)
   AND
4. No clear alternative demonstrable pathology (inherited dementia, psychiatric diagnosis, space occupying lesion, neuroinflammatory/neuroinfectious condition, related cerebral insult)

Atypical features may include:

1. Unusual rate of progression (e.g. rapid – this would be over weeks to months)
   AND/OR
2. Focal neurological symptoms including unsteadiness, jerking/involuntary movements, painful sensory symptoms, visual loss, seizures
   AND/OR
3. Neuropsychiatric symptoms including psychosis, hallucinations, significant new onset mood disturbance

Please note that the above has been developed to offer guidance for identifying atypical features of dementia.
Any patient who you feel is presenting with atypical features but you would like to discuss further, or confirm their eligibility, please do not hesitate to contact a member of the 65+ Dementia Study team on the contact details below.

Mrs Gemma Logan (Research Nurse): 0131-537-1980 / 07464-677-117 gemma.logan2@nhs.net
Dr. Briony Waddell (Research Registrar): 0131-537-1980 / bwaddell@nhs.net

Typical Features of Main Dementia Sub-Types

Alzheimer's Disease

- Initial / prominent features: impairment in learning and recall of recently learned information
- Progression: Insidious onset, typically over 8-10 years

Frontotemporal Dementia

- Initial / prominent features: behavioural disturbance which can include behavioural disinhibition, apathy, loss of sympathy or empathy, and/or compulsive/ritualistic behaviour
- Progression: Insidious onset, typically over 6-8 years

Dementia with Lewy Bodies

- Initial / prominent features: fluctuating cognition with pronounced variations in attention and alertness. Recurrent visual hallucinations that are typically well formed and detailed, in the presence of parkinsonism
- Progression: Insidious onset, typically over 6-12 years

Vascular Dementia

- Initial / prominent features: evidence from the history, examination, or tests, of a significant cerebrovascular disease, which may reasonably be judged to be aetiologically related to the dementia
- Progression: May be abrupt onset or insidious, with a variable rate of progression

APPENDIX F: PATIENT INFORMATION SHEET

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

Enhanced CJD surveillance in the older population (Scotland A REC ref:15/SS/0196)
Participant Information Sheet & Consent Form (Participants) version 1.2, 28/06/2016

Study Principal Investigator: Dr Anna Molesworth, PhD
Telephone: 0131 537 1980
Email: anna.molesworth@ed.ac.uk

THE 65+ DEMENTIA STUDY INFORMATION FOR PATIENTS

We understand that you have been diagnosed with a type of dementia. We would like to invite you to take part in our research study on dementia in people aged 65 and above.

Before you decide, we want you to understand why this research is being done and what it would involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information.

The 65+ Dementia Study Team

We are doctors, scientists and nurses from University of Edinburgh and NHS Lothian who have a special interest in patients with dementia, including a particular type of dementia due to prion disease. Prion diseases are a very rare group of diseases that affect nerve cells in the brain and spinal cord. Prion disease can exist in different forms, but the most common is Creutzfeldt-Jakob Disease (CJD). We provide doctors with information about prion disease, and advice on how to look after their patients. We also do research into some of the causes of prion disease. This research project may help us to find out what caused your dementia.

If, having read this leaflet, you are interested in the research, then we can arrange a meeting either in the clinic or at your home at a time that is most convenient for you and any family members you wish to be present. The purpose of this visit is to discuss the study and what is involved. **One of our research team will go through this information leaflet with you and answer any questions you have.**

What is the purpose of this study?

There are about 850,000 people living with dementia in the UK, the majority in people aged 65 year or over. Around 100 people in the UK are diagnosed with prion disease every year, however we think that more might be infected but their illness may not have been recognised, perhaps because the signs and symptoms are similar to different forms of dementia. **This research will use patient assessment, blood samples, brain scans and samples of brain tissue from people in Lothian when they die, to find if prion disease is being missed and why.**

Why have I been asked to take part?

We understand that this is a difficult time for you. All patients aged 65 and over who have recently had a diagnosis of dementia are being considered. There are many different types of dementia, and in the majority of patients the diagnosis can be made with confidence. However, because the signs and symptoms of dementia vary from patient to patient, we find that some characteristics are less common than others. You are being invited to join this study because you have some of these less common features and studying them may help us understand your type of dementia, why you developed your current illness and if it might be due to prion disease. This could benefit others in the future.

Do I have to take part?

No. It is up to you to decide whether you wish to take part in the research or not. If you do wish to participate, we will ask you to sign a consent form. You are still free to withdraw at any time, without giving a reason. Deciding not to take part or withdrawing from the study will not affect the healthcare that you receive, or your legal rights.

If you lose your capacity to make an informed decision about participation in the study after you have joined, then your previous wishes will be respected and the study will continue under existing consent arrangements. In these situations we will check with your representative that they are happy with these arrangements. We will then ask you to renew your consent when capacity is regained.

What will happen to me if I take part?

There are five parts to the research and you can contribute to any of them.

1. Assessment by the 65+ dementia study team

We would like to ask you some questions about your current illness and your memory and mood, and examine your ability to move. This will take about 1 hour, and will help us better understand your illness and if you have any symptoms or signs that might be due to prion disease. We will also review your medical notes to help investigate what may have caused your illness.

In some instances we may offer you the opportunity to undertake a magnetic resonance imaging (MRI) brain scan at a brain research imaging centre for research purposes, if you have not already had one organised by your doctor as part of your standard patient care. This scan might help identify a cause of your dementia.

MRI is a safe and painless procedure that uses a combination of powerful magnets and radio waves to create detailed pictures of your brain, which are then reviewed by a doctor qualified in medical imaging to help us in our research.

MRI will take approximately 30 minutes to one hour to complete. It does not involve any exposure to x-rays or other forms of radiation, and there is no evidence that the scanning poses any risk to the body. However, because not everyone can have an MRI scan, for example they are not always possible for people who have had certain types of implants fitted, we will check beforehand that it is perfectly safe for you to be scanned.

The research team will be able to explain more about this process when you meet with them, so you will have the opportunity to discuss this and the investigation will not proceed without your agreement.

2. Medical history questionnaire

We would also like to ask you some questions about your past medical history and any family history of dementia, the answers to which will be recorded on a questionnaire form. This will take about 30 minutes. The information you provide, together with a detailed review of your medical notes, may help us identify possible causes for dementia.

3. Blood sample

If you agree, we will also ask whether you wish to donate 2ml (just under half a teaspoon) of your blood, so we can study genetic influences on neurological conditions. Some of your genetic material (DNA) will be extracted from the blood sample. This helps us to understand the different forms of prion

disease. It may also help us identify genes that may make an illness more likely, sometimes when someone has other risk factors too.

4. Checking how you get on in the future

We would like to follow your progress on the hospital patient management system and will contact you on a regular basis by telephone in order to assess your illness and answer any questions you may have. How often we call you will vary from person to person according to the nature of your illness, but is likely to be within 1 month of joining the study and every 3 months thereafter. You may also contact us with questions and concerns any time you would like. A follow-up home visit may be suggested, with your agreement, if we feel a further clinical assessment or MRI scan could be helpful.

5. Examination of brain tissue

With all forms of dementia, the only way to be certain as to the exact cause of someone's symptoms is to perform a post-mortem examination. This means that we therefore are inviting you to consider donating samples of your brain to the Edinburgh Brain & Tissue Bank when you die, to assist us in this and future research. More information will be provided in relation to this in a separate information sheet.

What if we think you may have prion disease?

It is very unlikely that you have prion disease, however, if prion disease is suspected then, with your clinician's approval, you would be offered an immediate onward referral to the National CJD Research & Surveillance Unit (NCJDRSU) for further assessment.

Will my taking part in the study be kept confidential?

Yes. There are strict laws which safeguard your privacy and your identity is totally confidential. No identifying details will ever be made public. The NCJDRSU has a policy for data protection, confidentiality and information security and regular training is required for all staff and research partners.

How will information about me be handled?

The study is run by a team from the NCJDRSU working with colleagues from the University of Edinburgh and NHS Lothian. Information is processed by this team with the help of medical statistics, computing and administrative staff, and all staff have a professional duty of confidentiality. All information is held in secure, password-protected databases at NCJDRSU, the Brain Research Imaging Centre and Edinburgh Brain & Tissue Bank; paper records are kept locked up when not in use. Access to your personal information is for the purpose of this study only and is restricted to authorised personnel on a need-to-know basis.

To ensure that the study is being run correctly, we will ask your consent for responsible representatives from the Sponsors (University of Edinburgh and NHS Lothian) to access your medical records and data collected during the study, where it is relevant to you taking part in this research. The Sponsors are responsible for overall management of the study and providing insurance and indemnity.

What happens to the results of my assessment and brain scan?

You would not normally be told the outcome of the research investigations. However, for any person having a MRI scan there is the possibility that an abnormality may be found that was previously unknown about that could have an impact on your care. If this was to occur or if, as a result of the clinical assessment or MRI, we encounter evidence of prion disease, then we would discuss the findings with the local medical consultant in charge of your care and your GP, and either ourselves or your doctor will then discuss these findings with you.

What gene is being tested for and why?

Your genes can affect your health in different ways. Firstly, an abnormality in a gene may directly cause illness or secondly, a normal variation in a gene may make illness more, or less, likely, in combination with other factors.

We are looking at the prion protein gene and at one part in particular, called the "codon-129 genotype", which falls into the second group. We all have a codon-129 genotype. It does not cause prion disease, but variations in the codon-129 genotype, in combination with other risk factors, may make prion disease more likely. The codon-129 genotype also helps us identify the different types of illness in people who are known to have prion disease. To find out the codon-129 genotype, some of your genetic material (DNA) will be extracted from the blood sample and tested in our laboratory. Any remaining blood and genetic material will then be disposed of after the study has ended. Alternatively, if you agree, rather than disposing of the genetic material it can be stored by us for use in future genetic research into prion disease and other neurological conditions.

What do you mean by future genetic research?

Current knowledge of the genetics of neurological conditions is limited but as understanding increases there may be new studies that we can undertake to have a better understanding of these disorders. These new studies may, for example, involve genetic testing for individual genes or looking at all your genes - a process called whole genome scanning. In turn this could help prevent disease, develop diagnostic tests or lead to new and better treatments.

What are the possible benefits of taking part?

You may not get a direct benefit from taking part in this study, however if we suspect prion disease there may be the possibility of you and your family receiving additional care and emotional and practical support through the National CJD Care Package.

By participating in this research you will be helping us better understand the symptoms of dementia, and the reasons why people may develop less common symptoms and how a diagnosis of prion disease can be missed. This may help us to learn how we can improve the detection of prion disease in those aged 65 and over. This has potential benefits for the diagnosis of other NHS patients, their management and care, and in protecting public health. This could in the future inform routine practice in Lothian and elsewhere.

What are the possible disadvantages and risks of taking part?

Our initial visit will take between two to three hours – this may seem a long time but it will enable us to discuss the study fully with you, and for you to ask any questions you may have. This also allows time for the assessment and review, if you agree. The process of taking of blood may be a little uncomfortable or leave some bruising. Some patients may find the MRI scanning process claustrophobic – but the radiology staff who will be running the scan will be watching out for this and if this happens to you, the scan would not have to continue.

We will do our best to deal with any issues that worry you. You will also be given our contact details so you can speak to us at any point in the study if you have concerns.

What happens to the samples I have donated for future research?

The genetic material and samples of brain tissue will be retained indefinitely in a secure laboratory and used in an anonymised form for future medical research to benefit human health. They will then be disposed of lawfully when they have served this purpose. This may mean that we may work with other national and international research centres, sometimes including commercial organisations. We cannot predict every type of project but all research that we support is ethically approved. The samples are donated to researchers freely and neither you nor your relatives would benefit financially from any developments of this kind, even if the research results in the development of new treatments or diagnostic tests.

We may share with researchers information we have collected as part of the research, but no information that could identify you personally will be made available to research staff and your samples will be coded so that researchers who analyse these samples will not know who you are. This also means that you will not be told your results.

What happens when the study is finished?

The study will run until March 2018, with the possibility of an extension if we need time to continue follow-up. Samples will be retained until the end of the study, after which arrangements will be made for the disposal of any material not destined for long-term storage. Tissue samples that are suspected to be CJD or any other prionopathy will routinely be retained in the CJD Brain and Tissue Bank (part of the Edinburgh Brain Bank).

Information about you will be retained for a minimum of 5 years past completion of the last date of testing of samples for the final participant, and then it's retention will be reviewed with a view to permanent disposal or long-term archiving for future research, audit or as part of your medical record.

Will my doctors be informed about my participation?

Yes. We will contact your GP and the consultant in charge of your care to let them know, as a professional courtesy, that you have agreed to take part in this study and to request to see your medical notes. We will also discuss the results of our investigations with them if this is relevant to your treatment and care.

Can I agree now and change my mind later?

Yes. It is possible to withdraw from any or all parts of the study if you change your mind later on. The information we hold about you can be deleted to the minimum required for audit purposes and where relevant to your medical record, and will not be used in research. You can also withdraw permission for any samples to be tested up until the time they are tested and your sample will be destroyed.

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to a member of the 65+ dementia study research team who will do their best to answer your questions. If you wish to make a formal complaint, please contact the NHS Lothian Patient Experience Team by calling 0131 536 3370, or emailing feedback@nhslothian.scot.nhs.uk.

What will happen to the results of the study?

The results of the study will be written up for publication as journal articles and presented at national conferences and worldwide. We will also report our findings to the funding bodies, relevant expert panels and other stakeholders. Summary information will also be available through information published on the NCJDRSU website and we can send this to you directly if you wish. You will not be identifiable in any reports or published results.

Who is overseeing the research?

This study is lead by the NCJDRSU with oversight from an external steering committee and is co-sponsored by the University of Edinburgh and NHS Lothian. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee (REC). A favourable ethical opinion has been obtained from Scotland A REC.

Thank you for taking the time to read this information leaflet.

If you would like further information please contact one of the study team:

Mrs Gemma Logan (Research Nurse)
Dr Briony Waddell (Research Registrar)
Dr Anna Molesworth (Principal Investigator)

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Independent advice about the study is available from:

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APPENDIX G: PROPOSED AUDIT OUTLINE FOR SUBMISSION TO NHS LOTHIAN GOVERNANCE

Background

The prevalence of dementia in Scotland is 87,000 with 13,000 of such patients residing in Lothian. Approximately 97% of these patients are over the age of 65 years. With the ageing population, this figure is expected to rise. The National Institute of Clinical Excellence states that all patients with dementia should be diagnosed by a 'specialist assessment service'. The integrated care pathway in Lothian further defines standards and states that all patients should be diagnosed by a 'specialist diagnostic service', also referred to as 'memory clinics', the vast majority of which are managed by old age psychiatry.

With increasing age the correlation between clinical and pathological findings in dementia dissociate with an increasing number of patients who do not fulfil diagnostic criteria for syndromic diagnoses (e.g. Alzheimer's, frontotemporal dementia, dementia with Lewy bodies etc). It is therefore expected that a number of elderly patients with dementia will be reviewed by old age psychiatry each year where the cause for their cognitive decline is not clear.

The +65 study is seeking to answer whether there are missed cases of CJD in the population over the age of 65 years old. There is concern that there may be an under-ascertainment of cases of CJD in the older population; similar to

other forms of dementia, the clinical utility of diagnostic criteria reduces with increasing age.

Recruitment for this study relies on referrals from specialist memory services. Since initiation of this project there have been a lower than expected rate of referrals. One reason for this may be that original estimates of predicted numbers of eligible patients were inaccurate or that patients are not being referred. In order to answer whether cases are being missed we propose an audit of referrals to old age psychiatry and the syndromic classification of patients seen.

Results from this audit could also assist service planning. There are very few studies reviewing the proportion of patients with dementia in the older population in whom diagnoses cannot be made with confidence. Accuracy of syndromic diagnoses allows more accurate prognostication, future care planning and helps to identify suitable therapeutic options, all of which are important in planning of local services.

Audit aims

To determine the proportion of patients seen in old age psychiatry memory clinics over the age of 65 years diagnosed with dementia

To review the sub-classification of dementia diagnoses

To determine the proportion of those where diagnosis cannot be reached with confidence

Methods

The period of evaluation will be 1st April 2015 to 30th April 2016 inclusive. This will provide data reflecting very recent referral patterns, whilst also allowing for time for investigations to occur (which may increase diagnostic certainty of syndromic classification).

We propose undertaking a review of coding data with the following information collected:

1) The number of patients seen in an old age psychiatry memory clinic

2) How many appointments were new appointments

3) The number of patients coded with a diagnosis of dementia

4) The number of patients where diagnosis could not be reached with confidence

5) Basic demographic data will be collected on all (age and gender)

Dissemination of results

Results will be fed back to old age psychiatry / discussed at the NCJDRSU +65 study steering group meeting

APPENDIX H: SURVEY OF CLINICIANS / CPNS

Table H1: Survey of clinicians / CPNs

Job title	
Old age psychiatry consultant	
Old age psychiatry trainee	
Community psychiatric nurse	
Consultant medicine for the elderly	
Medicine for the elderly trainee	
Consultant neurologist	
Neurology trainee	

	Strongly agree	Agree	Agree somewhat	Disagree	Strongly disagree	N/A
I have seen eligible patients for this study						
I know who to refer to this study						
I know how to refer to this study						
Study referral is time consuming						
The study referral process is easy						

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