Brain biopsy in patients with suspected Creutzfeldt–Jakob disease

Clinical article

UTA HENEMANN, M.D.,1 ANNA KRASNIANSKI, M.D.,1 BETTINA MEISSNER, M.D.,1
KAIVALLENBERG, M.D.,2 HANS A. KRETZSCHMAR, M.D.,4
WALTER SCHULZ-SCHAEFFER, M.D.,3 AND INGA ZERR, M.D.1

Departments of 1Neurology, 2Neuroradiology, and 3Neuropathology, National Reference Centre for
Transmissible Spongiform Encephalopathies, Georg-August University, Goettingen; and 4Department of
Neuropathology, Ludwig-Maximilian University, Munich, Germany

Object. Creutzfeldt–Jakob disease (CJD) is a rare neurodegenerative disorder with diagnostic criteria defined as a combination of clinical symptoms, electroencephalography findings, cerebrospinal fluid (CSF) analysis, and MR imaging results. Special subtypes are known to present with an atypical course and test findings that can complicate the clinical diagnosis. In such patients a brain biopsy can support the clinical approach.

Methods. The authors studied the records on 26 brain biopsies conducted in patients with suspected CJD who had been referred to the CJD Surveillance Unit in Germany between 1993 and 2005.

Results. Of the 26 included patients, 11 suffered from neuropathologically confirmed CJD, which in 5 cases had been deemed clinically “probable” and in 2 had been deemed “possible.” The disease in the remaining 4 patients had been categorized as “other” prior to neuropathological confirmation of CJD. The results of 15 brain biopsies showed no features of prion disease. None of these 15 patients had received a probable diagnosis of CJD, 4 had a possible diagnosis, and 11 had received a diagnosis of “other.” Three of the cases classified as other and none of those with CJD presented with pleocytosis in the CSF. In 73% of the other cases, biopsy sampling did not reveal any results characteristic of CJD but did not provide specific findings on which to base a differential diagnosis. Autopsy confirmed the biopsy diagnosis of CJD in all cases, and additionally confirmed that CJD was not present in 3 patients who had nondiagnostic biopsy results.

Conclusions. Biopsy sampling may be helpful in the diagnostic approach to rare cases of dementia for which a reliable diagnosis cannot be established on the basis of clinical symptoms, CSF parameters, electroencephalography, and MR imaging results. (DOI: 10.3171/JNS/2008/109/10/0735)

KEY WORDS • brain biopsy • Creutzfeldt–Jakob disease • dementia

Creutzfeldt–Jakob disease is a rare and fatal neurodegenerative disorder with a worldwide incidence of 1 case per million people. The sporadic form of the disease is the most frequently seen, making up 85% of all cases of CJD; other types include genetic, iatrogenic, and infectious forms.10

The diagnosis of sporadic CJD is based on a clinical examination, EEG, and CSF findings. Clinically, sporadic CJD is characterized by rapidly progressive dementia of < 2 years’ duration combined with typical neurological symptoms such as cerebellar or visual disturbances, pyramidal or extrapyramidal signs, myoclonus, and akinetic mutism. Typical findings in the CSF are detection of 14-3-3 proteins, elevated tau-protein levels, and elevated levels of neurodegenerative markers such as neuron-specific enolase or S100B protein. On EEG, PSWCs are characteristically present. Not yet included in the diagnostic criteria—but suggestive of CJD—are hyperintense basal ganglia on MR imaging, especially on T2-, FLAIR- and diffusion weighted sequences.28

Based on the polymorphism of codon 129 in PRNP with either methionine or valine combined with the prion protein Type 1 or 2 on Western blot, 6 molecular subtypes of sporadic CJD have been defined.18 Some of these
subtypes, such as MV-2 or VV-1, are characterized by an atypical clinical course or the absence of typical sporadic CJD findings in technical examinations. Antemortem diagnosis according to the WHO criteria can be difficult in patients with these subtypes.

Only a few authors have investigated the importance of brain biopsy sampling in the diagnosis of prion diseases.\textsuperscript{27} Besides a number of case reports,\textsuperscript{2,14,20} there are some studies investigating the efficacy of brain biopsy sampling in patients with dementia. In a recent study, 11 cases of CJD were found in a series of 90 brain biopsies.\textsuperscript{24} Until now, the correlation between a clinical diagnosis based on typical symptoms, CSF, EEG, and MR imaging characteristics, and a diagnosis based on brain biopsy results in suspected cases of CJD has not been analyzed.

In the present study, we investigate the clinical characteristics and potential discriminating factors in all suspected CJD cases for which a brain biopsy was available in Germany between 1993 and 2005. The aim of this study was to define the relevance of this diagnostic technique in patients who were referred to the CJD Surveillance Unit.

Methods

All patients suspected of having CJD were referred to the National Reference Centre in Goettingen by the treating hospitals. The patients were referred most times on the basis of clinical signs before biopsy, but also after unexpected biopsy results. Cases of genetic CJD were excluded from the present study.

Since 1993, the CJD Surveillance Unit in Goettingen has examined all suspected cases of CJD in Germany and classified them according to the standard WHO criteria as “probable CJD,” “possible CJD,” or “other.” After informed consent was given by the relatives, a study physician at the referring hospital conducted a neurological examination in each patient and a complete case history and a detailed questionnaire on potential risk factors was obtained and assessed. Follow-up information was obtained from telephone interviews with the patients’ family doctor, hospital, and/or nursing home.

Detection of 14-3-3 proteins was performed by Western blot analysis as described in the literature.\textsuperscript{29} Magnetic resonance imaging evaluation for hyperintense basal ganglia\textsuperscript{15} and EEG analysis for PSWCs\textsuperscript{45} were performed by a neuroradiologist and a neurophysiologist experienced with CJD. Additionally, analysis of polymorphism of codon 129 was performed as described in the literature.\textsuperscript{27}

Biopsies were performed in the notifying hospitals, and indications for this procedure were determined by the hospitals. Biopsy analysis for prion disease was carried out in the Reference Centre for Spongiform Diseases Munich/Goettingen or by an authorized pathologist. In addition to histological analysis for spongiform changes, neuronal cell loss, and gliosis, immunohistochemical tests and paraffin-embedded tissue blot analysis for detection of PrPSc were performed.\textsuperscript{18,19} If autopsy was available, a postmortem neuropathological examination for prion disease was initiated.

Results

Patient Population

We analyzed the charts of 26 patients who underwent brain biopsy (15 women and 11 men), and were referred to the National Reference Centre for CJD in Goettingen between 1993 and 2005. The median age at the time of biopsy was 55 years (range 29–70 years). The biopsies were performed a mean of 8 months after disease onset (range 1–144 months), and in 20 patients after < 2 years’ duration (given as the limit for disease duration in sporadic CJD). Clinical classification of the 26 patients according to the established criteria yielded 5 probable cases, 6 possible cases, and 15 “other” cases.\textsuperscript{26,30} Clinical classification was established a mean of 7 days after biopsy sampling (range 6 months before to 3 months after biopsy), and in 18 patients before or at the time of brain biopsy. Only 4 biopsies were performed after 1998, when 14-3-3 protein testing was added to the diagnostic criteria and a diagnosis without brain biopsy could be more reliably reached. The most frequent brain area for biopsy was the frontal lobe in 14 patients (54%). The other brain areas were the occipital lobe (15%), cerebellum (12%), basal ganglia (8%), and parietal lobe (8%). In 1 patient, sufficient data on the biopsy site were unavailable.

The brain biopsies were performed in the referring hospitals for various clinical reasons: sporadic CJD was suspected in 15 patients, variant CJD in 2, brain tumors in 3, vasculitis in 2, and 1 patient each were suspected of having paraneoplastic encephalitis and unclear status epilepticus. One additional patient was suspected to have ALS, and biopsy sampling was performed to exclude any other (treatable) diagnosis. The reason for biopsy was unknown in 1 patient. In patients suspected of having CJD, confirmation by biopsy was sought because of decontamination consequences for gastric tubes, and because other suspected diagnoses would result in therapeutic implications. Adverse effects of biopsy sampling were observed in only 1 patient, who experienced a hemorrhage.

Neuropathologically Confirmed CJD

Using established neuropathological criteria, the diagnosis of CJD was confirmed in 11 (42%) of 26 patients based on biopsy results (Fig. 1). The age at onset in these patients was a median of 58 years (mean age 61 years, range 54–70 years), and the age at biopsy was a median of 65 years (mean age 62 years, range 54–70 years). There were 6 women and 5 men with biopsy-confirmed CJD.

In 8 of 11 patients, CJD was clinically suspected and given as the reason for biopsy. These 8 biopsies were performed between 1993 and 1997. Six of these 8 patients were referred to the Reference Centre after the biopsy. A clinical classification without knowledge of the biopsy results by a study physician of these 6 patients found 4 probable cases of CJD, 1 possible, and 1 other. The 2 patients who underwent biopsy sampling after clinical classification were classified as possible and other, and thus, a clinical diagnosis remained elusive. Another indication (that is, not CJD) for biopsy was given in 2 patients, and CJD was an unexpected diagnosis that led to referral to the Reference Centre. One patient had suspected status epilepticus that was not affected by a therapeutic regi-
Brain biopsy in cases of suspected CJD

In this person, an EEG with periodic sharp waves was found, which is often misinterpreted as status epilepticus. Because of early reduced vigilance, no dementia was documented, and the patient’s disease was classified as “other” with regard to CJD. The remaining patient was suspected to have vasculitis or hypoxic damage. These diagnoses were suspected due to the MR imaging findings with hyperintense signal in the basal ganglia and cortex—often found in these disorders, but also typical of sporadic CJD.

Genetic analysis of the prion protein gene (PRNP) was available in all confirmed CJD cases: 45% had the MM polymorphism, 36% had MV, and 18% VV (Table 1). In 5 patients with CJD, autopsies were also performed, and these confirmed the biopsy diagnosis of CJD in all cases.

Neuropathologically Confirmed “Other” Cases

In 15 of 26 patients no typical neuropathological changes suggestive of CJD were found on biopsy sampling. These patients were a median 49 years old at onset of symptoms (mean 47 years, range 26–69 years) and also at time of biopsy (mean 49 years, range 29–69 years). There were 9 women and 6 men.

In 9 of these 15 patients, human transmissible spongiform encephalopathy was suspected (7 sporadic and 2 variant CJD cases). Seven of these patients were referred to the Reference Centre after the biopsy although there was no hint of CJD in any of the 7 biopsies. A clear non-CJD diagnosis was established in only 2 of these 7 (PERM and chronic encephalitis). The patients were assessed clinically for CJD by a physician blinded to the results of pathologica testing. Five patients received disease designations of “other,” and 1 was considered to have possible sporadic CJD; the 2 patients suspected of having variant CJD based on pathological results were classified as “other” based on clinical examination. Autopsies were performed in 3 patients confirming the diagnosis of PERM in 1 patient, and additionally confirming a diagnosis in 2 patients in whom the biopsy had been nondiagnostic (Niemann–Pick Type C, and ALS and frontotemporal dementia).

In the remaining 6 patients, tumors were suspected in 3, and paraneoplastic disease, vasculitis, and ALS were suspected in 1 patient each. Tumors were suspected based on MR imaging results, paraneoplastic disease due to the presence of tumor marker CA72-4, and vasculitis because of mild pleocytosis and cortical Gd enhancement on imaging. Five of 6 biopsies were nondiagnostic with findings such as astrogliosis, and in 1 patient a diagnosis of glioma was reached based on imaging. An autopsy in this patient confirmed gliomatosis cerebri as the final diagnosis (Table 2). Analysis of the codon 129 genotype of PRNP revealed 45% MM and MV subtypes and 9% valine homozygosity in the non-CJD group.

Clinically, the disease in 4 of these patients was classified as possible CJD and 11 were determined not to have CJD. Of the 4 possible cases, 1 had the typical clinical symptoms of CJD and hyperintense basal ganglia on imaging, but did not have either PSWCs on EEG or 14-3-3 proteins detectable in the CSF.

Clinical Symptoms

A clinical analysis of symptoms is shown in Fig. 2. There is a remarkably high number of patients with CJD

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>neoplastic</td>
<td>1</td>
</tr>
<tr>
<td>WHO Grade II mixed glioma</td>
<td>1</td>
</tr>
<tr>
<td>gliomatosis cerebri</td>
<td>1</td>
</tr>
<tr>
<td>inflammatory/autoimmune</td>
<td>1</td>
</tr>
<tr>
<td>chronic subacute encephalitis or vasculitis</td>
<td>1</td>
</tr>
<tr>
<td>cerebral vasculitis</td>
<td>1</td>
</tr>
<tr>
<td>other</td>
<td>1</td>
</tr>
<tr>
<td>PERM w/o myoclonus</td>
<td>1</td>
</tr>
<tr>
<td>ALS &amp; frontotemporal dementia</td>
<td>1</td>
</tr>
<tr>
<td>adult Niemann–Pick Type C</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 1
Genetic analysis of PRNP with polymorphism of codon 129 stratified by CJD status

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Confirmed CJD (11 patients)</th>
<th>Non-CJD* (11 patients)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>5 (45)</td>
<td>5 (45)</td>
<td>0.697</td>
</tr>
<tr>
<td>MV</td>
<td>4 (36)</td>
<td>5 (45)</td>
<td>0.434</td>
</tr>
<tr>
<td>VV</td>
<td>2 (18)</td>
<td>1 (9)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* Data was unavailable for 4 patients in the non-CJD group.
† Fisher exact test.

TABLE 2
Neuropathological diagnoses other than CJD confirmed on biopsy or autopsy

Fig. 1. Clinical classification according to WHO criteria for CJD, biopsy results, and diagnosis by autopsy. FTD = frontotemporal dementia.
who did not have dementia at the time of brain biopsy (3 of 11; 27%). A significant difference between patients with CJD compared to those with a diagnosis of “other” was the presence of myoclonus (82% of patients with CJD vs 27% of “other” cases; p = 0.019). The other main symptoms of CJD were similarly frequent in both the CJD and non-CJD groups and showed no statistical difference. This was expected because the patients in the non-CJD group were selected on the basis of clinical symptoms suggestive of CJD.

Cerebrospinal Fluid Testing and EEG

Cerebrospinal fluid test and EEG results are summarized in Table 3. Assays for 14-3-3 proteins had a lower sensitivity (78%) in patients with CJD in this study than that described in the literature (95%). However, the sensitivity was still significantly higher than in the other cases in this study (27%; p = 0.07). Of the patients neuropathologically confirmed to have other diseases, 12 had no detectable 14-3-3 protein in the CSF, and the other 3 became negative for 14-3-3 protein after repeated lumbar punctures. The 3 patients with repeated lumbar punctures all had nondoniagnostic biopsies and did not undergo autopsies; 2 had inflammatory CSF signs and 1 had status epilepticus. Five patients with other diseases and no patient with CJD showed signs of inflammatory CNS disease such as slight pleocytosis or intrathecal IgG synthesis (14-3-3 protein assay sensitivity 78% and specificity 73%, after repeated lumbar puncture 100%). Periodic sharp wave complexes on EEG were found rarely, but all instances were in patients with neuropathologically confirmed CJD (in 3 of 8 with available EEG). No patient without CJD showed PSWCs on EEG (PSWC sensitivity 37.5%, specificity 100%). Thus, 14-3-3 protein is a helpful marker for determining whether or not a patient has CJD, and inflammatory CSF signs were present only in patients without CJD. Additionally, PSWCs can help in distinguishing between groups.

Imaging Findings

Magnetic resonance imaging was available in 4 of 11 confirmed cases of CJD (Table 4). The scans demonstrated in all patients typical hyperintensities of the basal ganglia in at least 1 sequence (FLAIR, T2-weighted, proton-weighted, and diffusion weighted imaging). Additionally, hyperintensities of the cortex and the thalamus were detected, albeit less frequently. In patients not diagnosed with CJD, 4 MR imaging studies were available, and in 3 of these patients, cortical hyperintensities were observed on imaging: 1 patient had a gliomatosis cerebri, 1 had a glioma, and in the third patient the cause of the hyperintensity was unknown. One patient had hyperintense basal ganglia; a diagnosis of glioma was later made in this patient on the basis of the biopsy. No patient with a diagnosis other than prion disease had thalamic hyperintensities (hyperintense basal ganglia, sensitivity 100%, specificity 80%; Table 4). The small number of patients with available MR images precludes a meaningful analysis of the value of MR imaging in these patients.

Potentially Treatable Diagnoses

Three patients with no signs of CJD on biopsy were diagnosed as having a potentially treatable disease: vasculitis, chronic encephalitis, and PERM in 1 patient each. Clinical clues for these diagnoses were present, but not decisive; the patient with vasculitis had mild pleocytosis (7 cells/µl), but this was noted only after repeated lumbar puncture and was therefore dismissed as irritation. In addition, biopsy sampling of the temporal artery and angiography of renal arteries showed no signs of a vasculitis. This patient is still alive and in stable clinical condition. The patient with chronic encephalitis showed an inflammatory CSF syndrome (6 cells/µl, intrathecal IgG synthesis) and MR imaging changes suggestive of an inflammatory process. Thus, clinical diagnosis of encephalitis was possible. Because antiinflammatory therapy had no effect, a brain biopsy was performed. The third patient received a diagnosis of PERM, a disorder associated with
Brain biopsy in cases of suspected CJD

The clinical presentation of prion diseases varies widely, and diagnosis can be challenging. Because an accurate diagnosis of the cause of dementia is essential for effective treatment, a biopsy that can verify diagnosis would be a helpful tool. Furthermore, pathological confirmation of a prion disease also has implications for treatment because of the hygienic considerations of endoscopic or open surgery in these patients. Because instruments used in CJD patients cannot be decontaminated by routine sterilization, special treatment is necessary as proposed by the WHO in 1998. During brain biopsy these decontamination precautions must be considered, which makes the decision to perform a biopsy more difficult in borderline cases. It is therefore important to emphasize the value of brain biopsy in the diagnosis of prion diseases.

The authors of only a few studies have investigated brain biopsy as a diagnostic tool in dementia. Warren and colleagues reported on 90 patients with dementia who underwent brain biopsies. These included 10 patients with sporadic and 1 with variant CJD, rendering prion diseases the second most frequent diagnosis after Alzheimer disease. In a study by Hulette et al., CJD was the most frequent diagnosis in 14 patients after biopsy, and accounted for 3 of 7 diagnostic and 7 nondiagnostic biopsies. Neither study compared the clinical classification according to CJD criteria with biopsy findings. Waltegny et al. examined 28 patients with presenile dementia who underwent stereotactic brain biopsy. These authors found that CJD was the second most frequent diagnosis (after Alzheimer disease), with 4 cases. Of these, 3 patients were already clinically suspected of having CJD before the biopsy.

In the present study we evaluated a group of patients with suspected CJD who underwent biopsy sampling. We analyzed the records of 26 patients with suspected CJD to define the value of biopsy in the diagnosis of CJD. Eleven patients suffered from CJD and 15 fulfilled no pathological criteria for CJD. A clinical diagnosis of probable CJD had been reached in 45% of the patients with CJD and none of the patients who proved to not have CJD. Those patients were also confirmed on brain biopsy or autopsy to have CJD. Thus, clinical classification is probably reliable in our patients, and a careful evaluation should be performed before considering invasive procedures such as biopsy.

According to our data, CSF parameters can further help to distinguish between patients with and without CJD: 14-3-3 proteins were present in 78% of patients with CJD and in only 27% (3 of 11 patients in the non-CJD group) of those without. These latter 3 patients had negative test results in follow-up punctures, demonstrating that follow-up should be conducted in cases of doubt. In addition, inflammatory CSF signs were only present in the non-CJD group.

The third helpful parameter for clinical diagnosis of CJD without the need for brain biopsy is EEG. All 3 patients in our study with PSWCs were later confirmed to have CJD. Magnetic resonance imaging with the characteristic findings of hyperintensity in the basal ganglia was found in the patients with CJD, but also in 1 patient with a glioma. Thus, this finding can support the diagnosis but should not be considered definitive. Thalamic hyperintensities are helpful, although this phenomenon is usually described only in patients with variant CJD, but recently have also been described in atypical subtypes. These findings were not observed in any patients without CJD in our study.

Therefore, the correct clinical classification of CJD was found in 16 (62%) of 26 patients (Fig. 1). In 10 patients the correct classification was difficult. This subgroup included 6 patients with disease classified as possible CJD and 4 classified as other but in whom CJD was suspected.

### Discussion

**Table 4**

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of Imaging</th>
<th>Other MRI Findings</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>T2-Weighted</td>
<td>FLAIR</td>
<td>Proton-Weighted</td>
</tr>
<tr>
<td>4</td>
<td>cortex</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus, cerebellum</td>
</tr>
<tr>
<td>6</td>
<td>cortex, basal ganglia</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus, cerebellum</td>
</tr>
<tr>
<td>7</td>
<td>cortex, basal ganglia</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus, cerebellum</td>
</tr>
<tr>
<td>11</td>
<td>cortex, basal ganglia</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus</td>
</tr>
<tr>
<td>17</td>
<td>cortex, basal ganglia</td>
<td>cortex, basal ganglia</td>
<td>suspected glioma multiple intracranial tumors</td>
</tr>
<tr>
<td>18</td>
<td>cortex</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus</td>
</tr>
<tr>
<td>25</td>
<td>none</td>
<td>none</td>
<td>NA</td>
</tr>
<tr>
<td>26</td>
<td>cortex</td>
<td>NA</td>
<td>cortex</td>
</tr>
</tbody>
</table>

* NA = not applicable.

nonspecific elevated antibody levels, especially of glutamic acid decarboxylase antibody. The patient described here had positive oligoclonal bands and intrathecal synthesis of IgG and IgM, but no pathological autoimmune antibodies. Thus, these findings were suggestive of a diagnosis of a chronic inflammatory process. All 3 diseases are treatable with immunosuppressive therapy, but no improvement with corticoid therapy could be achieved in any of these patients. The patients with PERM and chronic encephalitis died within 3 years of symptom onset.

**TABLE 4**

* Regions of hyperintensity on different types of MR imaging and on biopsy or autopsy diagnosis

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of Imaging</th>
<th>Other MRI Findings</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>T2-Weighted</td>
<td>FLAIR</td>
<td>Proton-Weighted</td>
</tr>
<tr>
<td>4</td>
<td>cortex</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus, cerebellum</td>
</tr>
<tr>
<td>6</td>
<td>cortex, basal ganglia</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus, cerebellum</td>
</tr>
<tr>
<td>7</td>
<td>cortex, basal ganglia</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus, cerebellum</td>
</tr>
<tr>
<td>11</td>
<td>cortex, basal ganglia</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus</td>
</tr>
<tr>
<td>17</td>
<td>cortex, basal ganglia</td>
<td>cortex, basal ganglia</td>
<td>suspected glioma multiple intracranial tumors</td>
</tr>
<tr>
<td>18</td>
<td>cortex</td>
<td>NA</td>
<td>cortex, basal ganglia, thalamus</td>
</tr>
<tr>
<td>25</td>
<td>none</td>
<td>none</td>
<td>NA</td>
</tr>
<tr>
<td>26</td>
<td>cortex</td>
<td>NA</td>
<td>cortex</td>
</tr>
</tbody>
</table>
later confirmed. Of these CJD patients, 3 were positive for 14-3-3 protein, 1 had PSWCs on EEG, and 1 had thalamic hyperintensities on imaging.

Biopsy sampling is typically considered an effective method for diagnosing reversible causes of dementia, such as inflammatory and metabolic processes. The proportion of potentially reversible dementias in the literature is 10–20%,3,7,22,25 but these conditions are more frequent in patients younger than 55 years of age. The differential diagnosis of reversible dementias includes depression, normal pressure hydrocephalus, and alcoholism, which can be diagnosed based on careful clinical assessment. Atypical forms of inflammatory and metabolic disorders are sometimes difficult to identify and therefore require invasive techniques for diagnosis. This may account for the relative youth of the patients in our study, as dementia in the elderly is still frequently assumed to be related to a neurodegenerative disease. The mean age of patients in our study, 52 years, is close to the mean age reported in other studies of brain biopsy for dementia, 50.5,24 and 52 years.8 In contrast, the mean age in patients with a proven prion disease was 61 years, corresponding to the mean age of patients with sporadic CJD according to demographic data.26

Three patients with potentially treatable causes of dementia were identified through neuropathological examination. Inflammatory signs were also present in the CSF. However, even immunosuppressive therapy did not lead to clinical improvement. These differences in potentially reversible and actually reversible dementia (either partly or fully) are well known in the literature; the frequency of actually reversing dementia is significantly lower than the incidence of potentially reversible conditions. For example, the authors of 1 study found 15% potentially reversible dementias, but only 9% were partly and 1.5% were fully reversible after treatment.25

The problem with using biopsy as a diagnostic tool in patients without focal lesions is the high number of nondiagnostic biopsies. In our study, 42% of biopsies performed did not lead to a clear diagnosis. However, a statement regarding prion disease was possible because of the absence of PrPSc detection or typical histological features. Similar to our study, Warren et al.24 reported a specific diagnosis in > 50% of patients, but a diagnosis of a treatable disease in only ~ 10% of their cases.

Because in 21 patients CJD was clinically suspected, decontamination precautions were followed. However, in 5 patients no special decontamination procedures were followed, and in 2 the diagnosis of CJD was a surprising biopsy result. Thus, rapidly progressing disorders positive for 14-3-3 protein, PSWCs, and/or hyperintense basal ganglia on imaging should be handled as potential CJD cases with regard to decontamination precautions.

Polymorphisms of codon 129 of PRNP on chromosome 20 are associated with a higher risk for CJD in cases of methionine homozygosis.17 Predominance of the MM subtype is described in 70% of cases of sporadic CJD. In contrast, it has been found in only 40% of the healthy population. The MV and VV subtypes are equally distributed in sporadic CJD with 14 and 16%, respectively, in contrast to 45% MV and 13% VV in the control groups.4 In our study, both groups with confirmed or excluded prion disease show similar genotype distribution as presented in Table 1. This distribution is similar to that previously reported in a healthy population.16 Interestingly, our patients with CJD had the MM subtype less often than in the literature (36%) and the MV subtype more often (29%). We may speculate that most patients have the MV2 subtype. These patients often present with neuropsychological deficits that develop over months, and only begin to demonstrate the typical neurological manifestations of CJD in the late stages of the disease.12 This might have impaired the clinical classification and argues for more frequent biopsies in this subtype.

Conclusions

In the diagnosis of CJD, brain biopsies appear to be a helpful tool in patients with dementia of unknown causes. However, clinical evaluation and classification according to established criteria should be performed first. Especially in atypical cases with long disease duration, young age at onset, or positive familial history, an analysis of PRNP and the polymorphism at codon 129 should be performed. If a clear diagnosis is still not possible, a brain biopsy can contribute to toward it if performed correctly. The correct diagnosis of CJD is extremely challenging because the symptoms and time course are highly variable. The “hit rate” is significantly higher if the diagnosis is made in a specialized center, and the results from brain biopsies appear to be more specific if the procedure is performed with cooperation from the neurology, neurosurgery, neuroradiology, and neuropathology departments.

Disclosure

This study was supported by the Robert Koch Institute with funds from the Federal Ministry of Health (Grant No. 1369-341).

Acknowledgments

We thank Mrs. Monika Bodemer, Mrs. Barbara Ciesielsczyk, and Ms. Staniszewski for technical assistance. The assistance of Ms. Jolante Ehrlich and Ms. Maja Schneider-Dominico is also gratefully acknowledged.

References

Brain biopsy in cases of suspected CJD


25. Weytingh MD, Bossuyt PM, van Crevel H: Reversible dementia: more than 10% or less than 1%? A quantitative review. J Neurol 242:466–471, 1995


Address correspondence to: Uta Heinemann, M.D., Department of Neurology, Georg-August University Goettingen, Robert-Koch-Strasse 40, 37075 Goettingen, Germany. email: uta.heinemann@med.uni-goettingen.de.