How to improve the clinical diagnosis of Creutzfeldt–Jakob disease

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Summary
This paper describes a prospective follow-up of 364 patients initially notified as suspected Creutzfeldt–Jakob disease to a Surveillance Unit in Göttingen, Germany. Six patients were diagnosed as having genetic prion disease by blood analysis and were excluded from the study. After examination and review of the remaining 358, 193 were classified as probable Creutzfeldt–Jakob disease. However, autopsy revealed that five of the 193 did not have Creutzfeldt–Jakob disease (four cases, Alzheimer’s disease; one case, cerebral lymphoma). Of the 54 patients classified as possible Creutzfeldt–Jakob disease, 10 had another diagnosis made at autopsy. Two of the 111 cases originally classified as having other diseases were found to have Creutzfeldt–Jakob disease on autopsy. Autopsy evidence, together with follow-up of the patients still living and those who died without autopsy, revealed a broad range of other diagnoses. In the younger age groups, the commonest were chronic inflammatory diseases including Hashimoto encephalitis, whilst rapidly progressive Alzheimer’s disease was most common in the older age groups. The presence of 14-3-3 protein in the CSF discriminated better between Creutzfeldt–Jakob disease and other rapidly progressive dementias than did the EEG pattern or the MRI. The inclusion of this CSF protein in the criteria of Masters and colleagues (Ann Neurol 1979; 5: 177–88) improves the accuracy and confidence in the clinical diagnosis of Creutzfeldt–Jakob disease.

Keywords: Creutzfeldt–Jakob disease; Alzheimer’s disease; Hashimoto encephalitis; differential diagnosis; 14-3-3 protein

Introduction
With the increasing awareness of the transmissible spongiform encephalopathies, the reported incidence of sporadic Creutzfeldt–Jakob disease now exceeds the commonly accepted figure of 1 per million population per year (Hainfellner et al., 1996). The prospective surveillance programmes in many countries within the BIOMED project of the European Community have all yielded similar and slightly increasing figures (Will et al., 1998). This increase is particularly pronounced in cases notified as suspected Creutzfeldt–Jakob disease. However, a significant number of these are eventually found not to have the disease. In Britain only about half of all suspected cases are found to fulfil the criteria for definite or probable Creutzfeldt–Jakob disease (Will and Zeidler, 1996). This figure is given in an editorial without further information on the diagnoses of the non-Creutzfeldt–Jakob disease cases.

There are three studies in the literature in which the accuracy of a Creutzfeldt–Jakob disease diagnosis was evaluated (Will and Matthews, 1984; Brown et al., 1994; Arpino et al., 1999). Will and Matthews analysed 147 cases from the UK, comparing the cause of death on the death certificate with the hospital notes (Will and Matthews, 1984). Using criteria formulated by Masters and colleagues (Masters et al., 1979), they felt that 42 did not, in fact, have Creutzfeldt–Jakob disease. Brown and colleagues reported on 1113 brains from persons where Creutzfeldt–Jakob disease was a possible diagnosis (Brown et al., 1994). In 300 cases a transmissible spongiform encephalopathy was found and of these 234 were classified as sporadic Creutzfeldt–Jakob disease. In Italy the proportion of misclassification for death certificates was 35.6% for the year 1993 (Arpino et al., 1999).

In these studies the disorders leading to death had apparently so many clinical similarities to Creutzfeldt–Jakob disease that this diagnosis appeared either on the death certificate, or the brain was sent to the National Institutes for Health, Bethesda, Md., USA for transmission studies. The wide spectrum of non-Creutzfeldt–Jakob disease disorders shows that the clinical diagnosis of Creutzfeldt–Jakob disease
is difficult during life. Although Creutzfeldt–Jakob disease
is still a fatal non-treatable disease, the correct diagnosis
as early as possible is important for two reasons: (i) so that
rare treatable dementias such as Hashimoto encephalitis are
not missed, and (ii) to support clinicians and relatives in
their decisions regarding further therapeutic steps.

Up to now, the EEG was the only well-established technical
investigation in the differential diagnosis of Creutzfeldt–Jakob
disease. Only recently, the value of CSF markers
(Hsich et al., 1996; Zerr et al., 1998) and the technique of
MRI (Finkenstaedt et al., 1996) were recognized as diagnostic
tools for the diagnosis of Creutzfeldt–Jakob disease.

This paper is a prospective follow-up of all patients notified
as having suspected Creutzfeldt–Jakob disease in Germany
over a 3-year period. The features that help to distinguish it
from other diseases are discussed and, in particular, there is
an assessment of the recently described 14-3-3 protein in
CSF (Hsich et al., 1996; Zerr et al., 1998) as a diagnostic
marker of Creutzfeldt–Jakob disease. Because this
epidemiological study was primarily concerned with the
sporadic form of Creutzfeldt–Jakob disease, familial cases
were excluded when genotyping revealed a genetic prion
disease. Iatrogenic cases were also excluded.

Methods

In Germany, all patients with suspected Creutzfeldt–Jakob
disease are notified to the Creutzfeldt–Jakob Disease
Surveillance Unit which is located in Göttingen. From June
1993 to May 1996, a total of 364 cases were notified. They
came from treating physicians in Neurological and Psychiatric
Departments all over Germany. After informed consent was
given by the relatives, the patients were seen by a physician
from the Surveillance Unit and had a detailed neurological
examination. Clinical data based on a semi-structured
interview was obtained from the patient’s relatives. The
hospital records were examined, a full medical history and
the results of any investigations were obtained and the
differential diagnosis was discussed with the treating
physician.

The EEG was evaluated using the criteria of Steinhoff and
colleagues: periodic sharp wave complexes were diagnosed
if the record contained strictly periodic cerebral potentials,
the majority had a duration of between 100 and 600 ms and
there was an inter-complex interval between 500 and 2000 ms
(Steinhoff et al., 1996). If available, CT scans and MRI
studies were analysed. The MRI was considered typical of
Creutzfeldt–Jakob disease if it showed bilateral areas of
increased signal intensity predominantly affecting the caudate
nuclei and the putamina on long repetition time images
(Finkenstaedt et al., 1996). In patients who could be tested,
dementia was diagnosed when the Mini-Mental State
Examination score was less than 24 out of 30.

CSF samples and blood were obtained in the majority of
cases after informed consent was obtained from a relative or
guardian and approval by the Ethics Committee of the
University of Göttingen. The 14-3-3 protein immunoassay in
CSF was performed as described by Zerr and colleagues
(Zerr et al., 1998). Detection of the bound polyclonal antibody
to the β-isoform of the 14-3-3 protein (Santa Cruz Biotech,
Santa Cruz, Calif., USA) was performed using the enhanced
chemiluminescence detection kit (Amersham Buchler,
Freiburg, Germany). A positive control from a case with
confirmed Creutzfeldt–Jakob disease and a negative control
were run on every gel.

All the cases were initially classified into three groups:
probable Creutzfeldt–Jakob disease, possible Creutzfeldt–Jakob
disease and other disease. A definite diagnosis of
Creutzfeldt–Jakob disease was only made if there was
confirmation by autopsy. The criteria used in the classification
were those of Masters and colleagues (Masters et al., 1979).
Probable Creutzfeldt–Jakob disease was diagnosed if patients
had rapidly progressive dementia, periodic sharp waves in
the EEG and at least two of the following four findings:
myoclonus, visual and/or cerebellar symptoms, pyramidal
and/or extrapyramidal signs, and akinetic mutism. Those
cases who fulfilled the above criteria but did not have a
typical EEG were originally classified as possible Creutzfeldt–Jakob
disease. The recent extension of these criteria, which
utilizes the presence of 14-3-3 protein in CSF allowed the
reclassification of a number of possible Creutzfeldt–Jakob
disease cases into the probable category. Thus, a patient who
presented with a typical clinical picture, but without periodic
sharp wave complexes on the EEG, was classified as a
probable case if 14-3-3 protein had been found in the CSF.
These extended criteria have been applied to the cases in
this paper (Fig. 1). The classification ‘other disease’ was
made if: (i) either dementia was insufficiently documented
or had been present for over 2 years; (ii) there was a lack of
the typical neurological symptoms and signs; and (iii) there
was CSF evidence of an inflammatory disease process.

The clinical diagnosis of Alzheimer’s disease was made
using the NINCDS-ADRDA criteria (McKhann et al., 1984).
Hashimoto encephalitis was diagnosed if there was a
significant elevation of anti-thyroid autoantibodies in the
serum and the typical findings of a Hashimoto thyroiditis
(Ghioka-Schmid et al., 1996; Kothbauer-Margreiter et al.,
1996; Seipelt et al., 1999).
During follow-up, patients were assessed and reclassified in accordance with the development of their disease. Hospital notes and discharge summaries were regularly reviewed, and family physicians and neurologists, nursing homes and relatives were contacted to obtain information about the clinical progress of the illness and the results of any investigations performed. Autopsies were performed by the local neuropathologist and/or the Reference Centre for Creutzfeldt–Jakob disease in Göttingen. A definite diagnosis of Creutzfeldt–Jakob disease was made when there were the typical neuropathological changes of spongiform degeneration, gliosis and nerve cell loss, and pathological prion protein deposits in brain tissue, detected immunohistologically using monoclonal antibody G6138 or 3F4 (Kretzschmar et al., 1996).

### Results

Of the 364 cases, six were excluded from further study when they were identified as having a genetic prion disorder. The initial classification of the remaining 358 using the extended criteria of Masters and colleagues (Masters et al., 1979), i.e. their criteria plus the presence of 14-3-3 protein, was: 193 probable, 54 possible and 111 other disease (Fig. 1). Note that on our initial assessment, we felt that almost one-third of the cases referred to us did not have Creutzfeldt–Jakob disease. Of the 358 cases, 136 autopsies were performed. Table 1 illustrates the results.

Of the 193 cases classified as probable Creutzfeldt–Jakob disease, 95 came to autopsy. Of these, five were shown not to have Creutzfeldt–Jakob disease. Four had Alzheimer’s disease and one had a cerebral lymphoma. All five had dementia of less than 2 years’ duration and all had myoclonus. Three had akinetic mutism, four had pyramidal signs and three had extrapyramidal signs. Visual and cerebellar signs were present in the patient with lymphoma but not in Alzheimer’s disease cases. 14-3-3 protein was negative in three cases and positive in one with Alzheimer’s disease; CSF was not available in the case of lymphoma. At the time of classification, the EEG recordings were considered to be typical of Creutzfeldt–Jakob disease. A re-evaluation revealed that in two cases the original assessment was still valid, although the other three (two Alzheimer’s disease, one lymphoma) may, in retrospect, not have fulfilled our criteria for probable Creutzfeldt–Jakob disease. In Fig. 2, two tracings at different dates are shown for a patient originally diagnosed as having probable Creutzfeldt–Jakob disease but for whom the autopsy revealed Alzheimer’s disease. The tracings clearly show the appearance of periodic sharp wave complexes during the course of the disease.

Of the 54 possible Creutzfeldt–Jakob disease cases, 21 came to autopsy. Ten were shown to have another diagnosis. Four had Alzheimer’s disease, two encephalitis, two vascular dementias, one unclassified dementia and one hypoxic brain damage. As already indicated, the EEG was not typical for Creutzfeldt–Jakob disease in these cases and the 14-3-3 protein was either negative or CSF was not available.

Of the 111 other disease cases, 20 came to autopsy. Of these, two were shown to have Creutzfeldt–Jakob disease. Both had typical neurological symptoms and signs during the course (myoclonus, akinetic mutism). No dementia was present in one case after 6 months of illness. The other developed aphasia 3 months after onset and before a dementing process could be verified. Although the EEG was not typical, 14-3-3 protein was positive in the CSF of both patients. Unfortunately, MRI was not available in the majority of these reclassified cases.

In Table 2 the final diagnoses of the other disease classification are listed. There were 124 cases, comprising 109 from the original classification (two of the original 111 were found to have Creutzfeldt–Jakob disease and omitted), 10 from the possible group and five from the probable group. Autopsy or genetic testing was done on 37 cases, with clinical information and assessment being utilized for the patients still alive and for those who died without autopsy. Alzheimer’s disease was the commonest diagnosis, followed by unclassified dementias, cerebrovascular disease and chronic encephalitis. There was a subgroup of 18 patients with chronic inflammatory neurological diseases (chronic encephalitis, multiple sclerosis, paraneoplastic encephalopathies and Hashimoto encephalitis). The average age of this group of patients was markedly lower than the age of the rest of the patients (46 years versus 61 years). In this younger age group, a chronic inflammatory illness was the most frequent final diagnosis.

<table>
<thead>
<tr>
<th>Classification</th>
<th>n</th>
<th>Autopsy performed</th>
<th>Diagnosis as shown by autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Correct</td>
</tr>
<tr>
<td>Probable Creutzfeldt–Jakob</td>
<td>193</td>
<td>95</td>
<td>90 (95%)</td>
</tr>
<tr>
<td>Possible Creutzfeldt–Jakob</td>
<td>54</td>
<td>21</td>
<td>11* (52%)</td>
</tr>
<tr>
<td>Other disease</td>
<td>111</td>
<td>20</td>
<td>18 (90%)</td>
</tr>
</tbody>
</table>

*Patients without CSF investigation.
In Table 4, a comparison is made of the sensitivity and specificity of the presence of 14-3-3 protein in CSF, the typical EEG recording and typical MRI in those patients where the tests were done. As can be seen, MRI is likely to become an important tool in the diagnosis of Creutzfeldt–Jakob disease. However, these are preliminary figures and further analysis will be required.

Discussion

This is the first prospective study in which an attempt is made to assess the reliability of an initial diagnosis of Creutzfeldt–Jakob disease. In regard to the question as to how often the diagnosis is missed, we cannot exclude the possibility that some cases are not notified to the Surveillance Unit. However, the awareness of Creutzfeldt–Jakob disease is very high in Germany and co-operation with the notifying hospitals improved considerably during the time of the study. In addition, comparison with the mandatory notification system introduced in July 1994 showed that treating physicians notified their cases earlier and more often to the Surveillance Unit than to the mandatory system. Unfortunately, data protection laws make the exchange of information impossible between the two systems.

In Italy, a comparison between death certificates and the prospective Creutzfeldt–Jakob disease register revealed a proportion of misclassification for the death certificates of 35.6% and under-reporting for the Creutzfeldt–Jakob disease register of 26.7% for the first year of the prospective study. For 1996, the mortality rate per million of 1.11 obtained by the Creutzfeldt–Jakob disease register was considered to be complete. At present, the most reliable incidence figures come from Austria where autopsy rates are over 90% for deaths in hospital. For the year 1995, Hainfellner and colleagues (Hainfellner et al., 1996) reported an incidence of 1.38 compared with 1.2 in Germany [extended criteria of Masters and colleagues (Masters et al., 1979)].

There are a large number of alternative diagnoses possible when Creutzfeldt–Jakob disease is suspected, either initially or during the course of illness. This reflects the overlapping clinical symptomatology with a number of other diseases, particularly with rapidly progressive Alzheimer’s disease.

Visual symptoms discriminated best between Creutzfeldt–
How to improve the clinical diagnosis of CJD

Table 2

Other final diagnoses of patients suspected of having Creutzfeldt–Jakob disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosis confirmed by autopsy or genetic testing ((n = 37))</th>
<th>Clinical diagnosis ((n = 87))</th>
<th>Total ((n = 124))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>13</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Unclassified dementias</td>
<td>1</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Chronic encephalitis of unknown cause</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>–</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>–</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Paraneoplastic syndromes</td>
<td>–</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Intoxication</td>
<td>–</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hashimoto encephalitis</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Familial spastic paraplegia</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Corticostriatogniral degeneration</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral lymphoma</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chronic epilepsy</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hereditary ataxia</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol induced atrophy</td>
<td>1</td>
<td>–</td>
<td>2</td>
</tr>
</tbody>
</table>

In addition one each of the following autopsy proven neurological disorders were found: leucodystrophy, fatal familial insomnia, congophilic angiopathy, lipoid histiocytosis, gliomatosis cerebri, hypoxic brain damage, astrocytoma.

Jakob disease and other diseases at the beginning of the illness. In later stages, myoclonus, gait ataxia, visual disturbances and particularly akinetic mutism all occurred more frequently in Creutzfeldt–Jakob disease when compared with other diseases. Epilepsy, however, occurred more frequently in other diseases. It should be noted that the symptomatology in our category ‘other disease’ does not reflect the true frequency of these signs in these disorders. They are biased towards a spectrum of signs considered to be suggestive or typical for Creutzfeldt–Jakob disease. Myoclonus, for example, is reported to occur in ~10% of unselected Alzheimer’s disease cases (Mayeux et al., 1985).

The EEG falsely suggested Creutzfeldt–Jakob disease in five of our cases that were originally classified as probable Creutzfeldt–Jakob disease but proved at autopsy to have Alzheimer’s disease or lymphoma. This has been known to occur in rare instances, mostly published as clinical reports (Watson, 1979; Steinhoff et al., 1996). During the first period of our study, EEG criteria were not so strictly defined and this resulted in three of the five cases being classified as probable instead of possible Creutzfeldt–Jakob disease.

CT helps to support the diagnosis of Alzheimer’s disease when atrophy is most pronounced in the temporobasal and hippocampus regions. CT is also useful in diagnosing vascular dementia. MRI showed basal ganglia hyperintensity both in the proton- and T2-weighted images in 23 of 29 of our initial Creutzfeldt–Jakob disease cases (Finkenstaedt et al., 1996). In a recent re-evaluation of 157 MRI scans of definite and probable Creutzfeldt–Jakob disease cases and of 56 other cases, the sensitivity was 67% and the specificity 93% (our unpublished results). It is likely that the value of MRI for the diagnosis of Creutzfeldt–Jakob disease will eventually be comparable with that of the EEG.

The CSF findings were useful in both excluding inflammatory diseases and in making a diagnosis of Creutzfeldt–Jakob disease. Twelve out of the 18 patients with chronic inflammatory processes had either pleocytosis and/or an oligoclonal appearance of the CSF γ-globulin region. On

Table 3

Presenting signs of definite and probable Creutzfeldt–Jakob disease patients compared with patients with other diseases

<table>
<thead>
<tr>
<th></th>
<th>Creutzfeldt–Jakob disease (%) ((n = 201))</th>
<th>Other diseases (%) ((n = 109))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia of &lt; 2 years duration</td>
<td>96</td>
<td>63</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>89</td>
<td>43</td>
</tr>
<tr>
<td>Gait ataxia</td>
<td>86</td>
<td>46</td>
</tr>
<tr>
<td>Rigor or other extrapyramidal signs</td>
<td>73</td>
<td>41</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>Akinetic mutism</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>Pareses and spasticity</td>
<td>52</td>
<td>25</td>
</tr>
<tr>
<td>Epileptic fits</td>
<td>12</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 4

Sensitivity and specificity of detection of 14-3-3 in CSF; periodic sharp wave complexes in the EEG and hyperintense signals in long repetition-time MRIs

<table>
<thead>
<tr>
<th></th>
<th>14-3-3 ((n = 289))</th>
<th>EEG ((n = 256))</th>
<th>MRI ((n = 213))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95%</td>
<td>65%</td>
<td>67%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td>86%</td>
<td>93%</td>
</tr>
</tbody>
</table>
the other hand, determination of 14-3-3 protein was helpful in diagnosing Creutzfeldt–Jakob disease. Although 14-3-3 is found in other neurologically diseases with rapidly progressive brain damage such as herpesencephalitis, these acute disorders are easily recognized and 14-3-3 does not persist. In two of our cases with inflammatory disease, 14-3-3 became negative after 3 weeks. We also found 14-3-3 protein in five cases, originally classified as other disease but who had no inflammatory findings. After autopsy, two were shown as having definite Creutzfeldt–Jakob disease, two had unclassified dementia and one a paraneoplastic syndrome. The detection of 14-3-3 is of most value in the differential diagnosis of Creutzfeldt–Jakob disease and Alzheimer’s disease. In a recent review Johnson and Gibbs reported a sensitivity of 96% and a specificity of 99% for patients with progressive dementia without pleocytosis (Johnson and Gibbs, 1998).

The presence and persistence of 14-3-3 protein is probably indicative of the more rapid brain destruction in Creutzfeldt–Jakob disease than that in Alzheimer’s disease and vascular dementia. In addition, the localization of the neuronal loss is important. Compared with cortical areas, biochemical markers from the basal parts of the brain equilibrate more easily with the CSF in the ventricles (Felgenhauer, 1998). This might explain the presence of 14-3-3 protein in the CSF of patients with herpesencephalitis.

A differential diagnosis that was not found in other series is Hashimoto encephalitis. We became aware of this treatable dementia through a patient with a known history of Hashimoto thyroiditis. Since then, six further cases without thyroiditis have been diagnosed and treated (Seipelt et al., 1999). Some of these did not enter our study because we suggested to the notifying hospitals that, prior to including them in our survey, they tested for anti-thyroid autoantibodies.

We are aware of only two other studies in the literature that present a sufficient number of cases for comparison with our survey (Will and Matthews, 1984; Brown et al., 1994). Although the methodology was different, the figures shown in Table 5 are comparable for most diagnostic groups. In all three series, the major diagnostic alternative was Alzheimer’s disease. The lower percentage of Alzheimer’s disease, the higher number of unclassified dementias and the lack of vascular dementia in the investigation by Brown and colleagues (Brown et al., 1994) probably reflects a less definitive neuropathological definition and scanty or insufficient clinical information.

All together, 34% of the patients notified to us as suspected Creutzfeldt–Jakob disease by the treating physicians eventually had another final diagnosis made, either at autopsy or by clinical follow-up. Of those patients our research team classified as probable or possible Creutzfeldt–Jakob disease after an original evaluation, 15 (6%) did not, in fact, have Creutzfeldt–Jakob disease at autopsy. Of these, five were probable and 10 possible cases. On the other hand, two patients who were originally classified as other disease were diagnosed as having Creutzfeldt–Jakob disease at autopsy.

Creutzfeldt–Jakob disease is difficult to reliably diagnose clinically. Both false positive and false negative diagnoses occur. In some cases, a treatable dementia such as Hashimoto encephalitis can be detected. We have shown that, by careful examination, appropriate laboratory investigations and regular and systematic follow-up a more accurate diagnosis can be made. The greater use of EEG, MRI and specialized CSF tests, when taken together with an accurate clinical history and careful examination, now allow an initial diagnosis of Creutzfeldt–Jakob disease to be made with increasing certainty. The category ‘probable’ can be called Creutzfeldt–Jakob disease for clinical purposes.

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References


Table 5 Other final diagnoses when Creutzfeldt–Jakob disease was suspected clinically

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Autopsy proven*</th>
<th>Autopsy series†</th>
<th>Death certificates‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>35%</td>
<td>16%</td>
<td>50%</td>
</tr>
<tr>
<td>Other (unclassified) dementia</td>
<td>3%</td>
<td>17%</td>
<td>–</td>
</tr>
<tr>
<td>Degenerative disease</td>
<td>8%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Vascular encephalopathy</td>
<td>8%</td>
<td>–</td>
<td>7%</td>
</tr>
<tr>
<td>Encephalitis of unknown cause</td>
<td>11%</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Our cases; †see Brown et al., 1994; ‡see Will and Matthews, 1984.


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