Clinical findings and diagnostic tests in Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease

Anna Krasnianski, Bettina Meissner, Uta Heinemann, Inga Zerr
Department of Neurology, Georg-August-University Göttingen, Germany

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare transmissible disease caused by accumulation of pathological prion protein in the CNS. sCJD typically affects patients in their sixties. The median disease duration in sCJD (6 months) is shorter than in variant Creutzfeldt-Jakob disease (vCJD) (14 months). The clinical diagnosis in sCJD is supported by the detection of periodic sharp and slow wave complexes (PSWC) in the electroencephalogram, 14-3-3 proteins in the cerebrospinal fluid (CSF) and hyperintense basal ganglia on magnetic resonance imaging (MRI). In contrast to sCJD, hyperintensities in the posterior pulvinar (the “pulvinar sign”) are seen in vCJD. Different sCJD subtypes characterised by distinct neuropathological lesion profiles, clinical features and codon 129 genotype of the prion protein gene (PRNP) are described, together with the type with a proteinase K-resistant core of the prion protein. The sensitivity of diagnostic tests varies considerably in different sCJD subtypes. Alzheimer’s disease and Lewy body dementia are the most frequent differential diagnoses in elderly patients, while chronic inflammatory CNS disorders have to be considered in younger patients.

key words: sCJD, vCJD, FFI, GSS, familial CJD, CSF, 14-3-3, EEG, MRI

INTRODUCTION

Human spongiform encephalopathy was first described by Hans Gerhard Creutzfeldt and Alfons Jakob in the early 1920s [16, 37]. Initially, Creutzfeldt-Jakob disease was considered as an exclusively neurodegenerative disorder. Later hereditary prion diseases were described: genetic/familial CJD, fatal familial insomnia (FFI) and Gerstmann-Sträussler-Scheinker syndrome (GSS). Finally, transmitted cases (resulting from iatrogenic exposure or by ritualistic cannibalism, as in kuru) were identified. A new variant of CJD linked to BSE was found in 1996 [92]. Recently vCJD transmission by blood transfusion has been reported in two out of 18 patients who received blood transfusions from donors who later developed vCJD [50, 65]. In contrast, sCJD transmission by blood transfusion has so far not been reported. The diagnosis of CJD during the patient’s life-time is rather difficult, especially in atypical CJD (about 30% of sCJD cases) because of the overlap of clinical symptoms with other neurodegenerative diseases.

According to current clinical criteria [89, 101], definite CJD diagnosis requires neuropathological investigation. However, improvements in the clinical characterisation of different CJD subtypes and diagnostic tests (CSF investigation, EEG and MRI) are increasingly enabling in vivo diagnosis to be made, especially in sCJD. Unfortunately, most diagnostic tests are negative in hereditary prion diseases, and family history is positive.
in only 30% [102]. The diagnosis in hereditary cases can be ensured by analysis of the PRNP gene. In vCJD MRI is the only sensitive non-invasive test. A long initial period without any focal neurological abnormalities makes in vivo vCJD diagnosis especially difficult. Whereas the pathological prion protein (PrPSc) in vCJD is detectable in some peripheral tissues (predominantly in the lymphatic tissue), making diagnosis by tonsil biopsy possible [34], brain biopsy remains the only method for definite sCJD diagnosis in vivo.

**CLINICAL FEATURES OF vCJD AND sCJD**

**Sporadic Creutzfeldt-Jakob disease**

Typically sCJD occurs in the seventh decade of life, although the very young and the very old can also be affected (median age 66; range 19–95 years) [6, 91]. Women are slightly more often affected than men (Fig. 1). The median duration of the disease is 6 months. Such unspecific initial symptoms as depression, sleep disorders or loss of weight are characteristic. Dementia is found in most patients and psychiatric features are frequent, so that about 12% of German CJD patients are referred to the Epidemiological Surveillance Unit by psychiatrists [102]. Initial presentation with visual disturbances, previously known as Heidenhain type [32] or ataxia (formerly Oppenheim type [61]), at disease onset is common (Table 1). Visual hallucinations are frequent and also the most common type of hallucination. Patients often develop frontal brain symptoms such as behavioural disinhibition, including hyperphagia or, in contrast, apathy and lack of interest in their daily activities. Extrapyramidal or pyramidal signs, especially myoclonus, are rare initial symptoms but quite common in the further course of the disease. Typically, myoclonus as a characteristic sign, which often leads to sCJD first being suspected, can be provoked by a loud noise or by tactile stimuli (the startle response). Myoclonus is sometimes spontaneously suspended in the final stage of disease. Sensory symptoms are rare in sCJD [102].

**Variant Creutzfeldt-Jakob disease**

vCJD mainly occurs in young patients (median age at onset 29 years, range 14–74 years). Since the first vCJD case was described in a 74-year old man, this differential diagnosis should be also considered in older patients [51]. vCJD is characterised by certain distinctive features. A wide range of psychiatric abnormalities such as withdrawal, delusions, aggression/irritability, anxiety, hallucinations, depression and first rank symptoms is found in almost all vCJD patients as initial or early stage symptoms. Pain in the limbs and joints as well as painful paraesthesia or dysesthesia is also common (Table 2). Dementia occurs as late as 5 months and the first neurological deficits such as ataxia or involuntary movements 6–7 months after disease onset. The median disease duration of 14 months is twice as long as for sCJD [98, 99].

**GENETICS**

**Genetic prion diseases**

Causal pathogenic mutations in the open reading frame of the human prion protein gene are found in

---

**Figure 1.** Distribution of the age and gender-specific mortality rate. German CJD Surveillance, Göttingen 1993–2005.
about 10% of CJD patients [42]. The familial occurrence of cases has been reported with a broad country-dependent range of frequency: from 1.2% in Switzerland to 69.5% in Slovakia [42]. The PRNP is localised on the short arm of chromosome 20. More than 30 mutations have been described up to now [43]. The inheritance modus of the pathogenic PRNP mutations is autosomally dominant. The most frequent mutations are located at codons 200, 178 and 102.

### MUTATIONS

#### Familial CJD with codon 200 mutation (E200K)

The clinical symptoms in patients with this mutation resemble those in sCJD, making the diagnosis of a hereditary prion disease difficult in the absence of positive family history. Clusters of patients with these mutations have been identified worldwide (Slovakia, Libya, Israel). In Slovakia, 69.5% of CJD cases reported to the local Surveillance Unit have the E200K mutation (glutamine to lysine) [42]. Penetrance of the E200K mutation shows considerable variability. While in Israeli carriers penetrance appears almost complete (89%), in Slovakian and Italian carriers it was reported to be partial (54–59%) [17, 26, 45, 58]. Patients carrying this mutation develop the disease somewhat earlier than sporadic cases (at a median age of 60; range 33–84 years), but later than those with other PRNP mutations. Disease duration is similar to that in sCJD (median 5 months) [43]. As with sCJD, dementia, visual and psychiatric disturbances are common initial symptoms followed by cerebellar ataxia, myoclonus and extrapyramidal and pyramidal signs.

#### Fatal familial insomnia (FFI)

The term “fatal familial insomnia” was first used in 1986 as a description of a neurodegenerative disease in a large Italian family [52]. PRNP analysis revealed a mutation in codon 178 (D178N), resulting in the substitution of asparagine with aspartate. In some countries such as Germany or Spain FFI is the most common prion disease [94, 97]. Age at onset is often lower than for sCJD (median 51; range 19–83 years) [42]. Disease duration is 12.4 months longer than in sCJD. Despite the name of the disease, insomnia is not always a prominent clinical feature in the FFI patients, although a complete disruption of the normal sleep-wake cycle is almost always detectable in polysomnography. As a rule, some autonomic disturbances (sympathetic hyperactivity resulting in loss of weight, restlessness or tachycardia) or disruption of the circadian oscillations of the endocrine functions are present in these patients, in most cases at an early stage of the disease. Myoclonus, pyramidal and extrapyramidal signs can be found later in the progression of the disease [14].

#### Gerstmann-Sträussler-Scheinker syndrome (GSS)

This syndrome was first described in 1936 in a large Austrian family. To date, 11 different mutations of the PRNP causing GSS have been described [96]. By far the most common mutation causing GSS is the P102L mutation (prolin to leucine). Interestingly, this mutation was also found in descendents of the family described by Gerstmann, Sträussler and Scheinker. Clinically, a combination of slowly progressive cerebellar symptoms and late cognitive decline can be found, consistent with the first description of the disease. However, initial presentation with dementia has also been reported [14]. Other typical CJD symptoms such as pyramidal and extrapyramidal disturbances or myoclonus can be observed at a late stage of the disease. Patients are usually affected in the fifth or sixth decade of life. GSS progression is slower than that of sCJD and may span between several months and several years (5 years on average).
Codon 129 genotype

Methionine/valine polymorphism at amino acid position 129 of the PRNP, either homoygosity for methionine (MM) or valine (VV) or heterozygosity (MV), influences the clinical and neuropathological characteristics of both sporadic and hereditary human prion diseases [22]. The MM genotype is the most frequently occurring genotype in sCJD (Table 3). Homozygosity at codon 129 is considered as a predisposing risk factor for sCJD. VV patients tend to be younger than MM or MV patients [46]. All vCJD patients reported so far have been methionine homozygous [93]. The only MV patient to show the asymptomatic changes typical of vCJD in his lymphatic tissues did so several years after a blood transfusion from a patient who later developed vCJD and died of a non-neurological disease [50]. It is, therefore, still unclear whether MV patients may also develop typical vCJD symptoms, remain asymptomatic disease carriers or present with other, as yet unidentified, clinical syndromes. It cannot be ruled out that the incubation period for vCJD in MV patients is longer, since heterozygous patients with iatrogenic CJD were shown to have shorter incubation periods than homozygous ones (the first MM and MV cases in 1989 and the first MV cases in 1994) [21]. Similarly, in homoygous kuru patients the disease occurred earlier and disease duration was shorter than in heterozygous cases [12]. Generally, codon 129 genotype is considered to affect CJD susceptibility, clinical presentation and survival time [67].

Molecular classification of sCJD

As mentioned above, polymorphism for methionine (M) or valine (V) at codon 129 of PRNP has been shown to influence the clinical features of sCJD [22]. In 1996 two PrPSc subtypes in brain homogenates of sCJD patients were identified [63]. The polymorphism at codon 129 and the prion protein types 1 and 2 were the basis for a new molecular classification of sCJD which showed a good correlation with the clinical and pathological phenotype of sCJD and replaced the previous attempts at CJD classification [64].

The MM1/MV1 subtype corresponds to the “classical” or “common” CJD subtype and comprises about 70% of CJD cases [64]. Other subtypes are rare. The data concerning the clinical and neuropathological features of different CJD subtypes are shown in Table 4.

**Table 3. Codon 129 genotype distribution**

<table>
<thead>
<tr>
<th></th>
<th>MM (42%)</th>
<th>MV (45%)</th>
<th>VV (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>42%</td>
<td>45%</td>
<td>13%</td>
</tr>
<tr>
<td>Sporadic CJD</td>
<td>67%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Genetic CJD</td>
<td>69%</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Iatrogenic CJD</td>
<td>54%</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Variant CJD</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>FFI</td>
<td>71%</td>
<td>29%</td>
<td>16%</td>
</tr>
<tr>
<td>GSS</td>
<td>52%</td>
<td>32%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*aLadogana et al., 2005  
bPopulation in Germany*

Neuropathology

Neuropathological investigation is currently the only method for definite CJD diagnosis. While tonsil biopsy allows a vCJD diagnosis [34], a brain biopsy or autopsy is necessary in other CJD types. The three classical neuropathological findings in CJD are spongiform degeneration, astrocytic gliosis and nerve cell loss. The immunohistochemical detection of the pathological form of the prion protein is the basis for the definite diagnosis of a prion disease. Since 2000 paraffin-embedded tissue blot (PET blot) has offered a new method, more sensitive than the conventional western blot and histoblot techniques, for the detection of pathological prion protein. PET blot was reported to detect PrPSc even in cases with negative immunohistochemistry [72].

CEREBROSPINAL FLUID

Standard investigations

Cell count, brain-blood barrier function and inflammatory response in CJD patients are generally normal [36]. In patients with definite and probable sCJD (n = 165), a slight pleocytosis (up to 14 cells/mm³) and a moderately impaired brain-blood barrier function was observed in 25% [36]. Oligoclonal bands were found in the CSF of some patients using isoelectric focusing [6, 36, 39, 60]. However, the presence of such bands or intrathecal synthesis of antibodies against herpes simplex or varizella zoster virus is not common in CJD patients, and the origin of these abnormalities is not clear. However, similar changes were also found in non-neurological controls and may represent a residuum of earlier inapparent infections [49, 78]. The development of a method which allows the detection of specific disease-associated PrPSc forms in a biological fluid remains the ultimate aim. However, the clinical diagnosis of sCJD could also have been improved in recent years by the detection of brain-derived proteins (so-called surrogate markers) in the CSF.
Surrogate markers

Amongst the earliest CSF markers reported were p130/p131 proteins, detected using a time and labour consuming two-dimensional gel electrophoresis. These were, however; also present in 50% of patients with herpes simplex encephalitis [31]. Amino acid sequence analyses showed that these proteins belonged to the family of 14-3-3 proteins [35]. Detection of 14-3-3 proteins by western blot made the CSF analysis for these proteins easier. Other brain proteins such as neuron-specific enolase (NSE), S-100B protein and tau protein were measured in high concentrations in the CSF of sCJD patients. An increase of these proteins with disease progression in follow-up examinations and a decrease in end-stage disease are typical for sCJD [38]. In contrast, S-100B as a gliosis marker sometimes increases in the final stage of disease when other CSF markers are no longer detectable. In keeping with the findings for Alzheimer’s disease, Aβ-amyloid is decreased in the CSF of CJD patients [87].

14-3-3 proteins

The detection of 14-3-3 proteins in the CSF is sensitive for the diagnosis of sCJD, and in patients with codon 200 and 210 mutations [69, 100]. 14-3-3 proteins were shown to be positive in 95% of sCJD patients [101]. The origin of 14-3-3 in the CSF is still unknown. It has been suggested that it could be the product of neuronal damage. Alternatively, 14-3-3 could be involved in the pathogenesis of the disease, since an upregulation could be shown recently in the glial cells in patients with sporadic CJD [40]. In a recent multi-centre European study the 14-3-3 protein detection rate in sCJD was lower than reported previously, potentially because of more restrictive laboratory protocols and a higher proportion of atypical sCJD subtypes (Table 5) [70]. 14-3-3 protein is typically negative in FFI and uncommon in GSS (Table 5). The sensitivity is low in patients with iatrogenic CJD (60%), but may increase when the CSF is taken in later stages of the disease [5]. In vCJD only about half of the patients reported so far have had elevated 14-3-3 levels [27, 70, 92] (Table 5). Simultaneous analysis for at least two of the proteins increases the sensitivity of the CSF investigation in CJD (Table 6). Factors associated with higher 14-3-3 sensitivity are a disease duration of less than 6 months, an age at onset of over 40 years, codon 129 homozygosity, PrPSc type I and an advanced disease stage at the time of lumbar puncture [70]. Elevation of 14-3-3 proteins is not CJD-specific and occurs in several conditions associated with acute neuronal damage [4, 7] (Table 7). Usually, these disorders can be differentiated from CJD by clinical history, brain imaging and CSF examination. In other neurodegenerative disorders only rare cases are positive for 14-3-3. Interestingly, 14-3-3 positive patients with neurodegenerative disease often show an unusually rapid course of the disease, presumably associated with pronounced neuronal damage and the resulting 14-3-3 protein emis-

Table 4. Molecular subtypes of sCJD (clinical and pathological characteristics)*

<table>
<thead>
<tr>
<th>Molecular disease subtype</th>
<th>Median age at onset</th>
<th>Median duration months (range)</th>
<th>Most prominent clinical signs/symptoms</th>
<th>Neuropathological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td></td>
<td></td>
<td>Dementia, cortical anopsia, myoclonus</td>
<td>Prominent involvement of occipital cortex, “synaptic type” PrP staining</td>
</tr>
<tr>
<td>MV2</td>
<td>64 (53–76)</td>
<td>12 (4–27)</td>
<td>Ataxia, dementia, extrapyramidal signs</td>
<td>Similar to VV2, focal involvement of the cortex, amyloid-kuru plaques in the cerebellum, plaque-like focal PrP deposits</td>
</tr>
<tr>
<td>VV2</td>
<td>61 (40–76)</td>
<td>7 (3–18)</td>
<td>Ataxia at onset, late dementia</td>
<td>Prominent involvement of subcortical structures including brain stem nuclei, spongiosis often limited to deep cortical layers, plaque-like PrP staining, prominent perineuronal staining</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
<td></td>
<td>Insomnia, dyautonomia at onset, later ataxia and cognitive impairment</td>
<td>Atrophy of the thalamus and inferior olive; spongiosis may be absent or focal</td>
</tr>
<tr>
<td>MM2-thalamic</td>
<td>52 (36–71)</td>
<td>16 (8–24)</td>
<td>Progressive dementia for several months</td>
<td>Large confluent vacuoles with perivacuolar PrP staining</td>
</tr>
<tr>
<td>MM2-cortical</td>
<td>64 (49–77)</td>
<td>16 (9–36)</td>
<td>Dementia at onset, late ataxia and extrapyramidal signs</td>
<td>Severe pathology in the cerebral cortex and striatum with sparing of brain stem nuclei and cerebellum</td>
</tr>
<tr>
<td>VV1</td>
<td>44 (19–55)</td>
<td>21 (17–42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data from German CJD Surveillance and according to Krasnianski et al., 2005; Meissner et al., 2005; Parchi et al., 1999; Zerr et al., 2000, Zerr & Meissner, 2005
sion. False-negative results have also been described and some explanations suggested. A lower sensitivity was found in sCJD with a longer disease duration and heterozygosity at codon 129 of the prion protein gene [10, 85, 103]. In doubtful cases lumbar puncture repeated about 4 weeks after the first test may be helpful, as an a 14-3-3 increase is usually observed in CJD patients. In patients with acute neuronal damage caused by other pathological events a 14-3-3 decrease is frequently seen. It should be emphasised that detection of an abnormal concentration of the brain proteins in the CSF should always be interpreted in the clinical context and is not suitable for general screening of patients with dementia [47, 103].

**EEG**

Periodic sharp and slow wave complexes are a characteristic electroencephalographic pattern in CJD (Fig. 2). Criteria for the detection of PSWC in the EEG in Creutzfeldt-Jakob disease are shown in Table 8. Some patients show PSWC as early as three weeks after disease onset, but in most cases they occur after about 12 weeks [75]. PSWC are observed in about 60–70% of CJD patients during the course of the disease and are more often in the classical MM1/MV1 form than in atypical CJD cases. Early in the disease process there is no correlation between PSWC and the severity of the disease. However, there is a correlation between early occurrence and shorter survival [48]. In genetic CJD

### Table 5. CSF marker sensitivity in prion diseases (positive cases/total)

<table>
<thead>
<tr>
<th>Disease subtype</th>
<th>14-3-3</th>
<th>Tau</th>
<th>S100B</th>
<th>NSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic CJD</td>
<td>85% (1240/1457)</td>
<td>86% (704/819)</td>
<td>82% (483/589)</td>
<td>73% (379/517)</td>
</tr>
<tr>
<td>Variant CJD</td>
<td>40% (37/93)</td>
<td>24% (21/86)</td>
<td>62% (55/87)</td>
<td>24% (6/25)</td>
</tr>
<tr>
<td>Iatrogenic CJD</td>
<td>75% (15/20)</td>
<td>53% (8/15)</td>
<td>81% (13/16)</td>
<td>44% (4/9)</td>
</tr>
<tr>
<td>Genetic CJD*</td>
<td>78% (109/139)</td>
<td>82% (47/57)</td>
<td>82% (28/34)</td>
<td>60% (21/35)</td>
</tr>
<tr>
<td>FFI</td>
<td>9% (2/23)</td>
<td>0% (0/12)</td>
<td>22% (2/9)</td>
<td>0% (0/10)</td>
</tr>
<tr>
<td>GSS</td>
<td>0% (0/7)</td>
<td>50% (1/2)</td>
<td>100% (1/1)</td>
<td>0% (0/2)</td>
</tr>
</tbody>
</table>

*FFI and GSS patients not included
Sanchez-Juan et al., 2005 (modified)
Cut-off Tau protein 1300 pg/ml; S100B 4.2 ng/ml (Byk-Sangtec kit) and 0.5 ng/ml (house kit used in the UK); NSE 35 ng/ml (Hoffman La Roche kit) and 25 ng/ml (Byk-Diasorin, Byk-Sangtec and Wallac kits)

### Table 6. Sensitivity and specificity of CSF marker combinations in sCJD (sensitivity as numerator; specificity as denominator)

<table>
<thead>
<tr>
<th>14-3-3</th>
<th>Tau</th>
<th>NSE</th>
<th>S100B</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-3-3</td>
<td>–</td>
<td>94%/68%</td>
<td>94%/68%</td>
</tr>
<tr>
<td>Tau</td>
<td>–</td>
<td>91%/88%</td>
<td>93%/69%</td>
</tr>
<tr>
<td>NSE</td>
<td>–</td>
<td>86%/82%</td>
<td></td>
</tr>
</tbody>
</table>

Sanchez-Juan et al., 2005 (modified)

### Table 7. Elevated 14-3-3 levels in neurological disorders other than prion diseases

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Ischemia, haemorrhage, vascular dementia</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Acute/chronic</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Tumour including metastasis and CNS lymphoma, meningeosis carcinomatosa, paraneoplastic syndromes</td>
</tr>
<tr>
<td>Neurodegenerative</td>
<td>Single cases of Alzheimer’s disease, Lewy body dementia, frontotemporal dementia</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Hashimoto encephalopathy</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypoxia, MELAS</td>
</tr>
<tr>
<td>Other</td>
<td>Shortly after epileptic fits</td>
</tr>
</tbody>
</table>
PSWC are seen in patients with codon 200 and 210 mutation but are absent in FFI and GSS. The EEG is not informative in iatrogenic human growth hormone cases and in vCJD [5, 99].

**Magnetic resonance imaging**

MRI has been included in the diagnostic criteria of vCJD as pronounced signal changes are observed in the posterior pulvinar in 71% of vCJD cases on T2-weighted images and in up to 100% on FLAIR (fluid-attenuated inversion recovery) images (“pulvinar sign”) [13]. The pulvinar sign is defined as the state in which pulvinar hyperintensities are more pronounced in the pulvinar than in the basal ganglia (Fig. 3) [13].

Although not yet part of the diagnostic criteria of sCJD, MRI has played an important role in the diagnosis of CJD since the late 1980s. In 1988 basal ganglia hyperintensities on T2-weighted images were first described as a characteristic finding in sCJD patients [25]. With the emergence of more sensitive MRI techniques such as FLAIR (Fig. 4) and diffusion-weighted image (DWI), cortical signal increase was additionally seen in sCJD patients [3], and hyperintense basal ganglia were detected more frequently (Fig. 5). In a former study analysing the findings on T2-weighted MRI a sensitivity of 63% was found for hyperintense basal ganglia [56]. Studies including FLAIR and DWI scans achieved a sensitivity of up to 92% [74] (Table 9). Hyperintense basal ganglia were also reported in other conditions [56] (Table 10). Specificity ranged from 88% [56, 80] to 94% [74]. There is evidence for DWI as the most sensitive technique for the detection of signal alterations in CJD patients, especially with respect to cortical hyperintensities [84] (Fig. 5). Furthermore, DWI has been shown to have the highest sensitivity for signal alterations in the early stage of disease [1, 74, 77]. By means of FLAIR and DWI signal increase in the cortex has been reported even more frequently than in the basal ganglia (Table 9) [82]. In a recent study analysing the MRI findings in 40 definite

---

**Table 8. Standardised EEG criteria for detection of periodic sharp and slow wave complexes in CJD**

- Periodicity
- “Sharp-wave” complexes
- At least five complexes
- Frequency 0.5–2/sec
- Duration 100–600 msec
- Amplitude > 150-300 $\mu$V

---

Figure 3. Pulvinar sign in vCJD (FLAIR). Dr. D. Collie, CJD, Surveillance Unit, UK.

Figure 4. Hyperintense basal ganglia in sCJD (FLAIR).
or probable CJD patients cortical signal increase was observed in 94% of the patients. In 68% the cortex was affected in combination with the subcortical structures (striatum and/or thalamus) while in 24–42% the cortex alone was affected [74, 95]. The pattern of MRI signal changes most likely depends on the underlying sCJD subtypes (Table 11). Only limited data is available on serial MRI in CJD. Usually signal changes increase as the disease progresses and become more widespread in all the regions affected [2, 55, 79]. Basal ganglia signal alterations may be seen only during the later disease stages, following the cortical signal increase [20, 44, 71, 79]. In some cases they represent an early finding too; since MRI sensitivity is high and signal changes can be observed even in the early stage of disease, the detection of pathognomonic changes by brain imaging seems to be a helpful test for early CJD diagnosis.

**SPECT AND PET**

Neuroimaging with specific ligand techniques or tracers is able to demonstrate the metabolic processes in the CNS. A reduction of glucose metabolism can be shown by positron emission tomography (PET), whereas a reduction of cerebral blood flow (CBF) can be displayed by sin-

---

**Table 9. Signal increase on MRI (review of the literature)**

<table>
<thead>
<tr>
<th>Studied cases</th>
<th>Cortex</th>
<th>Basal ganglia</th>
<th>Thalamus*</th>
<th>Imaging techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Finkenstaedt et al., 1996) n = 29</td>
<td>n.m.</td>
<td>79%</td>
<td>14%</td>
<td>T2</td>
</tr>
<tr>
<td>(Grisoli et al., 1999) n = 31</td>
<td>16%</td>
<td>26%</td>
<td>42%</td>
<td>T2, FLAIR</td>
</tr>
<tr>
<td>(Schröter et al., 2000) n = 162</td>
<td>4% (occipital)</td>
<td>67%</td>
<td>7%</td>
<td>T2, PD, FLAIR, (5 DWI)</td>
</tr>
<tr>
<td>(Meissner et al., 2004) n = 153</td>
<td>n.m.</td>
<td>63%</td>
<td>n.m.</td>
<td>T2 Sensitivity#: 63% Specificity: 88%</td>
</tr>
<tr>
<td>(Shiga et al., 2004) n = 36</td>
<td>81%</td>
<td>54%</td>
<td>n.m.</td>
<td>DWI</td>
</tr>
<tr>
<td>(Tschampa et al., 2005a) n = 144</td>
<td>n.m.</td>
<td>16% (T2) 33% (PD) 47% (FLAIR) 77% (DWI)</td>
<td>n.m.</td>
<td>T2, PD, FLAIR, DWI Sensitivity#: 63/63/74% Specificity: 88/89/77% (3 observers)</td>
</tr>
<tr>
<td>(Young et al., 2005) n = 40</td>
<td>68% Cortex + striatum and/or thalamus 24% cortex alone 5% striatum and/or thalamus alone</td>
<td>FLAIR, DWI Sensitivity#: 73%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n.m. = not mentioned

*Further case reports: Bahn et al., 1997; Fukushima et al., 2004; Pauri et al., 2004; Petzold et al., 2004; Puvaneswary et al., 1998; Rossetti et al., 2003; Samman et al., 1999; Shyu et al., 1996; Tribl et al., 2002

#for detection of basal ganglia
gle photon emission computed tomography (SPECT). Unlike Alzheimer’s or Lewy body disease, where specific lesion patterns on SPECT have been described [11], no characteristic pattern has been found in CJD. On the other hand, no CJD patient has been reported without SPECT or PET abnormalities. Hypoperfusion on SPECT is usually widespread and frequently includes the temporal and occipital lobes [33]. A reduction of CBF was also seen in the thalamic nuclei, the cerebellum and the basal ganglia in single cases [19, 24]. The findings on SPECT and PET usually correlate with the clinical symptoms and signal increase on DWI [23, 59, 76, 83]. An effect on brain regions may be seen on SPECT or PET very early, at a time when MRI is still normal [28, 41, 88].

Only limited data is available on SPECT/PET abnormalities in distinct sCJD subtypes. In patients with the MM2 thalamic type (sporadic fatal insomnia), hypoperfusion or hypometabolism of the thalamus has been reported as a typical finding, while MRI did not display any abnormalities [30, 54]. In a study on the rare VV1 subtype the temporal lobes were seen to be affected in all patients on SPECT or PET and in some as early as one month after onset. Other cortex areas were, however, affected as well [57]. PET may also be valuable for the identification of FFI, where no specific findings can be obtained by MRI, EEG or CSF investigation; hypometabolism of the thalamus and cortex has been displayed by FDG (18F-2-fluoro-2-desoxy-D-glucose) PET in FFI.

Table 10. Basal ganglia hyperintensities in non-CJD patients

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/chronic inflammatory</td>
<td>Germinoma</td>
</tr>
<tr>
<td>AIDS</td>
<td>Neurodegenerative</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Lewy body dementia</td>
</tr>
<tr>
<td>Cryptococcosis in HIV</td>
<td>Mitochondriopathies</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>Vascular autonomic dominant arteriopathy with subcortical infarcts and leukencephalopathy (CADASIL)</td>
</tr>
<tr>
<td>Poststreptococcal encephalitis</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td></td>
</tr>
<tr>
<td>Metabolic/toxic</td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
<td></td>
</tr>
<tr>
<td>GM1 gangliosidosis</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
</tr>
<tr>
<td>CO intoxication</td>
<td></td>
</tr>
</tbody>
</table>

Meissner et al., 2004

Table 11. Diagnostic tests in various CJD subtypes

<table>
<thead>
<tr>
<th>Typical tests</th>
<th>Sporadic MM1/MMV1</th>
<th>MM2 MV2</th>
<th>VV1</th>
<th>VV2</th>
<th>GSS</th>
<th>FFI</th>
<th>vCJD</th>
<th>ICJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>PSWCs</td>
<td>(+)/–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(+)</td>
<td>–</td>
</tr>
<tr>
<td>CSF</td>
<td>14-3-3</td>
<td>(+)/–</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>–</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
<td>(+)/–</td>
<td>+</td>
<td>(+)</td>
<td>–</td>
<td>?</td>
<td>?</td>
<td>(+)</td>
</tr>
<tr>
<td>Cortex</td>
<td></td>
<td>(+)/–</td>
<td>+</td>
<td>(?</td>
<td>?</td>
<td>?</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>MRI</td>
<td>Thalamus Hyperintensity</td>
<td>–</td>
<td>–</td>
<td>(+)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Pulvinar sign</td>
<td></td>
<td>–/–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

| c/t Cortical/thalamic subtype; # E200K and V210I mutation; °° Late in the disease; (+) = Reported but not frequent; ? = insufficient data |
| 1Corresponds to classical sCJD with a rapid disease course |
| 2The MRI may resemble vCJD |
| 3EEG may become positive during the later disease stage |

Abnormal PrPSc can be detected in the tonsils by biopsy. Tonsil biopsy is only recommended in suspected vCJD but no pulvinar sign in the MRI.
patients [15, 66]. The diagnostic utility of SPECT and PET has not been evaluated systematically in CJD patients, but the results obtained to date suggest that both techniques might be useful.

**DIAGNOSTIC CRITERIA**

**Sporadic CJD**

The clinical symptoms and signs are the basis for the diagnosis of sCJD. A few years ago the set of diagnostic criteria, which had previously included only EEG as an additional diagnostic test [53], was expanded by to include 14-3-3 protein investigation (Fig. 6) [89, 101]. The definition of ataxia and pyramidal/extrapyramidal symptoms and signs is usually not a subject of discussion, although the definition of some other typical CJD symptoms/signs sometimes leads to difficulties in clinical practice. We would like to emphasise the following aspects of definition: 1) Myoclonus may be defined as single or repetitive, abrupt, brief, rapid, lightning-like, jerky, arrhythmic, asynergic, involuntary contractions involving portions of muscles, entire muscles, or groups of muscles [9]. In contrast to focal epileptic fits, the muscle contractions are not rhythmic; 2) In contrast to elementary visual phenomena (flashes, coloured lights), the scenic hallucinations and other complex visual phenomena typically found in CJD [102] should not be interpreted as visual symptoms; 3) There is often some uncertainty with regard to the difference between akinetic mutism and apallic syndrome. Akinetic mutism is defined as a condition of apparent alertness along with a lack of almost all motor functions including speech, gestures, and facial expression [8]. In contrast to apallic syndrome, visual fixation is present [62].

**Variant CJD**

Clinical criteria for vCJD were established in 2000 [93]. Along with a number of clinical signs/symptoms MRI was included as the only non-invasive diagnostic test where a bilateral high pulvinar signal is required. Later the definition of “pulvinar sign” was made more precise (Table 12) [90].

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of sCJD includes a large number of neurological and psychiatric diseases (Table 13). In most cases the diagnosis of CJD as a primary diagnosis is not taken into account when patients are admitted to hospital. Alzheimer’s disease is the most important differential diagnosis in older patients [18, 29, 68, 81, 86]. Rapid disease courses, in particular, can rarely be discriminated from CJD, especially when myoclonus is present. The detection of the 14-3-3 protein in CSF helps to distinguish between CJD and Alzheimer’s disease and Lewy body dementia, as increased concentrations of

---

### Table 12. Diagnostic criteria for variant Creutzfeldt-Jakob disease.

<table>
<thead>
<tr>
<th>WHO criteria for variant CJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A Progressive neuropsychiatric disorder</td>
</tr>
<tr>
<td>B Duration of illness &gt; 6 months</td>
</tr>
<tr>
<td>C Routine investigations do not suggest an alternative diagnosis</td>
</tr>
<tr>
<td>D No history of potential iatrogenic exposure</td>
</tr>
<tr>
<td>E No evidence of familial prion disease</td>
</tr>
<tr>
<td>II A Early psychiatric symptoms</td>
</tr>
<tr>
<td>B Persistent painful sensory symptoms</td>
</tr>
<tr>
<td>C Ataxia</td>
</tr>
<tr>
<td>D Myoclonus or chorea or dystonia</td>
</tr>
<tr>
<td>E Dementia</td>
</tr>
<tr>
<td>III A EEG does not show the typical appearance of sporadic CJD</td>
</tr>
<tr>
<td>(or EEG not performed)</td>
</tr>
<tr>
<td>B Bilateral pulvinar high signal on MRI brain scan</td>
</tr>
<tr>
<td>IV A Positive tonsil biopsy</td>
</tr>
<tr>
<td>DEFINITE</td>
</tr>
<tr>
<td>PROBABLE</td>
</tr>
<tr>
<td>POSSIBLE</td>
</tr>
</tbody>
</table>

---

*Depression, anxiety, apathy, withdrawal, delusions.

*This includes both frank pain and/or dysesthesia.

*Generalised triphasic periodic complexes at approximately one per second.

*Tonsil biopsy is not recommended routinely, not in cases with EEG appearances typical of sporadic CJD, but may be useful in suspected cases in which the clinical features are compatible with vCJD and MRI brain scan does not show bilaterial pulvinar high signal.

*Spongiform change and extensive PrP deposition with florid plaques throughout the cerebrum and cerebellum.
this protein are only found in the CSF in exceptional cases of other neurodegenerative diseases [100]. Basal ganglia hyperintensities on MRI are extremely rare in the non-CJD dementias frequently found in elderly patients (Alzheimer’s disease, Lewy body dementia and vascular dementia) [56]. Chronic encephalitis is a common differential diagnosis in younger patients [68]. Encephalitis associated with Hashimoto’s disease is a form of dementia for which the treatment prospects are particularly good [73]. Investigation of thyroid antibodies should, therefore, be performed in all cases of unclear dementia, even if thyroid function is normal. In vCJD, other differential diagnoses have to be considered because of the different age of disease onset and the frequent sensory disturbances (polyneuropathy, vitamin B12 deficiency and Wilson’s disease). However, sCJD is still the most frequent differential diagnosis of vCJD.

CONCLUSIONS

In recent years there has been progress in in vivo CJD diagnosis, especially as a result of the use of MRI. However, this diagnostic method is still not a part of the diagnostic criteria of sCJD in spite of its sensitivity and specificity. It should be emphasised that CJD remains primarily a clinical diagnosis, and there is no diagnostic test to replace detailed clinical investigation and assessment of the clinical history. Differential diagnosis of CJD is rather difficult. There are several inflammatory and autoimmune diseases which may mimic CJD but which can be well treated. Therefore, if there is any doubt concerning CJD diagnosis, an effort at treatment with high-dose cortisone should be made.

ACKNOWLEDGEMENTS

We are grateful to physicians throughout Germany for referring patients to our Surveillance Unit. The assistance of Jolanthe Zellner and Maja Schneider-Dominco is gratefully acknowledged. We thank Monika Bode-mer and Barbara Ciesielczyk for technical assistance. We thank Dr. D. Collie (Edinburgh) for providing a typical vCJD MRI. This study in Germany was supported by grants from the Federal Ministry of Health and Social Security (325-4471-02/15), the European Commission (QLG3-CT-2002-81606), and the Federal Ministry of Education and Research (01GI0301). This work was supported in part by the grant of State Research Committee and formed a part of the EC concerted action “Neuroprion”.

REFERENCES


---

Table 13. Differential diagnosis of sCJD (n=143) *

<table>
<thead>
<tr>
<th>Causal treatment</th>
<th>n</th>
<th>Symptomatic treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>11</td>
<td>Alzheimer’s disease</td>
<td>38</td>
</tr>
<tr>
<td>Psychosis</td>
<td>6</td>
<td>Vascular dementia</td>
<td>31</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>6</td>
<td>Dementia with Lewy bodies</td>
<td>8</td>
</tr>
<tr>
<td>Paraneoplastic encephalopathy</td>
<td>4</td>
<td>Parkinson + dementia</td>
<td>5</td>
</tr>
<tr>
<td>Steroid-responsive encephalitis</td>
<td>3</td>
<td>Multiple system atrophy</td>
<td>4</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2</td>
<td>Frontotemporal lobar degeneration</td>
<td>3</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>Corticobasal degeneration</td>
<td>2</td>
</tr>
<tr>
<td>Intracerebral neoplasia</td>
<td>2</td>
<td>Chorea Huntington</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral metastasis</td>
<td>2</td>
<td>Glykogen storage disease</td>
<td>2</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
<td>Sporadic subcortical gliosis</td>
<td>2</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>1</td>
<td>Hypoxic brain damage</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin B 12 deficiency</td>
<td>1</td>
<td>Myoclonus epilepsy</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1</td>
<td>Spino cerebellar ataxia</td>
<td>1</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>42</strong></td>
<td></td>
<td><strong>101</strong></td>
</tr>
</tbody>
</table>

*D. Varges, medical thesis, Georg-August University Göttingen, Germany. Data from the German CJD Surveillance study Göttingen (Zerr & Meissner, 2005)
38. Jakob A (1921) Über eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Be-

Anna Krasnianski et al., Clinical findings and diagnostic tests in Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease

Llewelyn CA, Hewitt, PE, Knight, RSG, Amar K, Cousens S, Link H, Kostulas V (1983) Utility of isoelectric focusing of...


Pocchiari M, Poupolo M, Croes EA, Budka H, Gelpi E, Collins S, Lewis V, Sutcliffe T, Guivili A, Delasnerie-Laupretre N, Bran-
del JP, Alperovitch A, Zerr I, Poser S, Kretzschmar H, Ladoga-
na A, Rietveld I, Mitrova E, Martinez-Martin P, de Pedro-Cuesta J,
Glatzel M, Aguzzi A, Cooper S, Mackenzie J, Van Duijn C, Will
R (2004) Predictors of survival in sporadic Creutzfeldt-

68. Poser S, Mollenhauer B, Krauß A, Zerr I, Steinhoft BJ, Schröter A,
Finkenstaedt M, Schulz-Schaeferrer W, Kretzschmar HA, Fel-
genauer K (1999) How to improve the clinical diagnosis of

69. Rosenmann H, Meiner Z, Kanaha E, Halimi M, Lenetsky E,
Abramsky O, Gabizon R (1997) Detection of 14-3-3 protein in
the CSF of genetic Creutzfeldt-Jakob Disease. Neurology,
49: 593–595.

70. Sanchez-Juan P, Green A, Ladogana A, Cuadrado-Corrales N,
Sanchez-Valle R, Mitrova E, Stoeck K, Skilaviadis T, Kulczycki J,
Hess K, Bodemer M, Silvarichova D, Saiz A, Calero M, In-
Cerebrospinal fluid tests in the differential diagnosis of CJD.
Submitted.

71. Satoh A, Goto H, Sato H, Tomita I, Seto M, Furukawa H,
Tsujihata M (1997) A case of Creutzfeldt-Jakob Disease with
a point mutation at codon 232: correlation of MRI and neu-

72. Schulz-Schaeferrer WJ, Tschoke S, Kraneffus N, Drose W,
early in the incubation time in prion diseases. Am J Pathol,
156: 51–56.

73. Seipel T, Zerr I, Nau R, Mollenhauer B, Kropp S, Steinhoff
BJ, Wilhelm-Gössling C, Bamberg C, Janzen RWC, Berlit P,
Manz F, Felgenhauer K, Poser S (1999) Hashimoto enceph-
alitis as a differential diagnosis of Creutzfeldt-Jakob Disease.

74. Shiga Y, Miyazawa K, Sato S, Fukushima R, Shibuya S, Sato Y,
Kono H, Dohura K, Mugikura S, Tamura H, Higano S, Taka-
hashi S, Itoyama Y (2004) Diffusion-weighted MRI abnor-
malities as an early diagnostic marker for Creutzfeldt-Jakob dis-

75. Steinhoft BJ, Zerr I, Glatting M, Schulz-Schaeferrer W, Pos-
cerebral images in Creutzfeldt-Jakob Disease. Ann Neurol,

76. Sunada I, Ishida T, Sakamoto S, Tsuyuguchi N. A discrepan-
cy between Tc-99m HMPAO SPECT and Tc-99m EDC SPECT in


78. Tschampa HJ, Zerr I, Kallenberg K, Meissner B, Kretzschmar
HA, Knauth M, Urbach H (2005) Pattern of cortical changes in

79. Tsuji Y, Kanamori H, Murakami G, Yokode M, Mazaki T, Doh-
ura K, Taniguchi K, Matsubayashi K, Fukuyama H, Kita T,
Tanaka M (2004) Heidenhain variant of Creutzfeldt-Jakob Disease:

80. Ukimura R, Kushihashi T, Kitano S, Hakenaka H, Takenaka
O, Goto H, Kitanosono T, Fujisawa H, Takenaka H,
Ngoya Y, Gokan T, Minamihoka H (2005) Serial diffusion-
weighted MRI of Creutzfeldt-Jakob Disease. Am J Roentgenol,
184: 560–566.

81. Van Everbroeck B, Croes EA, Pals P, Dermout B, Jansen G,
van Duijn CM, Cruts M, Van Broeckhoven C, Martin JJ, Cras P

82. Van Everbroeck B, Bobbeler I, De Waele M, De Deyn P, Mar-

Decreased levels of amyloid-beta 1–42 in cerebrospinal fluid of

84. Watanabe N, Seto H, Shimizu M, Tanii Y, Kim YD, Shibata R,
Wakaguchi M, Tsuji S, Morijiri M, Kageyama M, Wu YY, Kak-
ishita M, Kurachi M (1996) Brain SPECT of Creutzfeldt-Jakob

85. WHO (1998) Human transmissible spongiform encephalop-

86. WHO (2001) The revision of the variant Creutzfeldt-Jakob
(vCJD) case definition. Report of a WHO consultation, 17 May
2001, Edinburgh, United Kingdom.

87. Will RG, Alperovitch A, Poser S, Pocchiari M, Hofman A, Mitro-
va E, de Silva R, D’Alessandro M, Delasnerie-Laupretre N,
1995. EU Collaborative Study Group for CJD. Ann Neurol

88. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibboe K,
Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG

89. Will RG, Zelidier M, Stewart GE, Macleod MA, Ironside JW,
Cousens SN, Mackenzie J, Estibboe K, Green AJ, Knight RS
Ann Neural, 47: 575–582.

90. Windl O, Giese A, Schulz-Schaeferrer W, Zerr I, Skwarc K, Arendt
Hum Genet, 105: 244–252.

91. Young G, Geschwind M, Fischbein NJ, Martindale J, Hen-
(2005) Diffusion-weighted and fluid-attenuated inversion
recovery imaging in Creutzfeldt-Jakob disease: high sen-
sitivity and specificity for diagnosis. Am J Neuroradiol, 26:
1551–1562.


