Experimental Transmission of Human Subacute Spongiform Encephalopathy to Small Rodents

III. Further Transmission from Three Patients and Distribution Patterns of Lesions in Mice

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Summary. Further experimental transmission of Creutzfeldt-Jakob disease (CJD) from three patients to mice and rats was carried out successfully. The clinical signs and pathologic features of spongiform encephalopathy transmitted to animals were much the same as in previous experiments, except that distribution of the lesions in the mice differed with each inoculated material taken from the patients. These observations suggest the multiplicity of CJD agents, as in the case of scrapie agents.

Key words: Subacute spongiform encephalopathy - Creutzfeldt-Jakob disease - Experimental transmission - Small rodents - Transmissible agent

We have already reported the experimental transmission of Creutzfeldt-Jakob disease (CJD) from three patients to small rodents (Tateishi et al. 1980) and most recently, preparations from three additional patients have been transmitted successfully to small rodents. As the distribution of the lesions differed in these mice, possible strain differences have to be considered.

Material and Methods

Sterilized preparations of brain tissue obtained at the time of autopsy were inoculated intracerebrally into CF1 mice and Donryu rats according to the method previously reported (Tateishi et al. 1980).

The clinicopathological details of these Japanese patients have been described in Japanese (Ishii et al. 1978; Kuroiwa et al. 1979; Suetsugu et al. 1980), therefore only brief summaries are given here.

Case 1. B. Y. A 69-year-old man complained of dizziness, headache, and dementia; muscle rigidity and myoclonus soon followed. His condition progressed rapidly to a state of akinetic mutism and he died 8 months after the onset of the disease. EEG examination revealed characteristic periodic synchronous discharges (PSD). At autopsy, the brain weighed 930 g, and a depopulation of nerve cells, astroglial proliferation and spongiform changes were observed histologically.

Case 2. K. A. A 57-year-old woman showed evidence of decreased mental activity, delusions, and hallucinations. Motor disturbance, myoclonus, dementia, muscle rigidity and finally an akinetic state followed. The total duration of the illness was 20 months. PSD were most frequently observed in the EEG 4 months after the onset of the disease. At autopsy the brain weighed 620 g. Severe loss of nerve cells, proliferation of astroglia, and rarefaction of the gray and white matter were seen.

Case 3. S. K. A 37-year-old woman complained of unsteady gait, decrease of visual and mental activities, and disorientation 1 month after the onset. Involuntary movements, urinary incontinence, primitive reflexes and "Gegenhalten" appeared within 5 months. She died after a long period of an akinetic state, and the total duration of the illness was 9 years and 4 months. Typical PSD were observed early in the disease. At autopsy the brain weighed only 575 g, this being the smallest brain heretofore reported in cases of CJD. Diffuse rarefaction in the gray and white matter, extensive loss of nerve cells and proliferation of astroglia were confirmed histologically.

Results

The number of rodents which lived longer than 2 months and were verified pathologically is listed in Table 1. In the first passage from the patients, the incidence of transmission to animals was not high and the incubation periods were long, particularly in case 1. After the second passage, however, the incidence was high and the incubation periods were reduced approximately to 4 months in mice. The clinical symptoms of these diseased animals were identical with those of the earlier experiments; mice showed plasticity of the body and tail, and rats crossed their hind legs, when they were held by the tail.

Pathologically, a spongy state and astroglial proliferation to a severe degree were commonly seen in mice and rats, and degeneration of nerve cells was minimal. These changes were also much the same as findings previously reported, except that the distribution of the lesions in the mice differed with the groups inoculated with different brain material, as shown in Fig. 1. The distribution in mice inoculated with ma-
terial from case 3 was similar to findings in mice in our earlier experiments, though the thalamus and basal ganglia were more severely involved in the present animals. On the other hand, in the groups transmitted from cases 1 and 2 maximal lesions were seen in the cerebral cortices, and in the case 2 group, the thalamus and basal ganglia were also severely affected. These peculiar distributions remained the same through serial propagations. The distribution in rats was identical with that seen in earlier experiments, viz., the cerebral cortices, subcortical areas, cerebral peduncles, optic tracts, thalamus, basal ganglia, brain stem, cerebellum and spinal cord were affected, in that order.

### Discussion

In our experiments using small rodents, CJD from five patients was transmitted directly to mice and preparations from one other patient have been transmitted exclusively to guinea pigs. As was the case in earlier experiments (Tateishi et al. 1980), the incubation periods were shortened approximately to 4 months in mice, after the second passage. Therefore, mice can serve as a convenient animal model for studies on CJD.

The pathologic features of the diseased mice were peculiar to each group inoculated with material from different patients. In the mice of the former experiments, severe lesions were found in the white matter of the cerebrum, cerebellum, and brain stem, and resembled the lesions seen in the patients from whom the material had been obtained. Different distributions in mice may be due to different strains of the CJD agents. In the experimental transmission of scrapie from sheep to mice, the distribution in mice differed with each strain of scrapie agents (Fraser and Dickinson 1973). Therefore, possible multiplicity of CJD agents should be given attention.

### Table 1. Transmission of material from three cases to small rodents

<table>
<thead>
<tr>
<th>Case</th>
<th>Passage</th>
<th>Animals (donor→recipient)</th>
<th>No. diseased/No. inoculated</th>
<th>Days after inoculation (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I</td>
<td>→ mice</td>
<td>9/32</td>
<td>641 ± 124.9</td>
<td></td>
</tr>
<tr>
<td>1 II</td>
<td>→ mice</td>
<td>18/19</td>
<td>111.2 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>1 III</td>
<td>→ mice</td>
<td>12/14</td>
<td>113.1 ± 18.3</td>
<td></td>
</tr>
<tr>
<td>2 I</td>
<td>→ mice</td>
<td>4/18</td>
<td>326.3 ± 97.9</td>
<td></td>
</tr>
<tr>
<td>2 II</td>
<td>→ rats</td>
<td>2/6</td>
<td>545.0 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>3 I</td>
<td>→ mice</td>
<td>7/8</td>
<td>146.9 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>3 II</td>
<td>→ mice</td>
<td>12/12</td>
<td>124.2 ± 12.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ mice</td>
<td>18/18</td>
<td>122.0 ± 9.3</td>
<td></td>
</tr>
</tbody>
</table>

* a, b, c: Inoculations from different animals

b Number of animals which lived longer than 2 months and verified pathologically

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Fig. 1a–c. Distribution of lesions in mice inoculated with material from cases 1 (a), 2 (b), and 3 (c)