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**Diagnosing variant Creutzfeldt-Jakob disease: A retrospective analysis of the first 150 cases in the UK.**

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## **Abstract**

### *Introduction*

Establishing an early clinical diagnosis in variant Creutzfeldt-Jakob disease (vCJD) can be difficult, resulting in extended periods of uncertainty for many families and sometimes a view that patients have been subjected to unnecessary investigations. This issue is accentuated by the progressive nature of vCJD and by the difficulty in achieving a confident clinical diagnosis before an advanced stage of illness. Although diagnostic delay may be a result of the non-specific early clinical features, a systematic analysis of the process of diagnosis was undertaken, with the aim of trying to achieve earlier diagnosis of vCJD.

### *Methods*

Retrospective case file analysis was undertaken of the first 150 definite and clinically probable cases of vCJD identified by the UK surveillance system.

### *Results*

There is a significant interval between illness onset and presentation to a primary care physician, which is influenced by the nature of the initial clinical features. Neurological review is invariably sought following the development of clinical signs and a diagnosis is then established relatively quickly. Despite the progressive clinical course, a confident clinical diagnosis is not usually achieved until a relatively advanced stage of illness (mean time to diagnosis 10.5 months) with a more rapid clinical progression accounting for those cases diagnosed earlier after symptom onset.

### *Conclusions*

Early clinical diagnosis in vCJD is not possible in the great majority of cases because of non-specific initial symptoms. Once neurological signs develop a diagnosis is usually made promptly, but this is often at a relatively advanced stage of illness. The inherent delays in the diagnosis of vCJD have implications for those involved in both public health and therapeutics.

## **Introduction**

A novel form of human prion disease, variant Creutzfeldt-Jakob disease (vCJD), was reported in 1996<sup>1</sup>. vCJD has provided both public health authorities and physicians with many challenges and achieving accurate early diagnosis has proved difficult<sup>2,3</sup>. This has left some families feeling that their affected relatives have been misdiagnosed or subjected to unnecessary, sometimes invasive, investigations. This issue, among others, was addressed by the BSE Inquiry, which concluded that 'Early diagnosis of this disease has been and continues to be a major problem as the first symptoms are depression and other non-specific psychiatric features.'<sup>4</sup> Difficulty in diagnosing vCJD may be the result of subtle early clinical features which are often insidious in onset. Non-specific psychiatric features dominate the early clinical course with few cases exhibiting objective neurological impairment. Neurological features develop early in a minority of patients, but are usually subjective symptoms, for example painful sensory symptoms<sup>5</sup>, which are not associated with neurological signs on examination. An analysis of a small number of the initial cases identified through UK surveillance supported the proposition that delay in diagnosis reflects the early clinical characteristics<sup>2</sup>, but a detailed analysis of the diagnostic process in vCJD has now been undertaken. The aim is to provide a detailed description of the diagnostic process in a large cohort of patients and to identify the reasons for diagnostic delay. This may have significant implications for counselling, public health and treatment. Although there is no proven treatment for vCJD, a number of promising agents are being tested in animal models and early introduction of therapy may be critical to efficacy<sup>6</sup>. This study aims to explore the diagnostic process of vCJD in detail and aims to determine whether earlier diagnosis is possible.

## Methods

Prospective surveillance of CJD in the UK has been ongoing since 1990. The methodology of the National CJD Surveillance Unit has been described in previous publications<sup>7,8</sup>.

Included in this study are the first 150 “definite” and “probable” cases of vCJD identified in the UK. Cases were classified according to current diagnostic criteria, Table 1<sup>9</sup>. The cases were referred to the UK National CJD Surveillance Unit (NCJDSU) between 1995 and 2005. Retrospective analysis of case data held at the NCJDSU was undertaken and included hospital records (n=149), GP records (n=147) and a structured questionnaire (n=147), which was completed during an interview with the next of kin. The symptoms and signs elicited during the record review were classified as psychiatric or neurological according to the system described in a previous publication on clinical features in vCJD<sup>7</sup>. (Table 2)

## Results

### *1. Basic demographics*

One hundred and fifty cases of vCJD were identified in the UK between 1995 and 2005. Autopsy was undertaken in 106 cases (definite cases) and 44 cases were classified as clinically probable. Of 150 cases, 84 were male and 66 were female (gender ratio=1.2; 1). The median age at onset was 26 years (mean 28 years, range 12-74 years) with a median age at death 28 years (mean 30.1 years; range 15-75 years). The median duration of illness was 14 months (mean 15.7 months; range 6.5-40 months). One case remains alive, 96 months after onset.

### *2. Diagnosing vCJD*

#### a) Seeking medical attention

Individuals with vCJD rarely sought medical attention early in the clinical course. Overall, the median time from onset to the first point of medical contact was 2.5

months (mean 3.4 months; range: 0-12 months). The time to presentation to a medical practitioner was dependent on the nature of the early clinical features. Those presenting with neurological features (ie. cases with isolated neurological symptoms or a combination of neurological and psychiatric symptoms) presented earlier to a medical practitioner in comparison to those with isolated psychiatric features (neurological onset: 2 months; psychiatric onset: 3.3 months; combined 1.7 months; Kruskal Wallis test-  $p=0.04$ ). Once medical attention was sought a neurological aetiology was suspected in a minority of cases (27/150) and the proposed initial diagnosis in the majority of cases was of a psychiatric disorder (Table 3). vCJD was not considered a potential diagnosis in any case at the first point of medical contact.

#### b) Neurological referral

The mean time from onset to referral to a neurologist was 7.4 months (95% CI: 6.5 to 8). There was a trend towards those with neurological features being referred earlier, but this did not reach statistical significance (neurological onset = 6.8 months; psychiatric onset= 7.9 months; both features at onset: 6.8 months Kruskal Wallis=0.056). The mean time from neurological referral to review was only 16 days. Figure 1 illustrates the source of neurology referral. 48% of referrals came from general practitioners, 24% from psychiatrists and 19% from physicians. Nine referrals (6%) came from other sources including paediatrics, a chronic pain team clinician, orthopaedics, obstetrics, a maxillary facial surgeon and a doctor working in armed forces. In one case a family member insisted on a neurology review (by-passing the GP) and in 2 cases the information was not available

#### c) Neurology review

149/150<sup>a</sup> individuals were reviewed by a neurologist during the illness. 116 cases were initially reviewed either in an outpatient clinic or as a ward review and 33 were directly admitted via primary care. Overall, 138 cases were admitted as

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<sup>a</sup> In a single case investigated overseas it is unclear whether a neurological opinion was sought.

inpatients during the illness and 11 remained as outpatients. The proposed differential diagnosis following the initial neurological review is summarised in Table 4. The diagnosis of vCJD was suspected in 54/149 (36%) following neurological review.

d) Suspecting CJD<sup>b</sup>

The diagnosis of CJD was suspected in 147 cases with a mean time from onset to a suspect diagnosis of 8.9 months (95% CI: 8.3 - 9.7 months; representing 60% of mean total illness duration). The time to suspect CJD was independent of clinical features at onset (psychiatric 9.1 months (95% CI: 8.3 - 9.8); neurological 9.4 months (95% CI: 7.9 - 11.0, both=7.9 months (95% CI 6.1 - 9.7), Kruskal Wallis Test p=0.3). A neurologist most often suspected the diagnosis, but in about a third of cases the diagnosis was proposed by another speciality. It is of note that one in 9 cases of vCJD were suspected by a radiologist underlining the diagnostic value of brain MRI in diagnosing vCJD (Table 5).

Two cases were only identified following autopsy and in one case detailed information was not available. Of the two cases not identified in life, both were significantly older than the mean (74 years old and 68 years old at onset) and neither of these cases retrospectively fulfilled the diagnostic criteria for “probable” vCJD in life (Table 1).

It is of interest to assess whether time to diagnosis has changed during the period of the study. Figure 2 provides an overview of the time to suspect CJD by year of onset. This illustrates that the most significant decrease in time to diagnosis occurred during the first years following the identification of vCJD, namely 1994 and 1995, but there has been little subsequent change in this parameter. In addition, there is no statistically significant variation in time to suspect CJD by

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<sup>b</sup> The more ambiguous term of CJD is used. The reason for this was two fold. Firstly it allowed the first ten cases to be included prior to the initial description of vCJD. Prior to this report vCJD was not recognised as a clinical entity. Secondly, more often than not when vCJD was being considered at an early stage of the diagnostic process vague terms like CJD or prion disease were used.

UK region (Table 6) despite regional variation in vCJD incidence<sup>10</sup>. There is also no good evidence of variation in time to vCJD diagnosis by neurological centre (not shown).

e) Providing an early diagnosis (< 6 months from onset)

The diagnosis of vCJD was suspected in 38 cases within 6 months of onset. The median age at onset in this cohort was 25 years (range: 13-62 years) and the median duration of illness was 10.5 months (range: 6.5-26 months). 17/38 cases presented with psychiatric features at onset, 11 with isolated neurological features and 10 with a combination of features. The symptoms at onset were not significantly different from those diagnosed after 6 months (58/109, 35/109, 16/109 respectively). Despite this, there was a trend for those diagnosed earlier coming to medical attention earlier with the median time from onset to first medical contact of 1.7 months (range 0-6.5 months) in comparison to 3.2 months (range 0-12 months) in the later diagnosed cohort (Mann-Whitney  $p=0.08$ ). In addition, the time from onset to neurology referral was significantly shorter ; 3.5 months (range 1.4-6.3 months) versus 8.4 months (range 1-23 months: Mann-Whitney  $p<0.0001$ ). This may be explained by the development of early neurological symptoms/signs. Figure 3 summarises the median time from onset to the development of specific neurological symptoms or signs and demonstrates that cases diagnosed earlier developed neurological features at an earlier time after the onset of illness. It is also of note that the median time taken for individuals to become dependent was also significantly shorter in this cohort of patients. Independent mobility was lost at 5.2 months (range 4.5-25 months; compared to 10.2 months, range 7-28.5 months: Mann-Whitney  $p<0.0001$ ) and the time until bed bound was 8.1 months (range 4.5-25 months; compared to 14.2 months, range 7-28.5 months; Mann-Whitney  $p<0.0001$ ). Independent feeding was also lost at an earlier stage, as was continence. (6.2 months, range 2.6-8.8 months compared to 12.5 months, range: 2.9-27.6) months; 5.5 months, range 1.5-14 months compared to 12.8 months, range 2.9-27.6 months), respectively (Mann Whitney  $p<0.0001$ ).

f) Confirmation of the clinical diagnosis

The mean time for vCJD to be considered the most likely diagnosis in life (or in 10 cases pathologically proven following cortical biopsy) was 10.5 months (95% CI: 9.8-11.2 months). A local neurologist confirmed the diagnosis in almost 70% of cases; the NCJDSU or National Prion Clinic (NPC) in 25% of cases. By the time the diagnosis was judged most likely 72% of cases were classifiable as definite or probable vCJD and 9% were classifiable as possible according to the diagnostic criteria (Table 1). Despite vCJD being considered as the most likely diagnosis, 25 cases did not fulfil the criteria for either a probable or possible case at this time. In this cohort 3 had a duration of illness of less than 6 months and thus could not be classified as a probable case and the remainder lacked some of the “core” clinical features. 20/25 cases that did not fulfil the diagnostic criteria for definite or probable vCJD had a characteristic pulvinar sign on brain MRI.

Of the ten patients undergoing cortical biopsy 7 fulfilled diagnostic criteria for probable vCJD at the time of the procedure and 8 fulfilled these criteria at some stage during life. Of the remaining two cases, one could not be classified in view of complex co-morbidity.

Twenty nine patients underwent tonsil biopsy and 28 were positive (1 provided an equivocal result), but the time to reach a confident clinical diagnosis of vCJD in these cases was similar to patients that did not undergo tonsil biopsy (mean time to confident clinical diagnosis; 10.9 months vs 10.5 months). All cases undergoing tonsil biopsy fulfilled criteria for probable vCJD at some stage and 21/29 fulfilled the criteria for a probable case prior to tonsil biopsy.

The mean time from achieving a confident clinical diagnosis to death was only 5.2 months.

### *3. Surveillance*

Of the 148 cases in whom the diagnosis of CJD was suspected in life, 147 were referred to the NCJDSU in life. In one case vCJD was proposed as a potential diagnosis but referral to the NCJDSU was not undertaken. The overall mean time to referral was 9.8 months (95% CI: 9.2-10.6 months, representing 65% of the mean total illness duration)

## **Discussion**

This study highlights the difficulties in achieving an early diagnosis in vCJD and this was not possible in the great majority of cases. The explanation is multi-factorial but one component is the time taken to seek an initial medical opinion, with few patients attending a primary care physician within the first few months of illness (Figure 4). This is likely to reflect the nature of the early clinical features, which are often insidious in onset, subtle in character and common in the general population. This hypothesis is supported by sub-group analysis, which showed that the cohort of individuals exhibiting early neurological features sought medical attention earlier. At the initial medical contact a variety of diagnoses were proposed, but vCJD was not considered in a single case and a neurological aetiology was suspected in only a small number of cases. This is not surprising given the frequency of psychiatric features seen by primary care physicians<sup>11</sup>. Primary care physicians refer to what they consider to be the most appropriate hospital specialist, but utilisation of these services can take time and may result in delay in diagnosis if, as in vCJD, the clinical features at referral are misleading as to the true cause of the illness. Almost half the cases of vCJD were reviewed by a psychiatrist prior to neurological referral.

A neurological aetiology was usually suspected promptly following the development of objective neurological features and resulted in neurological referral in all cases (it is likely that the UK case investigated in another country also saw a neurologist). Neurological review was arranged promptly (a mean of 16 days from referral to neurology review) indicating that delay in waiting to see a neurologist contributed little to the overall time to achieve a diagnosis, which is of note if one considers that many individuals were seen promptly when waiting time for a neurology appointment in some areas was in excess of 6 months<sup>12</sup>, during the period of study. This also suggests that, although the diagnosis of vCJD may not have been considered at this stage, the referral to neurology was judged to be urgent because of progressive neurological deficits occurring in individuals usually in younger age groups.

The single most important determinant of early diagnosis was the presence of objective neurological features. The cohort of individuals diagnosed within 6 months had a more rapidly progressive illness course, with earlier objective neurological

features, and this is likely to account for the earlier diagnosis. The reason for the short duration of illness in some cases is unknown, but may reflect variation about a mean rather than a specific biological factor.

Once suspected, the diagnosis of vCJD was confirmed relatively quickly, obviating the need for further investigations such as brain biopsy and alleviating the stress of diagnostic uncertainty for the next of kin. The study also indicates that diagnostic delay is not due to an absence of helpful diagnostic investigations, indeed one in 9 cases were initially suspected following MRI brain scan. Only rarely did brain MRI fail to support the clinical diagnosis (7/150 cases) and the majority of negative scans did not include the most sensitive MRI sequence, namely FLAIR<sup>13</sup>. Tonsil biopsy was used to support the diagnosis in the minority of cases<sup>14</sup>, but did not lead to a significantly earlier diagnosis. However, this procedure may be of particular value in cases in which the MRI brain scan is not diagnostic or in countries with limited experience of the clinical features of vCJD.

The difficulty in achieving an accurate early diagnosis in vCJD has an important influence on patient management. Once the diagnosis is confirmed most individuals have significant neurological impairment and usually require assistance to mobilise and, after a short period, assistance to feed. Once neurological signs develop there is rapid progression with accumulating deficits with implications for management at home or in the community<sup>3,15</sup>. There may be a need for domiciliary nursing care, adaptations to accommodation and an appropriate care package. It is therefore crucial that families who wish to care for their affected relatives at home have support made available without delay. In view of the rapid neurological deterioration in vCJD, delay in accessing appropriate aids and services is clearly inappropriate and the Department of Health have put in place a dedicated National Care Package for patients with human prion disease 15.

An analysis of changes in the time to suspect vCJD was carried out to determine whether there has been a decrease in the time to diagnose vCJD as clinicians have gained experience of this new disease. Significant reductions in time to diagnosis occurred in the early years after the identification of vCJD, but have remained stable since. This is evident in both the time to suspect vCJD (Figure 2) and the time to

confirm vCJD (not shown). These findings indicate that increasing awareness of the clinical phenotype of vCJD has not resulted in an incremental decrease in time to diagnosis with the implication that further measures to increase knowledge of vCJD may not necessarily lead to an earlier diagnosis. It may be that the clinical presentation, with non-specific early features, makes prompt diagnosis intrinsically difficult.

On the other hand all but two cases of vCJD in the UK were suspected in life. The two cases in which vCJD had not been considered were significantly older than the mean and this may have led to a failure to consider the diagnosis, although in both of these cases there were complicating factors: in one case an MRI scan was carried out but did not include a FLAIR or DWI sequence and in the other the illness occurred in the context of a severe general medical condition with encephalopathy. An important question is whether cases are being overlooked in an elderly population. Although vCJD may not be as readily recognised in the elderly, the clinical phenotype does not vary with age and there is a significant decrease in mortality rates in those aged 40-60 years and older, which includes patients in age groups in which intensive investigation is likely. There is no evidence of regional variations in time to diagnose vCJD and support for the NCJDSU from clinicians in the UK has been outstanding with cases promptly referred once suspected from all regions in the UK.

This study has significant implications for therapeutic development. Extrapolation from both in-vitro and in-vivo studies indicates that to achieve significant efficacy it is likely that any proposed therapy should be introduced at an early stage of illness<sup>16</sup>. This paper indicates that early identification of vCJD is likely to be very difficult prior to the development of objective neurological features and raises the question as to whether accurate early diagnosis and early introduction of therapy is an achievable goal in the majority of cases. In addition the issue of diagnostic delay may have public health implications. To date, there have been four instances of secondary transmission of vCJD by blood transfusion<sup>17-20</sup> and four affected individuals have donated blood in the early clinical phase. There is also concern about the potential for secondary transmission via contaminated surgical instruments<sup>21</sup> and twenty surgical interventions were carried out after symptom onset and before diagnosis (Table 6).

Early diagnosis remains a challenge in human prion disease. The data in this analysis suggest that achieving this in vCJD is difficult and the non-specific early clinical features may prohibit early diagnosis in the majority of cases.

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## Reference List

1. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; 347: 921-25.
2. Will RG, Stewart GE, Zeidler M, MacLeod M, Knight R. Psychiatric features of new variant Creutzfeldt- Jakob disease. *Psychiatric Bulletin* 1999; 23: 264.
3. Myles S, Douglas MJ, Ward HJT, Campbell H, Will RG. Variant Creutzfeldt-Jakob disease: costs borne by families. *Health and Social Care in the Community* 2002; 10(2): 91-98.
4. Phillips. *The BSE Inquiry*. 1 ed. London: The Stationery Office; 2000
5. Zeidler M, Stewart GE, Barraclough CR, Bateman DE, Bates D, Burn DJ, Colchester AC, Durward W, Fletcher NA, Hawkins SA, MacKenzie J, RG Will. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. *Lancet* 1997; 350: 903-7.
6. Trevitt CR, Collinge J. A systematic review of prion therapeutics in experimental models. *Brain* 2006; 129: 2241-2265.
7. Spencer MD, Knight RSG, Will RG. First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. *British Medical Journal* 2002; 324: 1479-82.
8. Will RG, Zeidler M, Stewart GE, Macleod MA, Ironside JW, Cousens SN, MacKenzie J, Estibeiro K, Green AJE, Knight RSG. Diagnosis of new variant Creutzfeldt-Jakob disease. *Annals of Neurology* 2000; 47: 575-82.
9. World Health Organisation. *WHO manual for surveillance of human transmissible spongiform encephalopathies including variant CJD*. Geneva 2003.

10. Cousens S, Smith PG, Ward H, Everington D, Knight RSG, Zeidler M, Stewart G, Smith-Bathgate EAB, Macleod MA, Mackenzie J, Will RG. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. *Lancet* 2001; 357: 1002-1007.
11. Lepine J, Gastpar M, Mendlwicz J, Tylee A. Depression in the community: The first paneuropean study. *International Clinical Psychopharmacology* 1997; 12: 19-29.
12. ABN. UK Neurology: The next ten years. 1 ed. London: Association of British Neurologists; 2003.
13. Collie DA, Summers DM, Sellar RJ, Ironside JW, Cooper SA, Zeidler M, Knight RGS, Will RG. Diagnosing variant Creutzfeldt-Jakob disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. *American Journal of Neuroradiology*
14. Hill AF, Zeidler M, Ironside J, Collinge J. Diagnosis of new variant Creutzfeldt-Jakob disease by tonsil biopsy. *Lancet* 1997; 349: 99-100.
15. Weller B, Knight R, Will R. An overview of the care issues for Creutzfeldt-Jakob disease. *European Journal of Palliative Care* 2003; 10(1): 5-8.
16. Knight R. Therapeutic possibilities in CJD: patents 1996-1999. *Exp Opin Ther Patents* 2000; 10: 49-57.
17. Llewelyn CA, Hewitt PE, Knight RSG, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004; 363: 417-421
18. Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient. *Lancet* 2004; 364: 527-529.

19. Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006; 368: 2061-2067.
20. Health Protection Agency. Fourth case of transfusion-associated variant-CJD infection. *Health Protection Report* 2007; 1(3).
21. National Institute for Health and Clinical Excellence. Patient safety and reduction of risk of transmission of Creutzfeldt-Jakob disease (CJD) via interventional procedures. November 2006; ISBN 1-84629-310-3.

**Table 1 Current diagnostic criteria for vCJD**

<b>I</b>	<p><b>A</b> Progressive neuropsychiatric disorder</p> <p><b>B</b> Duration of illness &gt; 6 months</p> <p><b>C</b> Routine investigations do not suggest an alternative diagnosis</p> <p><b>D</b> No history of potential iatrogenic exposure</p> <p><b>E</b> No evidence of a familial form of TSE</p>
<b>II</b>	<p><b>A</b> Early psychiatric features<sup>a</sup></p> <p><b>B</b> Persistent painful sensory symptoms<sup>b</sup></p> <p><b>C</b> Ataxia</p> <p><b>D</b> Myoclonus or chorea or dystonia</p> <p><b>E</b> Dementia</p>
<b>III</b>	<p><b>A</b> EEG does not show the typical appearance of sporadic CJD<sup>c</sup> in the early stages of illness</p> <p><b>B</b> Bilateral pulvinar high signal on MRI scan</p>
<b>IV</b>	<p><b>A</b> Positive tonsil biopsy<sup>d</sup></p>

**Definite:** IA **and** neuropathological confirmation of vCJD<sup>e</sup>

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

*or*

I **and** IVA

**Possible:** I **and** 4/5 of II **and** IIIA

<sup>a</sup> depression, anxiety, apathy, withdrawal, delusions.

<sup>b</sup> this includes both frank pain and/or dysaesthesia.

<sup>c</sup> the typical appearance of the EEG in sporadic CJD consists of generalised triphasic periodic complexes at approximately one per second. These may occasionally been seen in the late stages of variant CJD.

<sup>d</sup> tonsil biopsy is **not** recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.

<sup>e</sup> spongiform change and extensive PrP deposition with florid plaques throughout the cerebrum and cerebellum.

**Table 2: Categorisation of clinical features in vCJD**

<b>Psychiatric Features</b>	<b>Neurological features</b>
Anxiety	Gait disturbance
Irritability	Impairment of language
Insomnia	Pyramidal features
Social Withdrawal	Impaired coordination
Loss of interest	Impaired concentration
Dysphoria	Poor memory
Aggression	Myoclonus
Tearfulness	Dementia
Agitation	Abnormality of ocular motility
Weight Loss	Hypoaesthesia
Psychomotor retardation	Tremor
Behavioural change	Paraesthesia
Anergia	Dystonia
Poor Performance	Chorea
Hypersomnia	Other involuntary movements
Hallucinations	Pain
Paranoid delusions	Visual symptoms
Inappropriate affect	Primitive reflexes
Obsessive features	Swallowing impairment
Suicidal ideation	Incontinence
Panic attacks	Headache
Diurnal mood variation	Dizziness
Loss of confidence	Dysdiadochokinesia
Bizarre behaviour	Extrapyramidal features
Paranoid ideation	Seizures
Lack of emotion	Facial weakness
Change in eating preferences	Taste disturbance
	Hyperacusis

**Table 3 Proposed diagnosis following initial presentation to a medical practitioner**

	<i>Number of cases</i>	<i>Percentage(%)</i>
Depression	76	50.7
“Neurological”	27	18
Diagnosis	19	12.7
“unclear”		
*Other	12	8
Anxiety	7	4.6
“Stress”	4	2.7
Psychotic illness	2	1.3
Functional illness	1	0.7
No diagnosis suggested	2	1.3
Total	150	100

\*\*other” include- orthopaedic problems (n=3), glandular fever (n=3), an endocrine abnormality, asthma, a dental problem, a viral illness, anorexia nervosa and a grief reaction.

**Table 4: Proposed differential diagnosis at first review by a neurologist (some cases had more than one possible diagnosis)**

<i>Differential Diagnosis</i>	<i>Frequency</i>
vCJD	54
Infectious/post-infectious	41
Vasculitis	38
Demyelination (MS)	34
Wilson's disease	34
"Metabolic disease"	29
Malignancy/paraneoplastic	25
Non-organic	16
Huntington's disease	11
Neuroacanthocytosis	8
Drugs (illicit drug use or adverse drug reactions)	7
"Encephalopathy-unknown origin"	7
"Inflammatory disorder"	7
Porphyria	4
Hereditary ataxia (SCA, FA)	4
sCJD	4
Whipple's disease	3
Mitochondrial disorder	3
Posterior fossa "lesion"	3
Other*	34

\* Other includes: "sub-acute cerebellar syndrome", complex partial status, Alzheimer's, fronto-temporal dementia, Parkinson's disease, normal pressure hydrocephalus, alcohol related cerebellar degeneration, glioma, AV fistula, Leigh's syndrome, "leukodystrophy", sub-acute combined degeneration, "storage disorder", limbic encephalitis, Wernicke's Encephalopathy, toxins

**Table 5 Who suggested the diagnosis of CJD?**

<i>Diagnosis by:</i>	<i>Frequency</i>	<i>Percentage(%)</i>
Neurologist	100	66.7
Radiologist	17	11.4
Other*	11	7.3
Psychiatrist	9	6.0
GP	8	5.3
Not suspected**	3	2.0
Physician	2	1.3
Total	150	100

\* Including: psychology, genetics, NCJDSU, paediatrics, accident and emergency and next of kin.

\*\* In two cases the diagnosis was not suspected and in a single case it is impossible to determine who made the diagnosis.

**Table 6 Regional variation in “time to suspect CJD”**

<i>Region</i>	<i>No of cases</i>	<i>Mean time months (95% CI)</i>
South East England	38	8.6 (7.6 to 9.7)
North West England	24	9.6 (8.1 to 11.1)
Scotland	21	8.3 (6.7 to 9.9)
North East England	18	8.3 (6 to 10.7)
South West England	16	9.6 (7 to 12.2)
“Midlands”	11	9.7 (4.8 to 14.7)
“Yorkshire”	11	10.1 (7.5 to 12.7)
Wales	5	8.6 (5.8 to 11.3)
Northern Ireland	3	5.1 (0 to 12.7)
Total	147	8.9 (8.3 to 9.7)

“The Midlands”= Birmingham, Nottingham, Leicester

“Yorkshire”= Leeds, Bradford, Sheffield

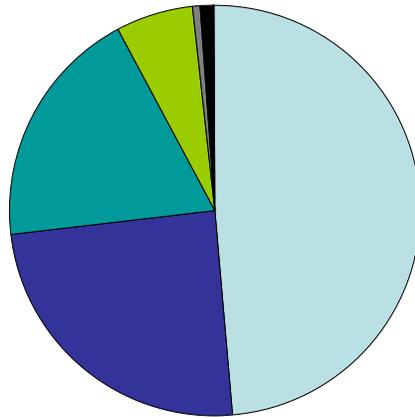
**Table 7 Surgical procedures\* (n=20) after onset and before diagnosis in 18/150 cases.**

<b>Case</b>	<b>Procedure</b>
1	Sutures to eyelid following road traffic accident
2	Caesarian section
3	Colonoscopy
4	Tooth extraction
5	Fenton's procedure (repair of episiotomy)
6	Skin removed surgically after burn to foot
7	Caesarian section
8	Wisdom teeth removed
9	Removal of epididymal cyst left testicle
10	Arthroscopy Elevation of left nasal bone
11	Caesarian section
12	Caesarian section
13	Pins and plate inserted in ankle
14	Hysteroscopy
15	Endoscopy and small bowel biopsies
16	MUA and percutaneous K wire second left metacarpal Hand infected – K wire removed
17	Watson/Jones reconstruction of ankle
18	Sutures to eyebrow

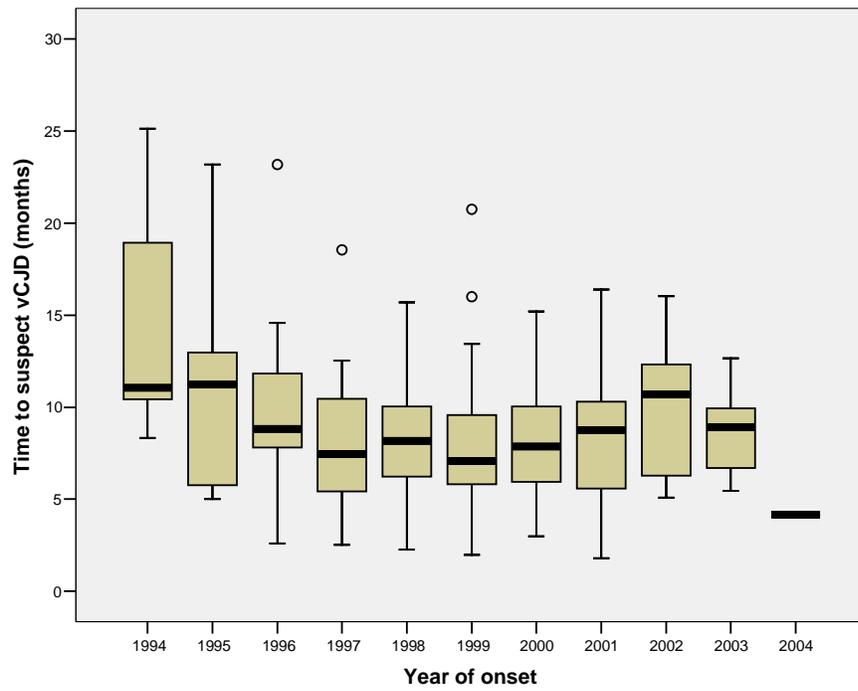
\*procedures relating to work up of the current diagnosis are not included

**Figure 1**      **Source of Neurology Referral**

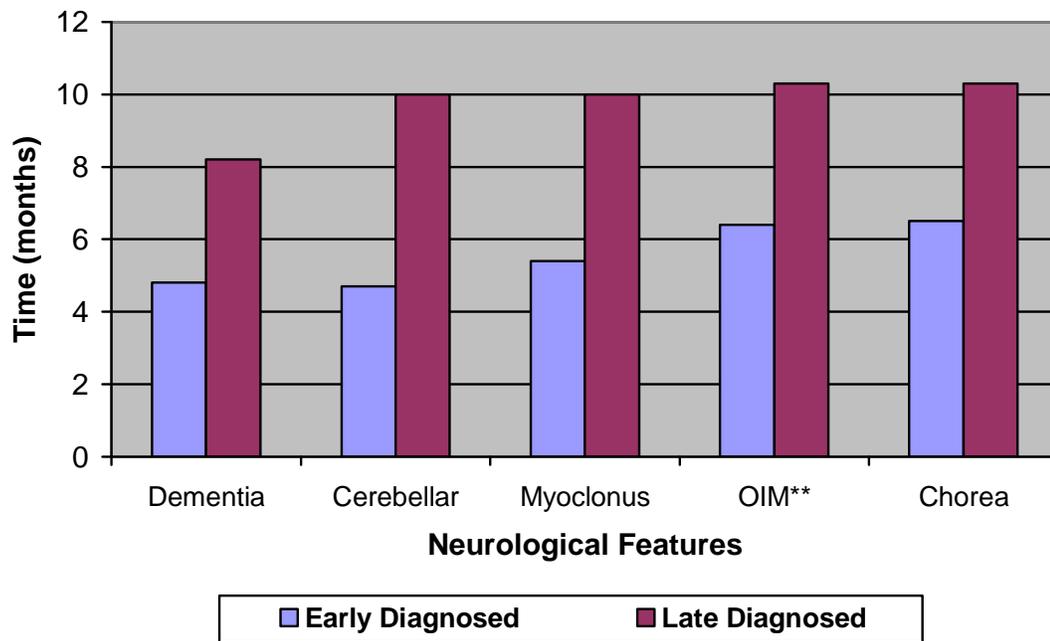
□ GP   ■ Psychiatrist   ■ Physician   ■ Other   ■ Family   ■ Info not available



**Figure 2 Time to suspect CJD by year of onset (n=147) (Median, range and 95% CI)**



**Figure 3 Development of “hard” neurological features  
Comparison of “early and late diagnosed” cohort\***



\* Less than 6 months (n=38) compared to diagnosed after 6 months (“later diagnosed” n=109)

\*\* OIM=other involuntary movements

**Figure 4 Time course in variant CJD in relation to the diagnostic process  
(Mean time in months)**

