ORIGINAL ARTICLE

Validation of Diagnostic Criteria for Variant Creutzfeldt–Jakob Disease

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Objective: Variant Creutzfeldt–Jakob disease (vCJD), a novel form of human prion disease, was recognized in 1996. The disease affected a younger cohort than sporadic CJD, and the early clinical course was dominated by psychiatric and sensory symptoms. In an attempt to aid diagnosis and establish standardization between surveillance networks, diagnostic criteria were established. These were devised from the features of a small number of cases and modified in 2000 as the clinical phenotype was established. Since then, only minor changes have been introduced; revalidation of the criteria in the current format is overdue.
Methods: Included in this study are autopsy/cerebral biopsy-proven cases of vCJD referred to the National CJD Surveillance Unit (NCJDSU) between 1995 and 2004 and suspect cases in which an alternative diagnosis was identified following autopsy/cerebral biopsy.
Results: Over the 10-year period, 106 definite cases of vCJD and 45 pathologically confirmed "noncases" were identified from the archives of the NCJDSU. The median age at onset of the cases was significantly younger than that of the noncases (27 years [range, 12–74 years] vs 43 years [range, 10–64 years]), and the median duration of illness was significantly shorter (14 months [range, 6–39 months] vs 22 months [range, 2–139 months]). The most commonly identified core clinical feature in cases was dementia; persistent painful sensory symptoms were the least frequent. Eighty-eight of 106 (83%) vCJD cases were retrospectively classified as probable in life, 6 cases were classified as possible. Most cases were classified as probable on the basis of core clinical features and brain magnetic resonance imaging. To date, the diagnostic criteria remain 100% specific, with no autopsy/cerebral biopsy-proven noncases classified as probable in life.
Interpretation: This study confirms that the diagnostic criteria for vCJD are sensitive and specific and provide a useful standard framework for case classification in a surveillance setting.

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In 1996, variant Creutzfeldt–Jakob disease (vCJD), a novel form of human prion disease with unusual clinical and demographic features, was recognized. The disease affected a younger cohort than was commonly recognized in sporadic CJD (sCJD), and the clinical phenotype appeared to be distinct, with psychiatric and painful sensory symptoms dominating the early clinical course.[1] In an attempt to facilitate the diagnosis of this emerging strain of human prion disease and provide a standard framework for case classification, diagnostic criteria for vCJD were formulated and later adopted by the World Health Organization.[2]

Experience gained from a small number of early cases allowed the formulation of the original criteria, and as the clinical phenotype became more established, modifications were introduced.[3] To incorporate the diagnostic

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TABLE 1: Current Diagnostic Criteria for vCJD

Subsection	Item	Criterion
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 features[a]
	B	Persistent painful sensory symptoms[b]
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sporadic CJD[c] in the early stages of illness
	B	Bilateral pulvinar high signal on MRI scan
IV	A	Positive tonsil biopsy[d]

Definite: IA and neuropathological confirmation of vCJD.[e]
Probable: I and 4/5 of II and IIIA and IIIB; or I and IVA.
Possible: I and 4/5 of II and IIIA.
[a]Depression, anxiety, apathy, withdrawal, delusions.
[b]This includes frank pain and/or dysesthesia.
[c]The typical appearance of the EEG in sporadic CJD consists of generalized triphasic periodic complexes at approximately 1 per second. These may occasionally be seen in the late stages of vCJD.
[d]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.
[e]Spongiform change and extensive prion protein deposition with florid plaques throughout the cerebrum and cerebellum.
vCJD = variant Creutzfeldt–Jakob disease; TSE = transmissible spongiform encephalopathy; EEG = electroencephalography; MRI = magnetic resonance imaging.

value of tonsil biopsy, an amendment was introduced in 2002.[4] Since then, the criteria have remained unchanged, except for the addition of a footnote relating to electroencephalographic (EEG) findings (Table 1). Case classification is based on both core clinical features and investigative aids, with autopsy/cerebral biopsy required for a definitive classification. Cases are considered "probable" if the core clinical features are present in combination with a characteristic brain magnetic resonance imaging (MRI) showing the pulvinar sign[5] or deposition of disease-associated prion protein on tonsil biopsy.[6] The absence of any supportive investigations in combination with the core clinical features result in a "possible" classification.

Despite the recognized value of the criteria to those involved in surveillance, formal validation of the current criteria is overdue.

The aim of this study was to evaluate the current diagnostic criteria for vCJD in a large cohort of pathologically confirmed cases identified by the CJD surveillance system in the UK.

Patients and Methods

Prospective surveillance of CJD in the UK has been ongoing since May 1990. The methodology of the National CJD Surveillance Unit (NCJDSU) has been described in previous studies.[3,7]

Included in this study are autopsy/cerebral biopsy-proven vCJD cases referred to the NCJDSU between 1995 and 2004.

The clinical and investigative phenotype was established following retrospective analysis of NCJDSU records of 106 confirmed vCJD cases, including hospital records (n = 105), general practitioner (GP) records (n = 104), and a detailed questionnaire (n = 104). The information contained in the semistructured questionnaire was obtained following an interview with the next of kin. Brain MRI was only considered positive if reviewed by the NCJDSU staff. Tonsil biopsy material was reviewed by a neuropathologist at either the NCJDSU or the National Prion Clinic, London.

The clinical and investigative phenotype of a cohort of pathologically proven "noncases" (n = 45) was also established. This cohort consisted of suspect cases (considered to be potential cases in life) in which an alternative diagnosis was estab-

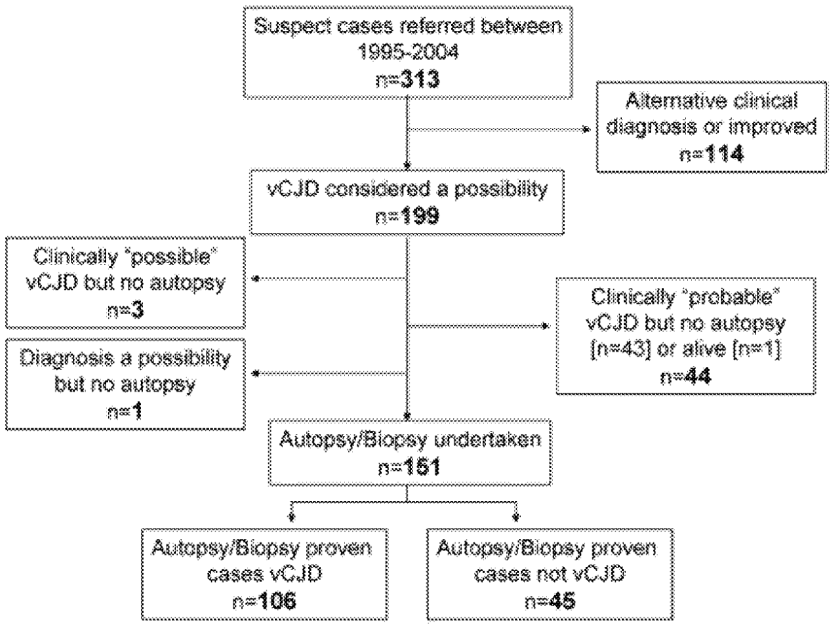

FIGURE 1: Outcome of suspect cases of variant Creutzfeldt–Jakob disease (vCJD) referred between 1995 and 2004.

lished at autopsy/cerebral biopsy. Clinical information in these cases came from hospital records (n = 28) or detailed questionnaire (n = 29); only rarely were GP notes requested (n = 4).

In addition, there were 114 cases of suspected vCJD, without autopsy or cerebral biopsy, in which there was judged to be an alternative clinical diagnosis or in which stabilization or improvement made the diagnosis of vCJD unlikely. With the exception of 12 cases in which specific details such as date of birth were unknown, these suspect cases were flagged at the Office of National Statistics (ONS) so that death certificates could be forwarded for those who died.

Results

Basic Demographics

A total of 313 suspect cases of vCJD were identified between 1995 and 2004. In 150 cases, the clinical diagnosis was vCJD (autopsy/cerebral biopsy confirmation in 106 and 44 with a classification as probable vCJD). In 3 cases, the final classification was possible vCJD. In 1 case, which did not fulfill criteria for possible vCJD and in which no autopsy/cerebral biopsy was carried out, the diagnosis of vCJD was still thought to be a possibility (the diagnosis could neither be confirmed nor refuted, but the clinical phenotype was consistent with vCJD). In addition, 114 cases with an alternative clinical diagnosis were established, and in 45 other cases an alternative diagnosis was established at autopsy/cerebral biopsy (definite noncases) (Fig 1).

Of the 106 definite cases of vCJD, 62 were male, and 44 were female. The median age at onset was 27 years (mean, 28 years; range, 12–74 years), with a median age at death of 28 years (mean, 30 years; range, 14–74 years). The median duration of illness was 14 months (mean, 15 months) with a range of 6 to 39 months.

Of the 45 noncases, 27 were male, and 18 were female. The median age at onset of the noncases was significantly older than that of the cases at 43 years (mean, 40 years; range, 10–64 years; Mann–Whitney $p < 0.001$), with a median age at death of 44 years (mean, 42 years; range, 15–66 years). Median duration of illness was significantly longer at 22 months (mean, 31 months; range, 2–139 months; Mann–Whitney $p < 0.001$).

Overall Assessment of Diagnostic Criteria

Assessment of the diagnostic criteria was undertaken using autopsy/cerebral biopsy-proven cases and autopsy/cerebral biopsy-proven not cases. All 106 definite cases fulfilled the preconditions in section I of the current criteria for vCJD.

Clinical Features—Section II

The frequency of core clinical features in the cases from subsection II is highlighted in Table 2. The most frequently identified clinical features were dementia (100%), ataxia (97%), involuntary movements (94%), and early psychiatric features (92%). Although persistent painful sensory symptoms are the least common clinical feature identified from the clinical requirements in subsection II, they were present in nearly $\frac{2}{3}$ of cases (63%).

Investigations

A positive brain MRI was identified in 96/106 cases (91%). In 15 cases, a tonsil biopsy was undertaken, with a positive biopsy in all but 1 case. A summary of the

TABLE 2: Frequency of Core Clinical Features from Subsection II of Diagnostic Criteria

Clinical Feature	Frequency	%
Dementia	106	100
Ataxia	103	97
Chorea, myoclonus, or dystonia	100	94
Early psychiatric features	98	92
Persistent painful sensory symptoms	67	63

clinical and investigative features of the 106 confirmed cases is shown in Figure 2.

Eighty-eight of 106 (83%) cases were retrospectively classified as probable cases in life. Of the 88 probable cases, 85 were classified on the basis of core clinical features and brain MRI, and only 3 with a positive tonsil biopsy. In each of the 3 cases, a positive MRI was available in life, but insufficient clinical features at the time of imaging prevented classification as a probable case prior to tonsil biopsy. The mean time to achieve a classification as a probable case was similar regardless of which investigative aid was used for classification (brain MRI, 9.5 months vs tonsil biopsy, 11.7 months).

A total of 205 EEGs were carried out on the 106 patients. A single EEG was carried out in 36 cases, 46 cases had 2 EEGs, 17 cases had 3 EEGs, 5 cases had 4 EEGs, 1 case had 6 EEGs, and 1 case had no EEGs. A typical EEG was not identified in any case of vCJD.

How Many Confirmed Cases Were Classified as Probable in Life?

Assessment of the sensitivity of the current vCJD diagnostic criteria was provided by analysis of the pathologically proven cases of vCJD. Eighty-eight of 106 (83%) cases were retrospectively classified as probable cases in life. The mean time from onset to classification as a probable case was 9.5 months (95% confidence interval, 8.9–10.2), corresponding to 66% of overall mean total illness duration. Fifty-two of 88 (59%) probable cases demonstrated all the core clinical features from subsection II of the current diagnostic criteria. The remaining 36/88 (41%) had 4/5 criteria required in subsection II.

How Many Confirmed Cases Were Classified as Possible in Life?

Six pathologically confirmed cases were retrospectively classified as possible cases in life. In each case, the core clinical features were present, but specific investigations were negative. In 2 cases, no MRI scan was available for review. In the remaining 4 cases, 2 had a single MRI brain and 2 underwent 2 MRI brain scans. However, only 1 case had a diagnostic quality fluid attenuated inversion recovery (FLAIR) sequence, and this was reported as equivocal (demonstrating extensive high signal in caudate, putamen, and pulvinar of equal intensity). The overall mean time to the first brain MRI in these cases was 9.2 months; all were carried out at a time when significant neurological dysfunction was present. Tonsil or brain biopsy was not carried out in any of the 6 cases.

Cases That Did Not Fulfill the Diagnostic Criteria

Twelve of 106 cases did not fulfill the diagnostic criteria for a probable or possible case. The explanation for this in 8 cases was a lack of core clinical features, in 3 cases preexisting comorbidity prevented accurate assessment of clinical phenotype, and in 1 case only limited clinical information was available.

Dementia was a universal finding. In 7 cases, persistent painful sensory symptoms were not identified, with

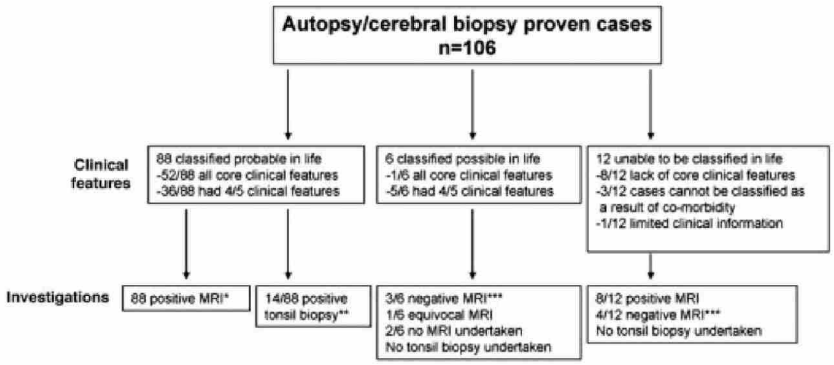

FIGURE 2: Summary of clinical and investigative features of pathologically proven cases of variant Creutzfeldt–Jakob disease. *Eighty-five of 88 classified on the basis of clinical features and brain magnetic resonance imaging (MRI). **Three of 14 positive tonsil biopsy allowed the probable criteria to be applied. In 11/14, the cases were already probable on the basis of brain MRI prior to biopsy. ***In these cases, the most sensitive sequence of MRI was not utilized.

TABLE 3: Clinical Phenotype of Cases That Do Not Fulfill the Diagnostic Criteria for Either a Probable or a Possible Case in Life

Case No.	Clinical Features Not Identified in Life	Brain MRI
1	No persistent painful sensory symptoms or ataxia	Positive
2	Limited clinical information[a]	Not available
3	No early psychiatric features or persistent painful sensory symptoms	Normal T1, T2, PD
4	No persistent painful sensory symptoms or ataxia	Normal T1, T2, PD
5	No early psychiatric features or persistent painful sensory symptoms	Positive
6	Complicated by pre-existing comorbidity[b]	Positive
7	No early psychiatric features or persistent painful sensory symptoms	Positive
8	Complicated by pre-existing comorbidity[b]	Positive
9	No persistent painful sensory symptoms or involuntary movements	Positive
10	No early psychiatric features or persistent painful sensory features	Positive
11	No involuntary movements or clear ataxia	Not available
12	Complicated by pre-existing comorbidity[b]	Positive

[a]Investigated in Spain.
[b]Premorbid conditions that made interpretation impossible include: choreoathetoid cerebral palsy, liver transplantation/hepatic encephalopathy, and learning disability.
MRI = magnetic resonance imaging; PD = proton density.

early psychiatric features absent in 4. In 3 cases, ataxia was not present, and 2 did not have involuntary movements. A detailed summary of absent clinical features is presented in Table 3.

In the 12 cases that did not fulfill the diagnostic criteria for either possible or probable vCJD, 8 had a positive MRI. Of the remaining 4 cases, none underwent a diagnostic quality FLAIR sequence (in 2 cases no scan was available for review, and in 2 cases limited sequences were available: axial T1, T2, and proton density).

Assessment of the Specificity of the Diagnostic Criteria for vCJD

Autopsy/cerebral biopsy was undertaken in 45 suspect cases in which an alternative neuropathological diagnosis to vCJD was identified. Of these, 32 cases did not fulfill the diagnostic criteria for vCJD, with only 13 classifiable as possible cases. A typical MRI brain scan was not identified within this cohort, and a single patient underwent a tonsil biopsy, which was negative. The cause of death is listed in Table 4. Interestingly, despite undergoing an autopsy/cerebral biopsy, a definitive diagnosis was not obtained in 5 cases, but in these cases there was no evidence of prion disease despite intense investigation.

The characteristic clinical features of the noncases are summarized in Figures 3 and 4 in comparison to vCJD. The noncases share many of the clinical features characteristic of vCJD, but the frequency of those core clinical fea-

TABLE 4: Cause of Death of Pathologically Proven Noncases

Cause of Death	Frequency
Sporadic CJD	11
Alzheimer disease	7
No definitive diagnosis reached	5
Paraneoplastic/malignancy	3
Viral encephalitis	3
Frontotemporal dementia	2
Demyelination	2
Subacute sclerosing panencephalitis	2
Myocardial fibrosis	2
Cerebrovascular disease	1
Metabolic disorder	1
Multisystem atrophy	1
Huntington disease	1
Wilson's disease	1
Autoimmune limbic encephalitis	1
Encephalitis, origin unknown	1
Dentatorubropallidoluysian atrophy	1

CJD = Creutzfeldt–Jakob disease.

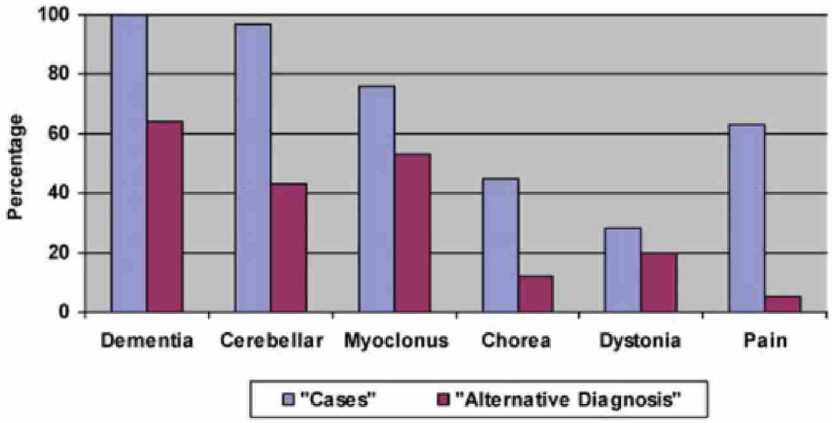

FIGURE 3: A comparison of definite cases versus those with an alternative diagnosis following autopsy/cerebral biopsy is shown by neurological features. Fisher exact test: dementia/cerebellar/chorea/pain, $p < 0.001$; myoclonus, $p < 0.04$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

tures (dementia, early psychiatric features, ataxia, painful sensory symptoms, and involuntary movements) is reduced in comparison to vCJD. Painful sensory features, a clinical feature that is less commonly identified than the other core clinical features in vCJD cases, is significantly less frequent in noncases in comparison to true cases.

Table 5 provides a summary of the overall value of the diagnostic criteria in autopsy-proven cases and noncases.

Case in Which the Highest Classification Was Probable vCJD

Forty-four cases had a classification of probable vCJD, and all, by definition, fulfilled the preconditions and exhibited at least 4 of 5 clinical features. The median age at onset was 25 years (mean, 27 years), and the median duration of illness was 15 months (mean, 17 months). This was similar to the pathologically confirmed cases. Thirty-eight cases were classified as probable on the basis of a positive MRI brain scan and 6 on the basis of a positive tonsil biopsy.

Diagnostic Outcome in Possible vCJD Cases

A retrospective analysis of the clinical features in all suspected cases of vCJD from 1995 to 2004 was carried out to identify cases that at some stage fulfilled criteria for classification as a possible case of vCJD. A total of 99 such cases were identified, and the final classification in this group was definite or probable vCJD in 83, possible vCJD in 3, sporadic CJD in 8, and not CJD in 5. Of these 5 cases, 3 had pathological diagnoses of Alzheimer disease, viral encephalitis, and subacute sclerosing panencephalitis. In 1 case, a clinical diagnosis of Wilson's disease was established, and the case remains alive. Finally, in a single case, significant improvement occurred, although a formal diagnosis has not been established.

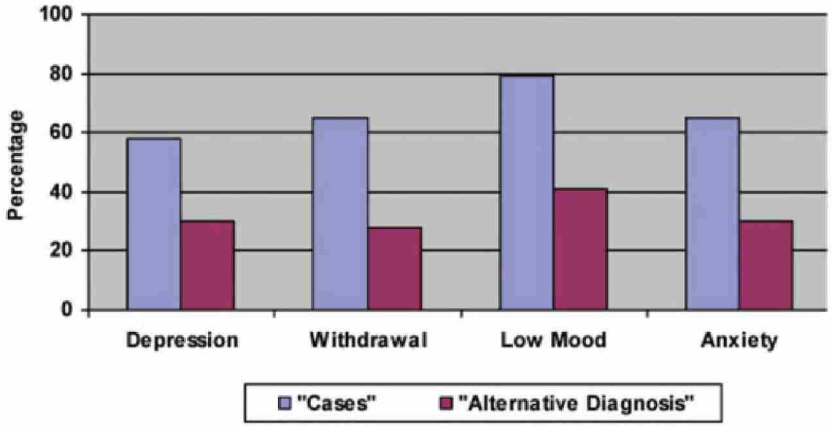

FIGURE 4: A comparison of definite cases versus those with an alternative diagnosis following autopsy/cerebral biopsy is shown by psychiatric features. Anxiety/withdrawal, $p < 0.02$ (Fisher exact test); depression, $p < 0.03$ (Fisher exact test); low mood, $p < 0.001$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 5: Overall Value of the Diagnostic Criteria Using Autopsy-Proven/Cerebral-Proven Cases and Noncases

Diagnosis	Autopsy-Proven Cases (sensitivity = 83%)	Autopsy-Proven Noncases (specificity = 100%)
Probable in life classification (positive predictive value = 100%)	88	0
Unable to classify as probable in life (negative predictive value = 71%)	18	45

Outcome in Suspect Cases Classified as Not CJD

There were 114 suspect cases in which there was an alternative clinical diagnosis or in which stabilization or improvement made the diagnosis of vCJD unlikely (Tables 6 and 7). In 25 patients, death certificates were obtained from ONS, and the causes of death listed on death certificates included Alzheimer disease, dementia, and a range of other neurological diagnoses. No case was certified as dying of vCJD. In 89 cases, no death certificates were forwarded by ONS, and these cases are presumed to be still alive. The mean age at referral in these cases was 31 years (range, 8–75 years), and the mean time elapsed since referral is 9.8 years (range, 4.7–13.7 years).

Discussion

This study indicates that the current diagnostic criteria have a high sensitivity and specificity for the diagnosis of vCJD, based on an assessment of cases referred between

TABLE 6: Alternative Clinical Diagnosis—Dead (n = 25)

Status	Number	Flagged
Improved/recovered	31	27[a]
No deterioration/condition stabilized	6	5
Encephalitis/encephalopathy, unknown cause	2	2
Progressive painful neuropathy with history of forgetfulness	1	1
Cerebral vasculitis	2	1
Wilson disease	1	1
Cortical LBD and/or Alzheimer disease	1	1
Possible hyperprolactinemia	1	1
Metachromatic leukodystrophy	1	1
Nonorganic cognitive syndrome with jerking movements	1	1
Anxiety related	1	0[a]
Susac syndrome	1	1
Type II spinocerebellar ataxia	1	1
GSS (Q212P mutation)	1	1
Primary cerebellar syndrome, unknown cause	1	1
Picture complicated by probability of cerebrovascular disease	1	1
Undiagnosed	1	1
At referral/visit NCJDSU vCJD considered unlikely because of lack of clinical features and/or results of investigations not supportive	29	25
No follow-up information available	6[b]	5

[a]One case emigrated.
[b]Only 1 case with no follow-up information that could not be flagged at the Office of National Statistics because date of birth was unknown.
LBD = Lewy body dementia; GSS = Gerstmann-Sträussler-Scheinker disease; NCJDSU = National CJD Surveillance Unit; vCJD = variant Creutzfeldt–Jakob disease.

TABLE 7: Alternative Clinical Diagnosis—Alive (n = 89)

Cause of Death Shown on Death Certificate	No.
Alzheimer disease	3
Dementia	5
Encephalitis	3
Parkinson disease/dementia	1
Huntington chorea	1
Limb girdle muscular dystrophy	1
Cancer	2
Acute myocardial infarction/dementia	1
Hypoxic encephalopathy/epilepsy	1
Head injury	1
Atypical leukoencephalopathy	1
Possible sporadic Creutzfeldt–Jakob disease	1
Myoclonic encephalopathy of uncertain cause	1
Pneumonia	1
Drowning	1
Degenerative neurological disorder	1

1995 and 2004. The vCJD epidemic is in decline, and this conclusion is consistent with the findings in the small number of subsequent cases in the UK (n = 18) and elsewhere. Eighty-three percent (88/106) of pathologically proven cases were classified as clinically probable in life, and the criteria allow differentiation of true cases from suspect cases with an alternative diagnosis with a high degree of confidence.

All of the core clinical features from subsection II of the current criteria are more commonly identified in cases in comparison to noncases. Dementia is a universal feature of vCJD and ataxia; involuntary movements and early psychiatric features occur in >90% of cases. Painful sensory symptoms were not reported in over a third of patients, but are useful at differentiating cases from noncases, justifying their continued inclusion in the criteria. Although the criteria have a high sensitivity, it is important to consider factors that led to an overall reduction in sensitivity. Analysis of autopsy/cerebral biopsy-only cases may underestimate the true sensitivity. Overall, as experience of vCJD has accumulated, the need for autopsy/cerebral biopsy to allow a confident diagnosis has declined, and this has been reflected in declining autopsy rates with time. Autopsy/cerebral biopsy is more likely to be undertaken in cases with unusual phenotypes or in which there is significant diagnostic doubt, leading to an overall reduction in the sensitivity (as only autopsy/cerebral biopsy-proven cases were included in analysis). It would be inappropriate to include probable cases in a formal assessment of the diagnostic criteria, but on the assumption that the probable cases truly had vCJD, the criteria have a sensitivity of 88% (132/150). Utilization of the most sensitive sequence of brain MRI may further increase sensitivity. Only 1/6 confirmed cases with a final classification in life as possible vCJD had a diagnostic quality FLAIR sequence on MRI brain scan. It is possible (given an overall sensitivity of MRI with FLAIR sequences of 98%) that FLAIR sequences in these cases may have been positive, leading to a classification as probable vCJD. Also, in 4/12 confirmed cases not classifiable as probable or possible vCJD, limited information or associated comorbidity meant that case classification was impossible. It is likely that the sensitivity of the criteria is significantly higher than the figure of 83% in cases with full clinical information and in which FLAIR MRI sequences are obtained.

Even if one accepts the above assumptions to be correct, there remains a small but important cohort for whom the "probable" classification cannot be applied (9/108 cases if the above conditions are assumed to be correct). It is of note that, except for 1 case dying in 2003, all of the cases not classifiable as probable vCJD in life died in 2000 or earlier. The increased recognition of the importance of obtaining the most sensitive MRI sequences and the use of tonsil biopsy in MRI-negative suspect cases may explain the absence of such cases in recent years.

The high sensitivity of the criteria in their current form is not obtained at the expense of specificity. In the 10 years of surveillance in the UK covered by the study (and subsequently), we have not identified any case classified in life as probable vCJD in which an alternative diagnosis was discovered at autopsy/cerebral biopsy. It is important to consider the precise definition of specificity for the purpose of this study and whether the use of this term is appropriate given the fact that only autopsy/cerebral biopsy-proven cases were included. Complete analysis would include all potential cases referred within the study period, not just the autopsy/cerebral biopsy-proven noncases. For complete analysis, 2 other groups would require further evaluation to ensure the statement concerning specificity is correct. This includes the cohort of patients suspected of having vCJD who did not undergo autopsy/cerebral biopsy. The postmortem/cerebral biopsy rate in vCJD suspects was 75%, and the number of potential cases who died without autopsy/cerebral biopsy or another plausible explanation for the clinical pre-

sentation was relatively small. Although the diagnosis in these cases has not been confirmed, sustained clinical improvement excludes the diagnosis of vCJD, and in the great majority of the remaining cases an alternative diagnosis was suggested on investigation (Table 6). In a minority of suspect cases without postmortem, the diagnosis of vCJD was judged to be unlikely on the basis of prolonged survival.

Three cases had a final classification as possible vCJD. An assessment of the likelihood that these cases were truly suffering from vCJD is important, because by convention only definite and probable vCJD cases are officially reported nationally and internationally. Furthermore, a fourth possible case of vCJD has been identified recently in the UK, and this was an individual with a MV genotype at codon 129 of the prion protein gene.[8,9] To date, 148/168 cases of vCJD in the UK with available genetic analysis and 44/44 vCJD cases in other countries have been methionine homozygous (in the remaining UK cases genetic analysis was not available) at this locus, and the identification of a case of vCJD with an MV genotype would indicate that individuals with this genotype were susceptible to bovine spongiform encephalopathy infection, with implications for the potential future course of the vCJD outbreak. Analysis of the diagnostic outcome of suspect cases classifiable as possible vCJD in this study indicates that 83/99 were finally classified as definite or probable vCJD, suggesting that there is an 84% chance that a possible case of vCJD is actually suffering from this condition.

vCJD has been identified in a number of countries outside the UK, and no case fulfilling the diagnostic criteria for vCJD with a final alternative pathological diagnosis has been reported. Indeed, a comparison of the clinical phenotype in cases of vCJD in the UK and France indicates that the clinical characteristics are remarkably consistent.[10]

The preconditions in section I of the criteria remain important, and this is underlined by a case of suspected vCJD in Hungary that fulfilled the criteria for probable vCJD but was found to be a genetic form of human prion disease with a codon 200 mutation of the prion protein gene.[11] The preconditions state that there must be no evidence of a familial form of transmissible spongiform encephalopathy (prion disease). Cases with the MRI appearances suggestive of vCJD and alternative final diagnoses have been identified rarely in the UK, and such cases have been reported from other countries, including a case of sporadic CJD in Germany,[12] but none fulfilled the diagnostic criteria for probable vCJD.

It is important to consider whether the criteria for vCJD should be amended, although this assessment indicates that the current criteria are already highly sensitive and specific. It has been suggested that addition of an age criterion may of value.[13] Eighty-nine percent of all vCJD cases are younger than 40 years of age at clinical onset, but including an age cutoff would exclude an older cohort of patients; 8 cases of primary vCJD were aged >50 years at death, and of the 3 secondary cases related to blood transfusion, 1 was aged 75 years at death and another 69 years at death. Furthermore, as cases are likely to have been infected in the 1980s and 1990s, the mean age at onset may increase in the future. The possibility that inclusion of the MM codon 129 genotype might increase the specificity of the criteria has not been adopted because of the possibility that individuals with alternative genotypes might be susceptible to vCJD. This position is justified by the identification of potential secondary vCJD infection in an MV individual, the VV genotype in 2 appendices in a prevalence study,[14] and the recent identification of a possible MV case of vCJD. A further potential amendment is to decrease the number of required core clinical features from subsection II (for example, to 3/5 as opposed to the current 4/5) to increase sensitivity. Such modifications would provide a modest increase in sensitivity (5/12 negative cases would be classifiable as probable), but a similar effect would be achieved if all possible cases underwent the most sensitive FLAIR MRI sequence.[5]

This study indicates that invasive investigations are rarely required to allow a "probable" case definition. Only 3/88 cases required the results of tonsil biopsy to allow classification as probable vCJD in the autopsy/cerebral biopsy-proven cohort, with all other cases classified as probable vCJD on the basis of the clinical features and MRI brain scan. In addition, if one includes all the definite and probable cases identified in the UK between 1995 and 2004 (n = 150), 20/29 cases in which a tonsil biopsy was undertaken were already classifiable as probable cases on the basis of clinical phenotype and MRI brain scan. Tonsil biopsy may demonstrate peripheral deposition of abnormal prion protein and clearly increase the diagnostic likelihood of vCJD, but this procedure has risks, and a negative result does not exclude the possibility of vCJD.[10] Tonsil biopsy may be of particular value in cases that do not fulfill the diagnostic criteria for a probable case on the basis of clinical and radiological features, if potentially hazardous treatments are being considered or if there are significant public health implications. The current recommendations state that tonsil biopsy should be reserved for those who do not fulfill the clinically probable criteria.

The role of EEG in establishing a clinical diagnosis

of vCJD is limited, with most recordings demonstrating nonspecific changes. A typical EEG has not been seen in any UK case of vCJD, but has been reported in single cases from Italy[15] and Japan,[16] in which the suggestive EEG tracings were found in the terminal phase of illness. The diagnostic criteria have been amended to take into account the possibility of typical EEG features at an advanced stage of illness. However, the criteria still include the recommendation that a typical EEG should remain as an exclusion criterion for the diagnosis of vCJD (Table 1, section III) unless identified in the terminal phase of illness. This reflects the UK (and French) experience and highlights that an EEG remains an important tool for excluding sporadic CJD in suspect cases.

The most frequently identified alternative diagnoses at autopsy/cerebral biopsy in suspected cases of vCJD were sCJD and Alzheimer disease. Despite modern laboratory techniques, a definitive diagnosis was not obtained in 5 autopsied cases, and in these cases, the possibility of a prion disease was definitively excluded. Although many of the alternative diagnoses were untreatable, the importance of appropriate diagnosis is underlined by the identification of potentially treatable conditions, including viral encephalitis, multiple sclerosis, limbic encephalitis, and Wilson's disease.

Acknowledgments

This study indicates that the diagnostic criteria for vCJD have significant utility, but the criteria, including the preconditions, must be applied with rigor to allow accurate diagnosis of vCJD and to avoid misdiagnosis.

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Potential Conflicts of Interest

Nothing to report.

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