Clinical Features and Diagnosis of the MM2 Cortical Subtype of Sporadic Creutzfeldt-Jakob Disease

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Objective: To describe clinical features and diagnostic tests of the MM2 cortical subtype in sporadic Creutzfeldt-Jakob disease.

Methods: Clinical symptoms, magnetic resonance imaging studies, electroencephalograms, and cerebrospinal fluid markers were studied in 12 patients with genetically and neuropathologically verified sporadic Creutzfeldt-Jakob disease. Histological findings were semi-quantitatively evaluated.

Results: Compared with classical sporadic Creutzfeldt-Jakob disease, the disease duration was prolonged (median, 14 months). All patients had dementia and early and prominent neuropsychological signs such as spatial disorientation, aphasia, or apraxia. Alzheimer disease was the most frequent initial diagnosis (33%). Increased S100B protein in the cerebrospinal fluid was found in 100%; the 14-3-3 protein test was positive in 91%. Electroencephalograms revealed periodic sharp wave complexes in 42%. T2-weighted magnetic resonance imaging showed basal ganglia hyperintensities in only 1 patient, and cortical hyperintensities were not necessarily present. Severe cortical damage was the most prominent histological feature.

Conclusions: The S100B (100%) and 14-3-3 (91%) protein investigations were the most sensitive diagnostic tests. Prolonged disease duration, dementia as the only typical Creutzfeldt-Jakob disease symptom for a longer time, and low sensitivity of magnetic resonance imaging studies and electroencephalograms make the diagnosis in the MM2 cortical subtype difficult. Therefore, detailed clinical investigation is especially important in this sporadic Creutzfeldt-Jakob disease subtype. We suggest that rapidly progressive dementia with early and prominent neuropsychological deficits in older patients should lead to suspicion of the MM2 cortical subtype even if other neurological deficits are absent. At least some cases of MM2 cortical sporadic Creutzfeldt-Jakob disease may be misdiagnosed as rapidly progressive Alzheimer disease.

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Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare fatal neurodegenerative disease characterized by accumulation of pathologic scrapie prion protein in the central nervous system. Polymorphism at codon 129 for methionine or valine and prion protein types 1 and 2 are the basis for a molecular sCJD classification. According to Parchi et al, the MM2 subtype is responsible for 4% of sCJD cases. Two different forms—cortical and thalamic—can be identified.

Unspecific features such as progressive dementia, lacking periodic sharp wave complexes, and prolonged disease duration were reported as typical for the MM2 cortical subtype. Neither magnetic resonance imaging (MRI) nor biochemical cerebrospinal fluid (CSF) analysis was performed in the study in which 6 patients with MM2 cortical sCJD were included. In a study of CSF in 10 patients with MM2 cortical sCJD, the relatively low sensitivity of 70% was found at 14-3-3 protein testing, and no other biochemical markers were investigated. Such unspecific symptoms as progressive dementia and lacking periodic sharp wave complexes were again reported as key features. Clinical criteria for diagnosing the MM2 cortical subtype of sCJD (progressive dementia, cortical hyperintensities at diffusion-weighted imaging, and positive 14-3-3 protein test results) recently proposed on the basis of investigation in 2 patients and review of the literature was consistent with most sCJD subtypes. The aim of the present study was to improve the diagnosis of the rare MM2 cortical subtype of sCJD. We performed a detailed analysis of the clinical features, electroencephalograms (EEGs), and MRI studies in 12 patients with MM2 cortical sCJD. For the first time, to our knowledge, biochemical CSF markers other than 14-3-3 protein and neuron-specific eno-
lase such as tau protein, S100B, and β-amyloid peptide 1-42 were investigated in this subtype.

METHODS

STUDY DESIGN

Patients suspected of having CJD were reported to the CJD Surveillance unit at the Georg-August University, Goettingen. The patients were examined by one of the unit's physicians in the notifying hospitals, and CSF and blood samples and copies of the important diagnostic findings (results from MRI, EEG, and laboratory tests) were obtained. The patients were classified according to established diagnostic criteria.6,7

MRI AND EEG FINDINGS

The MRIs were reviewed by a neuroradiologist (K.K.) who was aware of the diagnosis but not of the CJD subtype. Seven cortical regions, the basal ganglia, and the cerebellum were analyzed for hyperintensities in each available image. The EEGs were analyzed according to established criteria.8

NEUROPATHOLOGICAL AND MOLECULAR STUDIES

From June 2, 1993, through June 2, 2005, 610 neuropathologically confirmed sCJD cases were detected in Germany. The scrapie prion protein type was determined in 221 patients.2 Western blot and immunohistochemistry studies were performed, and the prion protein gene was analyzed by using standard methods.9-12 No prion protein gene mutations were found. Spongiform changes, neuronal loss, and gliosis were semiquantitatively evaluated as described previously.3 Eight brain regions were investigated—superior frontal, cingulate, and inferior parietal gyrus; visual cortex; head of the caudate nucleus; middle part of the putamen; insular cortex; and vermis of the cerebellum.

BIOCHEMICAL CSF ANALYSIS

The 14-3-3 protein test was performed at least twice in each CSF sample as described previously.13 Tau protein was measured by using Innotest h Tau enzyme-linked immunosorbent assay, and β-amyloid peptide 1-42 was measured by using Innotest β-Amyloid 1-42 enzyme-linked immunosorbent assay (Innogenetics NV, Ghent, Belgium). Neuron-specific enolase and S100B were quantified in CSF by means of a commercially available assay (Liaison NSE and Liaison Sangtec 100; Diasorin SpA, Saluggia, Italy).

STATISTICAL ANALYSIS

Significances and correlations were tested (SigmaStat 3.1; Systat Software Inc, Point Richmond, Calif) by using a t test and a Pearson product moment correlation test. P<.05 was considered statistically significant.

RESULTS

PATIENTS

The MM2 cortical subtype, defined on the basis of the methionine homozygosity at codon 129 of the prion protein gene, the scrapie prion protein type 2, and histological investigation, was found in 12 patients with sCJD (5.4% of 221 patients with known scrapie prion protein subtype). There were 6 women and 6 men (median age at onset, 67 years; age range, 60-82 years; median disease duration, 14 months; duration range, 3-24 months).

CLINICAL FINDINGS

Onset time and clinical symptoms and signs are shown in Tables 1, 2, and 3. Dementia (n=9) was the most common initial symptom, and each of the remaining 3 patients presented with amnestic aphasia, fatigue and hyperhidrosis, and extrapyramidal gait disturbance. Alz-
changes also were observed in 1 of 3 patients at proton-
tical hyperintensities was 25% at T2-weighted MRI. These
version recovery imaging results. The sensitivity for cor-
tient with proton-density–weighted or fluid-attenuated in-
with available diffusion-weighted imaging, and in no pa-
malities at MRI. Basal ganglia hyperintensities were found
in only 1 patient with T2-weighted MRI, in both patients
showed that all patients had dementia during the disease
course and that dementia was also the most frequent ini-
tal symptom. In contrast to patients in a previous study,5
hanced pyramidal signs was much higher than in classi-
ported previously3 and in patients with classical sCJD.3
more common than in patients with MM2 cortical sCJD
symptom for longer than 6 months. In 9 (75%) of 12 patients, no CJD was suspected initially. The CJD diagnosis was proposed for the first time a median of 5 months after symptom onset.

MRI FINDINGS

The semiquantitative evaluation of the MRI findings is given in Table 5. Five of 8 patients did not have any abnormalities at MRI. Basal ganglia hyperintensities were found in only 1 patient with T2-weighted MRI, in both patients with available diffusion-weighted imaging, and in no patient with proton-density–weighted or fluid-attenuated inversion recovery imaging results. The sensitivity for cortical hyperintensities was 25% at T2-weighted MRI. These changes also were observed in 1 of 3 patients at proton-
density–weighted and fluid-attenuated inversion recovery MRI and in 1 of 2 patients at diffusion-weighted imaging. The occurrence of signal hyperintensities revealed no significant correlation with disease duration or time at which the MRI was performed.

EEG AND CSF FINDINGS

Periodic sharp waves were found in only 5 patients (42%) 2 to 11 months (median, 6 months) after symptom onset. Table 6 lists biochemical marker sensitivity data. Lumbar puncture was performed in 11 of 12 patients. S100B protein was the most sensitive biochemical CSF marker (100%), the 14-3-3 protein investigation results were positive in 91%, and β-amyloid peptide 1-42 showed the lowest sensitivity (38%).

HISTOLOGICAL FINDINGS

Histological changes were semiquantitatively analyzed in 8 brain regions in 6 patients and in 6 brain regions in 1 patient whose insular cortex and caudate nucleus samples were missing (Table 7). Spongiform changes were the most prominent histological finding in all investigated regions. A high gliosis rate was found in the caudate nucleus and several cortical regions. Neuronal loss was more prominent in the cortex. No significant correlation was found between disease duration and severity of histological changes.

Until now, only unspecific findings such as slowly progressive dementia and longer survival time were reported as typical for the MM2 cortical sCJD subtype.3,5 These characteristics allow neither the diagnosis of CJD nor the differential diagnosis of other dementias.

In line with earlier study results,3 our study results showed that all patients had dementia during the disease course and that dementia was also the most frequent initial symptom. In contrast to patients in a previous study,5 who had a slow course of dementia, the patients in our study usually presented with a rapidly progressive dementia so that severe dementia was found a median of 5 months after disease onset. All patients had early and prominent neuropsychological deficits. Similar to results in a previous study,3 aphasia was common in our study; in contrast, the patients in our study had apraxia more often (83%) than reported earlier in the MM2 cortical subtype (33%). In classical sCJD, both signs are rare.1,3 Spatial disorientation not reported previously as typical for sCJD3 might explain this phenomenon.

Extrapyramidal signs in the patients in our study were more common than in patients with MM2 cortical sCJD reported previously3 and in patients with classical sCJD.1 Involuntary movements (50%) also occurred more often in our study than previously reported (17%).3 Identical to results in a previous study, our results indicated that prevalence of pyramidal signs was much higher than in classi-

### Table 3. Psychiatric and Neuropsychological Symptoms and Signs in 12 Patients

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>No. (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Fear</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Paranoid</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Apraxia</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Spatial disorientation</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Disorder of frontal brain</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Perseveration</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Agraphia</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Acalculia</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Alexia</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Echolalia</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Prosopagnosia</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

### Table 4. Initial Diagnosis in 12 Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>4</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>3</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
</tr>
<tr>
<td>Primary progressive aphasia</td>
<td>1</td>
</tr>
<tr>
<td>Multisystemic atrophy</td>
<td>1</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 5. MRI Findings

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>No. (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia hyperintensities</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Caudate nucleus hyperintensities</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Insular cortex hyperintensities</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>
A pronounced damage of motor and premotor cortex in the MM2 cortical subtype of sCJD may be the cause. The ataxia typical in classical CJD has been reported as unusual in the MM2 cortical subtype (17%). In our study, 67% of the patients developed ataxia; however, ataxia occurred late in the disease course and was never dominating. Myoclonus is a characteristic sign often leading to the first suspicion of sCJD. Consistent with previous study results, myoclonus occurred as late as 8 months after symptom onset.

Investigators in a previous study reported a 14-3-3 protein test sensitivity of 70% in the MM2 cortical subtype of sCJD, but we found a higher sensitivity of 91%. Thus, the 14-3-3 protein investigation seems to be the most sensitive established diagnostic test in the MM2 cortical subtype of sCJD. The S100B protein findings were positive in all patients and, therefore, the most sensitive CSF marker.

The MRI results were normal in 5 of 8 patients who underwent this investigation (Table 5). Only few cases of MM2 cortical sCJD with available MRI data have been reported so far. Investigators in a previous study in which only 2 patients with MM2 cortical sCJD were included proposed cortical hyperintensities at MRI as a diagnostic criterion for this subtype. However, cortical hy-
perintensities often are found in different sCJD subtypes and, therefore, cannot be considered specific for the MM2 cortical subtype of sCJD. Although our number of MRI studies is the largest until now, it is still insufficient for a significant statistical statement or consideration of these changes as diagnostic criteria. Sensitivity for cortical hyperintensities in the MM2 cortical subtype of sCJD is not necessarily higher than in other sCJD subtypes. Even at diffusion-weighted imaging, 100% sensitivity for cortical lesions was not reached in the patients in our study. In line with results in previous reports, basal ganglia hyperintensities at T2-weighted MRI were observed in only 1 patient (13%).

In line with results in previous studies, our results indicated that the cerebellum was relatively spared, whereas widespread cortical damage was a prominent histological feature, which explains the high frequency of neuropsychological symptoms in the MM2 cortical subtype of sCJD. Although visual symptoms were rare and no involvement of the occipital cortex was observed at MRI in any patient, the occipital cortex was severely affected. Nevertheless, a late cortical visual impairment cannot be excluded in the patients in our study because the pronounced dementia and aphasia could have prevented reporting of visual disturbances. No correlation was detected among disease duration, grade and pattern of histological lesions, and abnormalities at MRI. However, MRI was performed a median of 5 months before death, and the progression of the brain lesions during the later disease course may have influenced the analysis.

Our data show that diagnosing the MM2 cortical subtype of sCJD may be difficult, particularly in the early disease stage. Prolonged disease duration, monosymptomatic course (mostly with isolated dementia) for at least 6 months in 50% of patients, and low sensitivity of EEG and MRI cause the late sCJD diagnosis and often lead to the suspicion of Alzheimer disease (33%); CJD was proposed initially in only 3 patients in our study who were first examined by a physician only when they were at an advanced disease stage. At least some patients with MM2 cortical sCJD may have their condition misdiagnosed as being 14-3-3 protein positive or as rapidly progressive Alzheimer disease. Such misdiagnosis may be of crucial importance because sufficient hygienic measures for preventing prion transmission are not performed in these patients.

The S100B protein investigation results were positive in all patients, and the 14-3-3 protein test had a high sensitivity of 91%. Prolonged disease duration, late occurrence of typical CJD symptoms other than dementia, and low sensitivity of MRI and EEGs make the diagnosis of the MM2 cortical subtype difficult. Therefore, detailed clinical investigation is especially important in this sCJD subtype. We suggest that rapidly progressive dementia with early and prominent neuropsychological deficits in older patients should lead to suspicion of the cortical MM2 subtype of sCJD even if other neurological deficits are absent. A possibility of higher prevalence of the MM2 cortical subtype than previously assumed cannot be excluded because some patients with MM2 cortical sCJD may have their condition misdiagnosed as being 14-3-3 protein positive or as rapidly progressive Alzheimer disease.

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REFERENCES