Magnetic Resonance Imaging in the Clinical Diagnosis of Creutzfeldt-Jakob Disease

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Objective: To evaluate the diagnostic usefulness of magnetic resonance imaging (MRI) in the clinical diagnosis of Creutzfeldt-Jakob disease (CJD).

Background: Creutzfeldt-Jakob disease is a rare neurodegenerative disease that belongs to the group of human spongiform encephalopathies and usually affects elderly people. It is clinically characterized by rapidly progressive dementia and development of neurological symptoms, such as myoclonus or ataxia. Until now, neuroradiologic investigations have only played a minor role in establishing the clinical diagnosis of CJD, and they are often performed to exclude differential diagnoses.

Setting: A university hospital, base of the German National Creutzfeldt-Jakob Disease Surveillance Study.

Methods and Patients: In this study, MRIs from suspected cases of CJD were examined by one investigator blinded to the diagnosis. Patients were classified according to the established clinical and neuropathological criteria.

Results: Bilateral symmetric, high signal intensities on T2-weighted MRIs were present in the basal ganglia of 109 (67%) of 162 patients with CJD. In the control group, which consisted of non-CJD dementia patients, these abnormalities on T2-weighted MRIs were found in 4 (7%) of 58 patients. This corresponds to a high specificity in the differential diagnosis of CJD.

Conclusion: These results indicate that MRI is a useful and valuable tool with reasonable sensitivity (67%) and high specificity (93%) and should be considered as an additional cornerstone in the clinical diagnosis of CJD.

Reutzfeldt-Jakob disease (CJD) is a rare, transmissible brain disease with an incidence of one case per million per year and a lethal outcome usually within a few months that typically affects elderly people. Clinical diagnosis during lifetime is characterized by rapidly progressive dementia with a duration shorter than 2 years, myoclonus, ataxia and visual disturbances, extrapyramidal and pyramidal disturbances, and akinetic mutism. Periodic sharp wave complexes on an electroencephalogram or detection of the 14-3-3 protein in cerebrospinal fluid provides important corroborative evidence for the clinical diagnosis of probable CJD. Definite diagnosis is made by neuropathological examination, which reveals histopathologic evidence of nerve cell loss, gliosis, and spongiform change as well as the presence of the pathologic prion protein using immunohistochemical techniques.

Until now, magnetic resonance imaging (MRI) has only played a minor role in establishing the clinical diagnosis of CJD. It is often performed to exclude differential diagnoses, such as stroke (ischemic or hemorrhagic), multiple sclerosis, hydrocephalus, tumors, or chronic meningoencephalitis. In the literature, there are only a few case reports describing the presence of bilateral symmetric, hyperintense abnormalities in the caudate nucleus and putamen on T2-weighted or proton density–weighted MRI in patients with CJD. In a previous study performed by our group, a bilateral symmetric increase in signal intensity in the basal ganglia on T2-weighted and proton density–weighted MRIs was reported in 23 (79%) of 29 patients with CJD. Another study, conducted by an Italian group, reported these MRI alterations in 31 (100%) of 31 patients with CJD. The diagnostic value of this technique in the differential diagnosis of CJD has not yet been evaluated.
Therefore, the aim of this study, the largest so far at the time of this report, was to determine the diagnostic usefulness of MRI for the clinical diagnosis of CJD.

RESULTS

We analyzed 296 MRI scans of 245 patients and controls. Because of movement artifacts caused mainly by myoclonic jerks producing low-quality scans, 16 patients and 9 controls were excluded. In 162 patients, definite or probable sporadic CJD was diagnosed. The patient group consisted of 111 women and 51 men. In 70 patients, the diagnosis of CJD was confirmed by autopsy and in another 92 patients by using the established clinical criteria. These patients were found to have rapidly progressive dementia with a duration shorter than 2 years, periodic sharp wave complexes on an electroencephalogram, and/or the presence of 14-3-3 protein in CSF, and at least 2 of the 4 characteristic clinical findings: myoclonus, visual and/or cerebellar symptoms, pyramidal and/or extrapyramidal signs, and akinetic mutism. Patients who had initially been referred to the German CJD surveillance unit as having suspected cases, but who were later diagnosed as having other diseases either during the disease course or by autopsy, served as a control group. The MRI scans were retrospectively rated by an investigator blinded to the diagnosis (M.F.). Magnetic resonance imaging scans were performed with either 1.0-T or 1.5-T magnetic resonance imagers in different neuroradiological departments (65%) and offices (35%) throughout Germany. The following MRI studies were performed: T1-weighted (repetition time [RT], 450-600 milliseconds; echo time [ET], 12-20 milliseconds), T2-weighted (RT, 2000-5500 milliseconds; ET, 80-120 milliseconds), proton density–weighted (RT, 2000-5500 milliseconds; ET, 10-40 milliseconds), and fluid-attenuated inversion recovery (RT, 6000 milliseconds; ET, 100 milliseconds; inversion time, 2000 milliseconds).

Figure 1. High signal intensity in the basal ganglia on axial T2-weighted magnetic resonance imaging in a 54-year-old man with Creutzfeldt-Jakob disease and dementia with cerebellar, pyramidal, and extrapyramidal signs and myoclonus. Overall disease duration was 6 months.

Figure 2. High signal intensity in basal ganglia on axial fluid-attenuated inversion recovery magnetic resonance imaging in a 53-year-old man with Creutzfeldt-Jakob disease and dementia with cerebellar and extrapyramidal signs, myoclonus, involuntary movements, and vertigo. The figure shows movement artifacts due to myoclonic jerks.

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Diffusion-weighted images of 5 patients were studied. Abnormally high signals were found in the basal ganglia of all patients. These changes were best seen in diffusion-weighted images but also in other-weighted images (Figure 4).

In 37 patients, serial MRIs with a median time span of 7.5 weeks (range, 2-28 weeks) between 2 consecutive examinations were performed during the disease course. On the first T2-weighted MRI scans, high signal intensity was visible in the basal ganglia of 16 patients (43%), but there was no increase in signal intensity during the follow-up MRI examination. Only in 9 patients (24%) was there an increase in hyperintense abnormalities on MRIs, ranging from mild to moderate or marked, documented in a period of 4 to 20 weeks. In 12 patients (32%), no increased signal intensity in the basal ganglia developed. The time span between the 2 MRI examinations was longer in the group with increased hyperintensities (median, 8.1 weeks) as compared with the group without an increase (median, 6.9 weeks). This difference was not significant (P > .05). In the former group, none of these patients had a normal MRI without hyperintensities in the basal ganglia at the beginning of the study, and none of the patients developed such hyperintensities during the disease course.

Substantial brain atrophy was present in 47 (29.0%) of 162 patients. Five patients with serial MRIs develop-
oped a massive increase in atrophy over several months (Figure 5). Forty-four patients with CJD (27.2%) presented with a normal MRI without any hyperintense changes or atrophy. In 9 patients (5.6%), MRIs showed atrophy but no hyperintense alterations. In 38 patients (23.5%), both hyperintense alterations and atrophy were seen, and in another 71 patients (43.8%), hyperintense alterations without atrophy were documented. The T1-weighted images of 123 (75.9%) of 162 patients with CJD in whom this imaging sequence had been performed showed no signal intensity abnormalities in the basal ganglia or cortex.

Altogether, 58 patients with other causes of dementia, of whom 32 were women and 26 men, served as a control group. The median age of the control group was 61 years (range, 29-81 years). The most frequent diagnosis in this group, which was established either by autopsy or by clinical criteria, was Alzheimer disease, followed by unclassified dementias, cerebrovascular disease, chronic encephalitis of unknown cause, Parkinson disease, psychiatric diseases, paraneoplastic syndromes, and others. In this group, 54 patients (93%) with dementia showed no signal intensity abnormalities on T2-weighted or proton density–weighted images. Bilateral symmetric areas of hyperintensity in the caudate nuclei and putamina were detected in only 4 patients (7%). The follow-up investigation revealed the following: an improvement of the neurological functions during the disease course could be observed in 2 of these patients; in 1 patient, multiple sclerosis was diagnosed before the beginning of rapidly progressive dementia and onset of severe physical decline, and in 1 patient, no further information was available. No autopsy was performed in these 4 patients. Substantial brain atrophy was present in 33 control patients (56.7%).

In conclusion, the results of our investigations show that, in the differential diagnosis of CJD, MRI has a sensitivity of 67% and a specificity of 93% (Table). In addition, we compared our results with the findings of the neuroradiologists/radiologists located at the peripheral hospitals, where the MRI scans were performed. Written reports on initial neuroradiological assessment were available for 88 (81%) of 109 patients with CJD and hyperintense alterations on T2-weighted MRIs. The neuroradiologists/radiologists found hyperintense alterations on T2-weighted or proton density–weighted MRIs in the basal ganglia of 18 patients (20%). In 70 (80%) of 88 patients, the alterations were overlooked.

**COMMENT**

Early publications on CJD and neuroimaging (cranial computed tomography and MRI) described only cortical atrophy in the affected patients. Gertz et al first reported increased signal intensity in the basal ganglia.

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**Table:** Sensitivity and Specificity of MRI in Differential Diagnosis of CJD

<table>
<thead>
<tr>
<th>MRI†</th>
<th>Patients, With No. (%)</th>
<th>Controls, No. (%)</th>
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<tbody>
<tr>
<td>Positive</td>
<td>109 (6.3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Negative</td>
<td>53 (2.7)</td>
<td>54 (93)</td>
</tr>
</tbody>
</table>

* MRI indicates magnetic resonance imaging; CJD, Creutzfeldt-Jakob disease.
† Positive indicates increased signal intensity on T2-weighted MRI; negative, no abnormal signal intensity on T2-weighted MRI.
on T2-weighted MRIs in a 55-year-old woman with sporadic CJD. Until now, several case reports have confirmed these findings\textsuperscript{20,21} but without giving any information about the frequency of these changes. A previous study with 29 patients reported a sensitivity of about 80%.\textsuperscript{23} In the present study, investigating MRI in CJD, we were able to show bilateral symmetric, hyperintense abnormalities in the basal ganglia on T2-weighted MRIs in 67% of the patients with CJD. This sensitivity is lower than previously described.\textsuperscript{23}

One reason for this discrepancy could be that the assessment of the examined hyperintensities on MRI is subjective. In cases in which the scans were selected by the study physicians before analysis by one of the raters, unintentional preselection and selection bias could have also played a role. In contrast, in the present study, we evaluated all MRI scans from an unselected patient group. The evidence shows that the frequency of increased signal intensities on MRI has not been determined in large patient groups. Zeidler et al\textsuperscript{20} reported the interesting finding that bilateral symmetric, hyperintense alterations in the basal ganglia on T2-weighted MRIs had only been seen in 4 (4%) of 96 patients with CJD. These MRI examinations were performed by radiologists/neuroradiologists in different hospitals throughout the United Kingdom. The results were reported to the national CJD surveillance unit, but the scans were not provided. Another article from the United Kingdom described 12 CJD patients, none of whom had shown high signal intensity in the basal ganglia on T2-weighted MRIs.\textsuperscript{29} Again, these scans were not analyzed a second time by a specialist. In our own series, we found that in 80% of the cases, neuroradiologists/radiologists had not noticed the hyperintense alterations. One possible explanation might be that MRI scans in CJD are usually performed to exclude other treatable disorders. These abnormalities may be overlooked because of symmetric changes. If more attention is paid to them, the differential diagnosis of CJD and experience increases with this rare disease, more cases with MRI alterations may be observed in the future. This is in line with recent data from an Italian group, which reported a study in which MRIs of 31 patients with CJD had been analyzed.\textsuperscript{24} All patients with definite CJD presented with symmetric bilateral, hyperintense signal changes in the caudate nuclei and putamina on T2-weighted and proton density–weighted MRIs. It is conceivable that the sensitivity of these alterations is higher if the MRI examination is done under standardized conditions by analyzing all patients with the same magnetic resonance imaging.

The spongiform changes and the gliosis in the affected gray matter have been suggested as the reason for the signal intensity alterations on T2-weighted and proton density–weighted MRIs. In the vacuoles, fluid is accumulated that causes increased signal intensity on T2-weighted images. Gliosis causes increased signal intensity on proton density–weighted images.\textsuperscript{14,21,30} Another study compared the neuropathological findings with MRI in an animal model.\textsuperscript{31} Signal hyperintensity on T2-weighted MRIs in the thalamus was noted on day 50 after intracerebral injection of 236K scrapie-infected brain homogenate, before the onset of disease, correlating with marked gliosis. Furthermore, hyperintense alterations on the T1-weighted MRI were observed on day 50, which corresponds with a striking accumulation of prion protein. The authors suggest that the hyperintense alterations in the T2-weighted MRIs were probably caused by gliosis, whereas the high signal intensity in the T1-weighted MRI was due to the accumulation of prion protein. Recently, a new MRI finding in CJD was reported—high signal intensity in the globus pallidus on T1-weighted MRI.\textsuperscript{32} This finding seemed to correspond with a heavy deposition of the proteinase-resistant prion protein. This very early alteration may disappear in later stages of the disease because of other MRI phenomena. To date, this observation has not been made in our study. However, we did not study CJD at similar early disease stages as did de Priester et al.\textsuperscript{32}

One possible reason for the absence of abnormalities in 33% of the patients could be that the neuropathological changes in the basal ganglia are not very prominent and that the contrast is too low to be observed. In patients with CJD without increased signal intensity in the basal ganglia on T2-weighted images, the predominant neuropathological changes were reported in the cortex,\textsuperscript{30,33-35} whereas in patients with hyperintense abnormalities in the basal ganglia on T2-weighted images, predominant neuropathological changes were also noted in the basal ganglia.\textsuperscript{9,12,15,30} To analyze this subject further, we are currently correlating MRI with clinical and neuropathological findings.

Although only a few cases have been studied so far, it seems that, in accordance with the literature, abnormally high signals in the basal ganglia and also in other brain regions, such as the cortex, were best seen using diffusion-weighted imaging,\textsuperscript{36-38} which proved to be the better imaging technique compared with fluid-attenuated inversion recovery and T2-weighted images.

In some patients with CJD serial MRIs, an increase in hyperintense abnormalities in the basal ganglia and atrophy was observed over weeks and months. It is still unknown why some patients developed no hyperintense alterations and why some patients with hyperintense alterations showed no increase in these alterations over the disease course. Thus, the time between the 2 examinations in the patient group without an increase in hyperintense alterations was probably too short to observe an increase. At the time of this report, only 3 articles on this subject had been published.\textsuperscript{19,22,32} In contrast to our study, the authors only reported an increase in brain atrophy without an increase in hyperintense abnormalities over a period of 5 weeks to 2 years.

In other brain regions, such as the occipital\textsuperscript{34} or cerebellar cortex, hyperintense abnormalities were observed only in some patients. This may be because of anatomical and technical reasons: the gray matter of the cortex is smaller than that of the basal ganglia and the cortex is surrounded not by unaffected white matter but by CSF. Thus, the contrast is probably too low and the validation of hyperintense alterations in the cortex...
therefore very difficult. In addition to hyperintense alterations in the basal ganglia, high signal intensity in the thalamus was observed in about 7.5% of the CJD patients in our study. In new variant CJD, hyperintense alterations can be seen in the posterior thalamus, but this MRI pattern differs from that of sporadic CJD: whereas the hyperintensities in the posterior thalamus are striking in new variant CJD, the most prominent involvement of the basal ganglia is observed in sporadic CJD, and the changes in the thalamus are only mild.

In the control group, which consisted of non-CJD dementia patients, no hyperintense alterations in the basal ganglia were found in 93% of the patients. This corresponds to the specificity of 93% in the differential diagnosis of CJD that is first reported in our study. Increased signal intensity in the basal ganglia of 4 control patients was detected on T2-weighted MRIs. None of these 4 patients had a definite neuropathological diagnosis, but at least 2 of them definitely did not have CJD. Bilaterally increased signal intensity in the basal ganglia corresponds to the specificity of 93% in the differential diagnosis of CJD that is first reported in our study. Increased signal intensity in the basal ganglia of 4 control patients was detected on T2-weighted MRIs. None of these 4 patients had a definite neuropathological diagnosis, but at least 2 of them definitely did not have CJD. Bilaterally increased signal intensity in the basal ganglia on T2-weighted MRIs can be seen in some other diseases, such as Leigh disease or other mitochondrial disorders, but these diseases have onsets only in childhood. In diseases with acute processes, like hypoxia, hypoglycemia, carbon monoxide poisoning, or hemolytic-uremic syndrome, bilateral hyperintense alterations can be observed. Therefore, these MRI alterations are not pathognomonic for CJD. Based on the clinical history and the results of the technical investigations, such as CSF and blood analyses, it is possible to differentiate between these diseases and CJD.

In our control group, substantial brain atrophy was observed in 57% of the control patients, in contrast to only 29% of the CJD patients. This result shows that atrophy is an unspecific sign of CJD and was more frequent in our other patients with dementia disorders, like Alzheimer disease or unclassified dementias. A reason for this could be that the survival time of the CJD patients is too short to develop brain atrophy. However, CJD patients with a long survival time could develop severe brain atrophy in late-stage disease.

A methodological disadvantage of our study was that the MRI scans were performed under different conditions in hospitals all over the country, which led to a reduced comparability of the MRI scans in our study. However, this circumstance was unavoidable because it is not possible to take all patients with CJD to one medical center. This problem is well known from other multicenter clinical trials investigating multiple sclerosis and MRI. The sensitivity achieved in our study may be too low and might be even higher under standardized conditions. On the other hand, our results show that MRI examination in CJD represents a reliable diagnostic tool, even under suboptimal conditions.

In conclusion, this is the first large study correlating CJD and MRI. The results indicate that MRI has a reasonable sensitivity and a high specificity and is thus a useful and valuable tool that should be considered as a third cornerstone in the clinical diagnosis of CJD and added to the other technical investigations, such as electroencephalography and CSF analysis.

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REFERENCES


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