Creutzfeldt–Jakob disease (CJD) is a rare, fatal neurodegenerative disorder with a worldwide incidence of 1–1.5 per million. As in other countries, a CJD surveillance unit with a clinical and neuropathological approach was established in Göttingen (Germany) in 1993. Here we report the epidemiological data from a prospective 12-year surveillance. Since 1993, there has been an increasing incidence of CJD, from 0.7 in 1993 to 1.6 in 2005 with a quite stable level since 1998. During this period, the proportion of patients with MV and VV codon 129 genotype rose, possibly because of better identification of atypical subtypes. Six percent of all patients had a PRNP mutation, mainly D178N-129M (FFI), E200K and V210I. Iatrogenic CJD was a rare phenomenon. No patient infected by cadaveric growth hormone extracts was reported. Furthermore, no variant CJD patient has yet been identified in Germany. Differential diagnoses revealed a variety of neurodegenerative diseases, with Alzheimer’s disease in the lead. One-third of the non-CJD patients included in this study suffered from a potentially treatable disorder such as metabolic or inflammatory diseases. The incidence and mortality rates in Germany are similar to those in other European countries. In contrast, however, acquired forms, such as iatrogenic and variant CJD are still rare in Germany or have not yet been identified.

**Keywords:** CJD; dementia; epidemiology; diagnosis; CSF; MRI; codon 129 genotype; genetic CJD; reversible/treatable dementia

**Abbreviations:** BSE = bovine spongiform encephalopathy; CJD = Creutzfeldt–Jakob disease; FFI = fatal familial insomnia; GSS = Gerstmann–Straussler–Scheinker syndrome

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**Introduction**

Creutzfeldt–Jakob disease (CJD) is a rare, fatal disorder characterized by rapidly progressive dementia (Johnson, 2005). There are a number of distinct aetiological subtypes. Sporadic CJD (sCJD) is the most common form, which occurs worldwide with an incidence of 1–1.5 per million (Ladogana et al., 2005). Inherited forms include Gerstmann–Straussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI) and genetic CJD, caused by mutations of the prion protein gene (PRNP) on chromosome 20 (Kovacs et al., 2005). Furthermore, CJD is associated with iatrogenic procedures such as treatment with human pituitary growth hormones, dura mater and cornea grafts, deep brain electrodes and neurosurgery (iCJD) (Brown et al., 2000; Will, 2003).

In the United Kingdom, a new variant of CJD (vCJD) was described in 1996, which is linked to bovine spongiform encephalopathy (BSE) (Will et al., 1996; Bruce et al., 1997). Up to now, 201 patients with vCJD have been identified; the cases occurring not only in European countries, but also in Canada, the USA, Saudi Arabia and Japan. To date, four patients with neuropathologically confirmed vCJD, probably transmitted via blood transfusion (one of them subclinically or potentially preclinically infected), have been reported in the literature (Llewelyn et al., 2004; Peden et al., 2004; Wroe et al., 2006).
These new findings imply further iatrogenic risk of transmission between humans. Thus, extensive epidemiological research focusing on cluster analysis, risk factors and means and routes of transmission is essential.

CJD surveillance systems were established in many countries worldwide during the 1990s (Will et al., 1998; Nakamura et al., 1999; Collins et al., 2002; Glatzel et al., 2002; Puopolo et al., 2003; Pocchiari et al., 2004; Sanchez-Valle et al., 2004; Ladogana et al., 2005; de Pedro-Cuesta et al., 2006; Van Everbroeck et al., 2006).

In the present manuscript, we report on 12 years of investigative data from a prospective German CJD surveillance study.

Methods

Since 1993, the CJD Surveillance Unit in Goettingen has centralized data of all suspected CJD patients in Germany. ‘Suspected CJD patients’ were defined by referral from the treating physicians as suspected CJD or during discussion of the 14-3-3 test result with a surveillance neurologist. All suspected patients were examined by a neurologist of the surveillance unit at the reporting hospital, and copies of patients’ records and all available test results were taken. Additionally, analyses of CSF parameters, EEG, MRI (performed for diagnostic reasons by the reporting hospital, and copies of patients’ records and all available test results were taken. Additionally, analyses of CSF parameters, EEG, MRI (performed for diagnostic reasons by the treating hospital following routine standard methods) and in some cases PET or SPECT were carried out. Clinical diagnoses were done in cooperation with the treating physician in case of a non-CJD diagnosis and classification for CJD by the surveillance team according to the established clinical criteria (WHO, 1998; Zerr et al., 2000a). The clinical classification other diagnosis was established as a result of our advisory service for differential diagnosis using biochemical parameters, MRI or therapeutic regimens. Follow-up data was collected by telephone calls to the relatives, treating physicians and in some cases by a second examination by the surveillance group. Classification was revised if new results gave reason to (e.g. new clinical symptoms, laboratory findings). For this study, the final clinical classification available was used. Confirmation of the diagnosis was sought by autopsy or brain biopsy when consent by the relatives was available according to the pathological criteria for prion disease such as nerve cell loss, spongiosis, astrogliosis and PrPsc detection by immunohistochemistry/PET-Blot (Kitamoto et al., 1992; Kretzschmar et al., 1996; Schulz-Schaeffer et al., 2000). Genetic analysis of the PRNP gene for codon 129 polymorphism (methionine or valine) and, if available, pathological prionprotein (PrPsc) typing (either as type 1 or 2) completed the data set (Parchi et al., 1999). PRNP full sequence analysis for mutation was performed and identified as GSS, FFI and inherited CJD according to the literature (Kovacs et al., 2005). 14-3-3 was determined in western blot by standard methods in all patients if CSF was available (Zerr et al., 1998). EEG analysis for periodic sharp wave complexes (PSWCs) was performed by an experienced neuropyschologist (B.J.S.) and the MRI analysis likewise by an experienced neuroradiologist (K.K.) (Steinhoff et al., 1996; Kallenberg et al., 2006). ‘CJD-typical’ EEG was considered when PSWCs were detected, and ‘CJD-typical’ MRI in case of hyperintense basal ganglia (in at least one weighting) at the time of clinical classification. Symptom onset was defined as the first neurological or psychiatric symptom described by a physician or the relatives. Disease duration was counted as time from symptom onset to death; therefore no duration data is available for patients who are still alive.

Statistical analysis was established with SigmaPLOT 9.0 (SYSTAT). Incidence was calculated as the number of new detected sCJD patients per year per million inhabitants, mortality likewise as the number of sCJD patients died per year.

Results

Patients

Between June 1993 and December 2005, 2094 patients with suspected CJD were referred to the CJD Surveillance Unit

<table>
<thead>
<tr>
<th>Table I</th>
<th>Incidence, mortality and core clinical data of all confirmed and probable CJD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients notified prospectively</td>
<td>34</td>
</tr>
<tr>
<td>Sporadic CJD</td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td>18</td>
</tr>
<tr>
<td>Probable</td>
<td>7</td>
</tr>
<tr>
<td>Incidence</td>
<td>0.6b</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.4</td>
</tr>
<tr>
<td>Median age</td>
<td>67</td>
</tr>
</tbody>
</table>

<table>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>8%</td>
<td>6%</td>
<td>7%</td>
<td>8%</td>
<td>9%</td>
<td>8%</td>
<td>9%</td>
<td>4%</td>
<td>7%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1(+)</td>
<td>5(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
<td>1(+)</td>
</tr>
</tbody>
</table>

a66 Patients were only neuropathologically acquired.
bExtrapolated.
cMostly patients with suspected genetic TSE were tested in 2005.
d10 Patients were only genetically acquired.
Goettingen. Additionally, 76 patients were notified at the time of autopsy (these were included in incidence and mortality calculations) or because a mutation in PRNP was detected without clinical evaluation (Table 1). Of this total of 2170 patients, the diagnosis of sporadic CJD was confirmed neuropathologically in 753 (35%) patients and further 575 (26%) patients were classified as probable sCJD. This reveals an incidence of 0.7 in 1994 to 1.6 in 2005 but an almost stable level since 1998. One hundred and six (5%) patients were classified as possible sCJD with typical clinical symptoms but negative 14-3-3 test and no PSWCs in EEG. Neupathology failed to detect any hints for prion disease in 102 patients (5%), and in 447 patients (21%) clinical classification as other disease was established. The autopsy rate of all patients was 66% (836/1266), the autopsy rate within the patients classified as other disease 50%. Thus, single cases of unidentified prion disease might be included within the clinically other patients. Additionally, genetic analysis revealed 123 patients with inherited prion disease (6% of all spongiform encephalopathies in this study). A further 10 patients were classified as iatrogenic CJD. Up to now, no patients with vCJD has been confirmed in Germany despite careful surveillance.

**Classification**

Six hundred and fifty-eight patients were clinically classified according to the diagnostic criteria and neuropathologically confirmed. The majority of 88% (n = 581) of these patients were finally classified as probable sCJD, and in 47 (7%) patients clinical symptoms allowed the classification as possible sCJD (Table 2a–d). Only in 35 patients (5.3%) sCJD could not be identified by the established clinical criteria and thus were initially classified as other disease. Further analysis of these patients showed five patients classified as other case because of inflammatory findings on routine examination in CSF. Another problem was absence of dementia, isolated dementia or only dementia with cerebellar ataxia at last classification during follow-up, so that these had to be classified as other case (n = 26). The remaining patients were classified as other case (and neuropathology turned out sCJD) because of indications for other diagnoses, such as genetically proven SCA12, paraneoplastic disease (predominant neupolyneuropathy and massive elevated protein content in CSF), epileptic fits (initially epileptic fits, later reduced vigilance and EEG suggestive of status epilepticus similar to PSWCs) or fluctuations (interpreted as repetitive epileptic events).

MRI of these 35 sCJD patients classified as other was available in 26 patients. Thirteen of them (50%) showed the sCJD typical finding of hyperintense basal ganglia.

The highest final clinical classification and neuropathological results stratified by age are shown in Table 2a–c. Autopsy rate was similar over the age groups, ranging between 45 and 88% of the probable and possible sCJD patients, and 39–80% of the patients with other diagnoses. In those classified as probable sCJD, neuropathology confirmed the diagnosis in most patients across all age groups (95–100%). Non-CJD patients within the patients classified as probable (n = 16) suffered mainly from Alzheimer’s disease (Table 2d). MRI analysis of these patients found none with sCJD typical hyperintense basal ganglia. Clinical classification as possible sCJD shows a broad range of the proportion of confirmed sCJD patients (33–79%). A high number of patients classified as other disease are still alive, which makes a prion disease unlikely in the majority of patients.

**Clinical and epidemiologial characteristics in sporadic CJD**

Age- and sex-matched incidence showed a peak for both sexes between 70 and 79 years with 5.27 (females) and 5.97 (males), but a marked decrease in the age over 80 years to 1.62 and 1.65, respectively (Fig. 1). Since 1994, there has been an increase in incidence for all age groups.

Genetic analysis for polymorphism of codon 129 in all confirmed and probable sCJD patients (available in n = 992) revealed 655 (66%) methionine homozygous (MM), 159 (16%) valine homozygous (VV) and 178 (18%) heterozygous (MV) sCJD patients. Although the numbers of all patients who underwent a genetic analysis per year remained stable, there was a decrease in the proportion of MM in contrast to an increase of MV and VV, but without statistical significance (P = 0.438) (Fig. 2). Median disease duration stratified by genotype was the shortest for MM with 5.3 months (range 1.1–81.4), followed by VV with 7 months (1.6–48.2) and a prolonged disease duration in the MV type with 12 months (range 2–45) (ANOVA P < 0.001). Interestingly, we found a disease duration of more than 24 months mostly in the MV genotype (9.6% of all MV patients), followed by the VV type (7.1% of all VV patients) and the MM type (4.3% of all MM patients) (Fig. 3). MM patients (46%) were predominant within the other cases (39% MV and 15% VV). Additionally, we investigated the influence of codon 129 within the sCJD patients on clinical core data and test sensitivity resulting for the patients with at least one methionine allele in shorter disease duration (P < 0.001) and higher sensitivity of PSWCs (P < 0.001) (Table 3).

In 243 patients, PrPSc type 1 or 2 was available. PrPSc type 1 was associated with shorter disease duration (P < 0.001), higher 14–3–3 sensitivity (P = 0.0013) and higher PSWC frequency (P < 0.001) (Table 3). In combination with the polymorphism at codon 129, the subgroup allocation [according to (Parchi et al., 1999)] is shown in Table 3.

Altogether 56 sCJD patients with age at onset below 50 years were examined (3%), the youngest patient at the age of 19 years. The age group over 80 years at onset consisted of 118 patients (8.8%). Median disease duration in the young patients was longer (16.6 months, range 2.5–81) than in all sCJD (median 6.2 months, P < 0.001).
Instead, we found shorter disease duration in the patients over 80 years (3.7 months, range 1.2–18.9, \(P < 0.001\)). Results of technical analyses stratified by age at onset revealed a reliably high value for 14-3-3 in over 95% of the age groups over 40 years. In younger patients, 14-3-3 was less frequently positive (76%). In EEG, PSWCs were very rarely found in younger age groups, and there was a continuous increase up to 66% in the age over 80 years. In contrast, MRI showed a decreasing value in the elder patients (Fig. 4). Genotype distribution of codon 129 in the patients below 50 years showed 52% MM, 15% MV and 33% VV with an increase of MM with increasing age and with a relative decrease of the VV subtype (Fig. 5).

### Table 2: Patients sorted by age group and clinical classification with autopsy results and follow-up information

<table>
<thead>
<tr>
<th>Age at onset (years)</th>
<th>Notified patients (n)</th>
<th>Deceased patients (n)</th>
<th>Autopsy CJD (% of autopsies)</th>
<th>Disease duration (months)</th>
<th>Non-CJD Disease duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Clinical classification as ‘probable CJD’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>50</td>
<td>36</td>
<td>22 (100%)</td>
<td>9 (3–48)</td>
<td>0</td>
</tr>
<tr>
<td>50–60</td>
<td>178</td>
<td>166</td>
<td>94 (99%)</td>
<td>6 (2–48)</td>
<td>2</td>
</tr>
<tr>
<td>60–70</td>
<td>474</td>
<td>437</td>
<td>232 (96%)</td>
<td>5 (1–49)</td>
<td>10</td>
</tr>
<tr>
<td>70–80</td>
<td>372</td>
<td>345</td>
<td>183 (99%)</td>
<td>4 (1–41)</td>
<td>2</td>
</tr>
<tr>
<td>&gt;80</td>
<td>71</td>
<td>62</td>
<td>36 (95%)</td>
<td>4 (1–19)</td>
<td>2</td>
</tr>
<tr>
<td>(b) Clinical classification as ‘possible CJD’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>21</td>
<td>16</td>
<td>7 (50%)</td>
<td>19 (5–32)</td>
<td>7</td>
</tr>
<tr>
<td>50–60</td>
<td>39</td>
<td>29</td>
<td>14 (79%)</td>
<td>7 (3–32)</td>
<td>4</td>
</tr>
<tr>
<td>60–70</td>
<td>49</td>
<td>35</td>
<td>16 (73%)</td>
<td>9 (3–27)</td>
<td>6</td>
</tr>
<tr>
<td>70–80</td>
<td>49</td>
<td>31</td>
<td>7 (33%)</td>
<td>4 (2–16)</td>
<td>14</td>
</tr>
<tr>
<td>&gt;80</td>
<td>17</td>
<td>11</td>
<td>2 (40%)</td>
<td>4; 5</td>
<td>3</td>
</tr>
<tr>
<td>(c) Clinical classification as ‘other case’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>80</td>
<td>20</td>
<td>7 (44%)</td>
<td>12 (7–81)</td>
<td>9</td>
</tr>
<tr>
<td>50–60</td>
<td>89</td>
<td>36</td>
<td>9 (60%)</td>
<td>12 (2–29)</td>
<td>6</td>
</tr>
<tr>
<td>60–70</td>
<td>153</td>
<td>61</td>
<td>11 (44%)</td>
<td>7 (2–20)</td>
<td>15</td>
</tr>
<tr>
<td>70–80</td>
<td>119</td>
<td>54</td>
<td>7 (35%)</td>
<td>5 (2–24)</td>
<td>13</td>
</tr>
<tr>
<td>&gt;80</td>
<td>114</td>
<td>14</td>
<td>1 (20%)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(d) Diagnoses of the non-CJD patients from Table 2a–c sorted by highest clinical classification for sCJD</td>
<td></td>
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</tr>
</tbody>
</table>

#### Probable
- Alzheimer’s dementia AD (n = 7)
- Vascular dementia (n = 2)
- Dementia with Lewy bodies DLB (n = 1)
- AD + DLB (n = 1)
- Encephalitis (n = 1)
- Paraneoplastic syndrome (n = 1)
- Chronic sinus thrombosis (n = 1)

#### Possible
- Alzheimer’s dementia (n = 15)
- Mixed dementia (n = 4)
- Encephalitis (n = 3)
- Metabolic disorder (n = 3)
- Lymphoma (n = 3)
- Vascular dementia (n = 2)
- Dementia with Lewy bodies (n = 1)
- Progressive encephalitis with rigidity and myoclonus (PERM) (n = 1)
- Vasculitis (n = 1)
- One not clarified (n = 1)

#### Other
- Alzheimer’s dementia (n = 19)
- Vascular dementia (n = 7)
- Dementia with Lewy bodies (n = 2)
- Amyotrophic lateral sclerosis with frontotemporal dementia (n = 2)
- Encephalitis (n = 1)
- Metabolic disorder (n = 3)
- Lymphoma (n = 2)
- Glioblastoma multiforme (n = 2)
- Vasculitis (n = 1)
- Paraneoplastic syndrome (n = 1)
- Corticobasal degeneration (n = 1)
- Non-specific findings such as astrocytosis (n = 8)
Inherited prion diseases

Genetic TSE had a frequency of 6% of all TSE patients in this study. Within the group of patients with available mutation analysis, 7.3% were positive for a PRNP mutation. Genetic analysis for PRNP revealed 32 patients with FFI (26%) (D178N-129M), 12 GSS (10%) and 79 inherited CJD (64%) patients with various mutations. Within the group of inherited CJD we identified 21 patients with E200K and 15 with V210I mutations. Inherited prion disease led to a younger age at onset of 61 years (range 20–83, \( P<0.001 \)) and for some mutations to lower sensitivity of clinical tests (Table 4). Several mutations were already reported as case reports (Krasemann et al., 1995; Grasbon-Frodl et al., 2004a, b; Krebs et al., 2005; Roeber et al., 2005).

Iatrogenic CJD

During the 12 years of surveillance, we identified nine patients with iatrogenic CJD (eight patients due to dura mater grafts and one patient after cornea transplant). The dura patches or the corneal transplant were performed between 1979 and 1987. Incubation time varied from 10 to 24 years (median 18 years) for dura cases and 31 years in the cornea case. Median disease duration is longer than in sCJD with 10 months (range 2.4–19.2) (Lang et al., 1995, 1998, 2001; Kretzschmar et al., 2003). An additional patient died in 2005, suffering from neuropathologically confirmed CJD. Medical history found a cornea transplant 13 years before onset of symptoms, but the donor is not yet identified. Thus, because of the incubation time and medical history, iatrogenic CJD is very likely, but the final confirmation is still pending. Up to now, no human growth hormone-related disease transmission was identified.

Differential diagnosis

Differential diagnosis included mainly neurodegenerative diseases [Alzheimer’s disease (35%), Lewy-body dementia (9%), multiple system atrophy (MSA 3%),] vascular dementia (16%), malignancies/paraneoplastic diseases (6%) and metabolic dysfunction (8%) (Table 5). Fourteen of these other cases were initially clinically classified as probable sCJD: neuropathologically, these patients suffered from Alzheimer’s disease (AD; \( n=7 \)), vascular dementia (\( n=3 \)), encephalitis (\( n=2 \)) and each one from dementia...
with Lewy bodies (DLB) and DLB associated with Alzheimer's disease. Clinical criteria for possible sCJD were fulfilled in 34 patients, namely 15 patients with Alzheimer's disease and several other diagnoses (inflammatory disease \( n = 5 \), mixed dementia \( n = 4 \), lymphoma \( n = 3 \), metabolic disorder \( n = 3 \), vascular dementia \( n = 2 \), DLB \( n = 1 \), one without clear pathological diagnosis). Alzheimer's disease represents the major group of non-reversible (mainly neurodegenerative) diseases (50%) within all differential diagnoses. A substantial group of 28% \((n = 49)\) suffered from a potentially treatable disorder such as encephalitis.

### Table 3

<table>
<thead>
<tr>
<th>Subtype Distribution of Neuropathologically Confirmed sCJD with Clinical and Technical Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MM1</strong> ((n = 153))</td>
</tr>
<tr>
<td>Median age (years)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
</tr>
<tr>
<td>14-3-3 positive</td>
</tr>
<tr>
<td>Typical EEG</td>
</tr>
<tr>
<td>Typical MRI</td>
</tr>
</tbody>
</table>

**Fig. 4** Frequency of sCJD typical diagnostic test results in CSF, EEG and MRI in different age groups. Typical for sCJD is considered when 14-3-3 was positive in CSF, periodic sharp waves complexes are found in EEG and hyperintense basal ganglia in MRI scan (independent of weighting). The differences among the groups are statistically significant for 14-3-3 (ANOVA \( P = 0.002 \)), EEG (ANOVA \( P < 0.001 \)) and MRI (ANOVA \( P = 0.001 \)). Grey = 14-3-3; black = PSWC; light grey = basal ganglia hyperintensities.

**Fig. 5** Genotype distribution at different age groups. The differences between the age groups are statistically significant (ANOVA \( P = 0.04 \)). grey = MM; light grey = MV; black = VV.
Table 4 Clinical data and technical investigations in genetic prion diseases

<table>
<thead>
<tr>
<th></th>
<th>DI78N-I29M (n = 28)</th>
<th>E200K (n = 2I)</th>
<th>V210I (n = 15)</th>
<th>PI102L (n = 8)</th>
<th>sCJD (n = 1213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>57 (23–70)</td>
<td>63.5 (39–74)</td>
<td>61.5 (45–80)</td>
<td>49 (39–63)</td>
<td>66 (19–91)</td>
</tr>
<tr>
<td>f/m</td>
<td>1 : 2.1</td>
<td>1 : 2</td>
<td>1 : 1.1</td>
<td>1 : 1.7</td>
<td>1.4 : 1</td>
</tr>
<tr>
<td>Disease duration</td>
<td>10.5 (0.7–25)</td>
<td>6.5 (1–18)</td>
<td>3.6 (2–19)</td>
<td>5.1 (15–77)</td>
<td>6.2 (1–116)</td>
</tr>
<tr>
<td>I4-3-3 positive</td>
<td>1/26, 4%</td>
<td>17/19, 89%</td>
<td>14/14, 100%</td>
<td>1/5, 20%</td>
<td>1087/1134, 96%</td>
</tr>
<tr>
<td>EEG (PSWC)</td>
<td>0/16, –</td>
<td>11/15, 73%</td>
<td>8/15, 53%</td>
<td>0/3, –</td>
<td>542/1031, 53%</td>
</tr>
<tr>
<td>MRI (hyperintense basal ganglia)</td>
<td>1/12, 8%</td>
<td>5/8, 62.5%</td>
<td>5/11, 45%</td>
<td>1/2, 50%</td>
<td>398/713, 56%</td>
</tr>
</tbody>
</table>


Table 5 Differential diagnoses according to clinical criteria and median age (range)

<table>
<thead>
<tr>
<th>Potentially reversible disorders</th>
<th>Paraneoplastic/tumorous disease</th>
<th>n = 11</th>
<th>63 years (50–87)</th>
<th>n = 48 [28%], 61.5 years (26–87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disease</td>
<td>n = 10</td>
<td>56 years (29–70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>n = 9</td>
<td>68 years (27–72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalitis ^a</td>
<td>n = 9</td>
<td>60 years (26–76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol induced disorders</td>
<td>n = 4</td>
<td>70 years (56–73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>n = 3</td>
<td>53 years (27–65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>n = 2</td>
<td>73.5 years (62–85)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-reversible disorders

| Alzheimer’s disease             | n = 61                          | 65 years (35–89) | n = 121 [72%], 67 years (35–89) |
| Vascular dementia               | n = 28                          | 70.5 years (44–87) |
| Lewy-body dementia              | n = 15                          | 74 years (42–81) |
| Multiple system atrophy         | n = 5                           | 69 years (49–77) |
| Frontotemporal dementia         | n = 5                           | 55 years (35–72) |
| Parkinson’s disease             | n = 4                           | 68 years (60–76) |
| Corticobasal degeneration       | n = 3                           | 68 years (57–71) |

^a Metabolic disorders include M. Wilson, orthochromatic leukodystrophy, M. Niemann-Pick C, osmotically myelinolysis, lithium intoxication, hyperparathyroidism and in three patients neuropathological changes suggestive for metabolic disorder.

^b Herpes encephalitis, vasculitis, progressive myelo-leuencephalopathy PML, progressive encephalitis with rigidity and myoclonus PERM and inflammatory CSF and pathological findings.

tumour-associated diseases or metabolic disorders. As expected, patients with neurodegenerative disorders had a higher median age at onset than those with potentially treatable disorders (Table 5).

Discussion

This study analyses a large number of patients with spongiform encephalopathy with different aetiological origin within the population of 83 million inhabitants of Germany since 1993. In keeping with a number of other epidemiological studies in many European countries, we used a prospective approach. We found an increase in incidence (1.1–1.6) and mortality (0.9–1.3) of sCJD during the years 1994–2005 as also described for other countries, but more or less stable levels since 1998. This might be the years 1994–2005 as also described for other countries, incidence (1.1–1.6) and mortality (0.9–1.3) of sCJD during used a prospective approach. We found an increase in epidemiological studies in many European countries, we Germany since 1993. In keeping with a number of other origin within the population of 83 million inhabitants of spongiform encephalopathy with different aetiological

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This study analyses a large number of patients with spongiform encephalopathy with different aetiological origin within the population of 83 million inhabitants of Germany since 1993. In keeping with a number of other epidemiological studies in many European countries, we used a prospective approach. We found an increase in incidence (1.1–1.6) and mortality (0.9–1.3) of sCJD during the years 1994–2005 as also described for other countries, but more or less stable levels since 1998. This might be associated with improvement in the diagnostic techniques and better recognition of atypical clinical presentations, which is underlined by a trend towards higher proportion of MV and VV (Brandel et al., 2000; Zerr et al., 2000b; Saiz et al., 2001; Krasianski et al., 2006b). Furthermore, after the recognition of vCJD and its connection to BSE became widespread, an increased awareness on the part of physicians and relatives might have influence differential diagnostic considerations. In 2001, Switzerland described a rise of incidence from 1.4 in 2000 to 2.5 in 2001 and a stable level of about 2.5 within the last few years (Glatzel et al., 2003). Initial surmises for the presence of a cluster and possible connection to BSE could not be confirmed. Instead, these figures seem to be the effect of better surveillance with a potentially higher percentage of the atypical MV2 subtype. An equivalent sudden rise is not observed in Germany (Table 1).

The median age of our sCJD patients (66 years) was comparable to the data from the literature. Incidence and mortality clearly decrease after a peak between 70 and 79 years similar to other studies on sCJD, but in contrast to other neurodegenerative diseases which tend to increase with age (Ott et al., 1998; Ladogana et al., 2005). This finding can be explained by an under-ascertainment of patients in the group of old and very old people. Another potential explanation could be that clinical presentation is less typical in elder people. However, our data found similar diagnostic value of 14-3-3 (>80 years, 94%; 60–69 years, 96%), higher frequency of PSWCs (>80 years, 66%; 60–69 years, 54%), but lower sensitivity of MRI findings.
 (>80 years, 35%; 60–69 years, 57%) in patients over 80 years as compared to the median age groups. The correct clinical classification for sCJD by comparison of clinical classification and autopsy result is similar to middle age groups (Table 2). Hence, there might be other (clinical) factors, which influence the decrease of incidence in the elderly.

The patients with 50 years age or younger at symptom onset are rare (3% of all sCJD). While up to now no patient with vCJD in Germany was identified, these patients are of special interest. The clinical syndrome in young sCJD patients in Germany differs not only from vCJD, but also from sCJD patients at the typical age at onset between 60 and 70 years (Boesenberg et al., 2005). Thus, it seems unlikely that a patient with variant CJD was misclassified as sCJD. The detection of the pulvinar sign in the MRI is an important non-invasive tool to distinguish vCJD and sCJD and is reported in 78% of vCJD patients (Will et al., 2000), but also in MV2 sporadic CJD subtype (Krasnianski et al., 2006b). In our subgroup of young sCJD patients, we observed hyperintense basal ganglia in 56%, but no pulvinar sign (Boesenberg et al., 2005). However, because the MRI might be normal in early disease stages, we would like to stress the importance of neuropathological examination of all suspected CJD patients, being extremely important in young patients with dementia.

Many reports on patients with clinical syndromes mimicking CJD are found in the literature with a broad range of diagnoses (Haik et al., 2000; Tschampa et al., 2001; Slee et al., 2006; Valadi et al., 2006). Additionally, reports on false positive 14-3-3 and EEG findings exist (Vander et al., 2004; Bersano et al., 2006; Hoffman Snyder et al., 2006). This raises the question of the value of the clinical criteria which include clinical signs and symptoms and technical investigations. In our patient group, the value of these criteria seem to be very high, especially for the classification as probable sCJD. The clinical symptoms can be masqueraded by several syndromes, and they might be hard to distinguish without positive 14-3-3, PSWCs or MRI scans. This is underlined by a worse reliability of the classification possible sCJD (in autopsy only 58% confirmed sCJD, 42% other disease). The patients classified as other and later confirmed as sCJD were not recognized because the clinical criteria were not fulfilled (missing dementia, isolated dementia, dementia and ataxia only). The proportion of these patients is relatively low and change of the criteria for less-stringent clinical symptoms might result in decreased specificity. On the other hand, 50% of these patients had typical MRI changes. Thus, MRI can support diagnosis also in atypical patients.

Codon 129 polymorphism analyses revealed a genotype distribution as known for sCJD, with an increase of methionine homozygous in favour of MV compared to the normal population. In recent years, the proportion of patients with the MM genotype is slightly decreasing in favour of the MV and the VV type (Fig. 1). This might be due to better diagnosis in patients with atypical subtypes and also explains in part the increase in overall incidence of sCJD since 1993 in Germany. The homozygous patients presented with shorter disease duration than MV patients as reported previously (Deslys et al., 1998; Parchi et al., 1999; Pocchiari et al., 2004). Clinical characteristics in our cohort were influenced by PrPSc type 2 (longer disease duration, less sensitivity of 14-3-3 and EEG) and the presence of at least one valine allele (longer disease duration, less sensitivity of EEG, trend to younger age at onset) (Table 3). These data are in line with studies on sCJD which showed higher sensitivity for 14-3-3 and PSWCs and shorter disease duration for patients with PrPSc type 1 protein (Zerr et al., 2000a; Castellani et al., 2004; Pocchiari et al., 2004; Sanchez-Juan et al., 2006) and lower sensitivity of EEG in presence of a valine allele (Collins et al., 2006).

Genetic analysis of the PRNP gene revealed a number of mutations resulting in GSS, FFI or genetic CJD (Windl et al., 1999). The proportion of patients with inherited prion disease in Germany (6%) is comparable to the data given in the literature. The percentage of inherited prion diseases varies among the countries and is higher in Slovakia (69.5%), Italy (17%) and Austria (14%) and lower in Switzerland (1%) and the Netherlands (2%) (Kovacs et al., 2005). The average rate of inherited prion diseases in Europe is 10.2%, and after exclusion of Slovakia (nearly 70% inherited prion diseases), the rate is 9.45%. Thus, the figures from Germany are only slightly lower. The cause of the large variance in proportion of inherited prion diseases between the countries is not clear. One reason of high incidence of inherited prion diseases in other countries might be due to the founder effect (Lee et al., 1999). Because of quite long disease duration, atypical clinical course and low sensitivity of the technical analyses, patients with genetic TSE might be misdiagnosed as another neurodegenerative disorder (Table 4).

In Germany, the incidence of iatrogenic transmission has been much lower than for other countries with CJD surveillance. Most iatrogenic cases worldwide (n = 138) are associated with human pituitary growth hormone (n = 105), especially in France and UK (Brown et al., 2000, 2006; Swerdlow et al., 2003). In Germany, there has been no patient with such a transmission reported to date. Of the 10 iatrogenic patients in Germany, eight came from transmission by lyophilized dura mater grafts and two by corneal transplant. As described in the literature, incubation time in the patients in our study varied from 1 to 30 years (Brown et al., 2000; Will, 2003).

Analysis of differential diagnosis revealed Alzheimer’s disease as the most frequent other diagnosis among our selected patients. This is not surprising, as it represents the most frequent cause of dementia in the elderly (Ruitenberg et al., 2001; McMurtray et al., 2006). Other diagnoses such as inflammatory diseases and metabolic disorders presented with a clinical syndrome similar to that of prion diseases in our study. Surprisingly, a few cases later
neuropathologically confirmed as sCJD (supplemental data) were diagnosed clinically as other diseases because of results of the CSF tests which were suggestive of inflammatory illnesses. Thus, in particular, inflammatory diseases of the CNS might represent a problem in differential diagnosis (Poser et al., 1999). Neurodegenerative disorders are especially frequent in patients over 75 years at onset. In contrast, as expected, in younger patients below the age of 50 years at onset, potentially reversible disorders play a major role (Harvey et al., 2003; Sampson et al., 2004).

Despite intensive analysis and careful epidemiology, no patient with vCJD has been found in Germany so far. Since the first description in 1996 in the UK, 201 patients have been registered with vCJD worldwide. Although by far most of the cases are still identified in UK, a few patients with vCJD have been reported in several other countries. Thus, further surveillance and evaluation of all suspected CJD patients is necessary to recognize the implications for the healthcare system and allow it to react promptly.

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