CT Contrast Enhancement on Brain Scans and Blood-CSF Barrier Disturbances in Cerebral Ischemic Infarction

C. R. Hornig,* O. Busse,* T. Buettner,*† W. Dorndorf,* A. Agnoli,† and Z. Akenji†

SUMMARY CT contrast enhancement of the ischemic infarction, blood-CSF barrier function for albumin, and severity of neurological symptoms were evaluated at predefined intervals in 41 patients with supratentorial ischemic infarctions. Contrast enhancement was most frequently observed in the 2nd and 3rd week after the stroke. This late CT enhancement was not related to infarction size and severity of blood-CSF barrier disturbance. The rare appearance of CT enhancement in the 1st week was usually associated with extensive infarctions and accompanied by blood-CSF barrier disturbances. These barrier disturbances, which occurred with higher frequency and greater severity in extensive infarctions (peak 3rd day), generally persisted for several weeks. We suggest that contrast enhancement in the 1st week after an ischemic stroke is due to diapedesis from necrotic capillaries; the more frequently observed late enhancement might be the result of a blood-brain barrier disturbance which in turn is hypothetically attributed to increased pinocytotic activity of regenerated endothelial cells.

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AN ENHANCEMENT of the infarcted region of the brain often appears in CT after injection of contrast medium. Blood-brain barrier disturbances and hyperemia in the infarcted region caused by increased vascularity have been discussed as possible causes of this enhancement. The latter was also assumed to be the reason of an increased radionuclide uptake in brain scintigraphy. Measurements of cerebral blood flow show that such contrast enhancement, however, cannot be explained by focal hyperemia in the sense of a luxury perfusion. The aim of our study was to examine the relationship between contrast enhancement on CT scans and Blood-CSF barrier (BCB) disturbances of patients with cerebral infarctions.

Patients and Methods

Neurological examination, CT scan and evaluation indicators of BCB function were, at predefined intervals, completed in 41 patients with single supratentorial cerebral infarction demonstrated on CT scan (20 women, 21 men; mean age 60.6 years, range 33 to 83 years), who were admitted to University Hospital, Department of Neurology, in Giessen/FRG. All patients were informed about the aim of the study and consented to it. Infarctions were localized in the area of the middle cerebral artery in 40 cases and of the posterior cerebral artery in one case. In 27 cases the cause of the infarction could be established. Eighteen patients demonstrated angiographically or sonographically proven cerebral or cranial arteriosclerosis: 7 had occlusion and 2 had marked stenosis of the ipsilateral internal carotid artery. In 9 cases cardiac embolism was assumed to be the cause of the infarction; arrhythmia caused by atrial fibrillation existed in 5 cases, a recent myocardial infarction was found in 1 case and a prolapsed mitral valve was found in a young patient.

Neurological Examination

The following neurological symptoms were evaluated on the 1st, 3rd, 7th, 14th, 21st, 28th and 42nd day after the stroke: consciousness level, orientation, degree of aphasia, facial palsy, hemianopia, extremity paresis, Babinski sign, and sensory disorders. The severity of the neurological deficit was rated on a scale of 0 to 25 according to that of Patten et al. Strokes receiving a score higher than 13 were considered severe. Marked improvement of neurological symptoms was assumed when the score fell more than 3 points during the period of hospitalization.

Blood-CSF Barrier Parameter

The level of albumin in CSF obtained by lumbar puncture and in serum was determined on the 1st, 3rd, 14th, 21st and 28th day of the disease using a radioimmunodiffusion technique (LC-Partigen plates, Behringwerke, Marburg/FRG), and the CSF-serum quotient calculated. None of the samples were xanthochromic; unfortunately spectrophotometry was not done.

Computerized Tomography

A CT scan was performed with a Siretom 2000 (Siemens, Erlangen/FRG; 256 × 256 matrix) before and after intravenous injection of contrast medium (1 ml/kg BW; Conray 60, Byk Gulden, Constance/FRG) on the 1st, 3rd, 7th, 14th, 21st, 28th and 42nd day. The volume of the hypodensity was estimated by the following equation: (longest dimension × greatest width × number of 10 mm sections) / 2). The infarcted region was considered large when its volume exceeded 30 ml. After injecting contrast medium, the enhancement pattern of the infarcted region was recorded.
CSF specimens and CT scans were not available for all patients at all predetermined intervals.

Results

Contrast Enhancement on CT Scan

Contrast enhancement was present on CT scans from 21 of 29 patients (72%) with CT scans over a 4-week period. It appeared most frequently on the 14th day (39%, \( p < 0.05 \); chi square test). An enhancement was first observed on the 3rd day after the stroke in 6 of 38 patients (16%) and within 24 hours after the infarction in none of the patients (fig. 1). Contrast enhancements appearing on the 3rd or 7th day persisted until at least the 21st day and usually until the 28th day. The probability of an enhancement, therefore, was highest in the 3rd week (see table 1). This frequency was statistically significant (\( p < 0.01 \); chi square test). Contrast enhancement appeared in 78% of infarctions assumed to be embolic in origin but only in 50% of those of thrombotic origin. Accordingly enhancement was more intensive in embolic infarctions. Time pattern of enhancement of thrombotic and embolic infarction showed no significant difference.

Four different enhancement patterns were observed (fig. 2):

1. Patchy enhancement
   Several small hyperdense areas diffusely scattered over the hypodensity.
2. Ring-shaped enhancement
   Hyperdense ring around a hypodense or isodense zone.
3. Cortical enhancement
   Enhancement of cerebral cortex and adjacent tissue with visualization of gyri.
4. Homogenous enhancement
   Confluent contrast intensification evenly distributed over hypodensity.

Patchy enhancement was the most frequently observed pattern in the period studied. A preference of any pattern for one particular interval could not be established (table 1).

In the 1st week of the infarction, there was a significant correlation between the estimated volume of the hypodense zone on the CT scan and the probability of contrast enhancement (\( p < 0.05 \); chi square test). Enhancement in the 1st week was found in 47% of all infarctions with a volume exceeding 30 ml, but in only 14% of those with a volume of less than 30 ml. Accordingly, contrast enhancement appeared more frequently in large infarctions causing a compression of the ventricular system or a midline shift.

A CT enhancement in the 1st week was observed in 8 of 16 patients with evidence of swelling in CT, but in only 4 of 20 patients without ventricular compression or midline shift (\( p < 0.1 \); chi square test). The probability of an enhancement appearing for the first time in the 2nd or 3rd week was not dependent on the infarction size (fig. 3).

Blood-CSF Barrier Disturbance

The CSF-serum quotient for albumin was taken as an indicator of impaired BCB function. This quotient was high in 61% of the patients during the 1st week of infarction, in approximately 50% during the 2nd and 3rd week, and in 33% during the 4th week. The barrier disturbance was generally moderate, the CSF-serum quotients for albumin ranging primarily between 0.0077 and 0.0150. Relatively high values (>0.0150) were detected more frequently on the 3rd day (table 2). Impairment of barrier function increased significantly between the 1st and 3rd day (\( p < 0.05 \); Wilcoxon signed rank test for paired samples). The mean CSF-serum quotient for albumin reached its maximum on the 3rd day of disease and then fell steadily during the

### Table 1: Frequency and Pattern of CT Enhancement at Different Time Intervals after Stroke

<table>
<thead>
<tr>
<th>Day</th>
<th>Number of CTs</th>
<th>Enhancement %</th>
<th>Pattern of enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3rd</td>
<td>38</td>
<td>6</td>
<td>15.8 patchy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ring enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cortical enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>homogeneous</td>
</tr>
<tr>
<td>7th</td>
<td>30</td>
<td>10</td>
<td>33.3 patchy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ring enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cortical enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>homogeneous</td>
</tr>
<tr>
<td>14th</td>
<td>27</td>
<td>16</td>
<td>59.3 patchy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ring enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cortical enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>homogeneous</td>
</tr>
<tr>
<td>21st</td>
<td>23</td>
<td>12</td>
<td>52.2 patchy</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>cortical enhancement</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>homogeneous</td>
</tr>
<tr>
<td>28th</td>
<td>14</td>
<td>6</td>
<td>42.9 patchy</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>cortical enhancement</td>
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<td></td>
<td></td>
<td></td>
<td>homogeneous</td>
</tr>
<tr>
<td>42nd</td>
<td>7</td>
<td>1</td>
<td>14.3 patchy</td>
</tr>
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<td></td>
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<td>ring enhancement</td>
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<tr>
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<td></td>
<td>cortical enhancement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>homogeneous</td>
</tr>
</tbody>
</table>

![Figure 1: Time of first appearance of enhancement.](http://stroke.ahajournals.org/)

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FIGURE 2. Different CT enhancement patterns in infarction. Upper left: Patchy enhancement; Lower left: Ringshaped enhancement; Upper right: Cortical enhancement demonstrating gyri; Lower right: homogenous enhancement.

course of the disease (fig. 4). There was no significant difference in the degree of BCB disturbance for albumin depending on the etiology of infarction. Mean CSF-serum albumin ratio in cases of embolic infarctions was 0.0085 ± 0.0041 and 0.0099 ± 0.0040 in those of thrombotic etiology.

Patients with severe neurological deficits, on the average, also had a pronounced BCB disturbance on the 3rd day (p < 0.05; Wilcoxon signed rank test). A BCB disturbance was present on the 3rd day of the infarction in 14 of 17 patients with severe neurological symptoms, 10 of whom had a CSF-serum quotient for albumin higher than 0.0100. By contrast, BCB was intact in 9 of 17 patients with less severe neurological deficits, and only 3 of these patients had a CSF-serum quotient for albumin higher than 0.0100 (fig. 5). The mean CSF-serum quotient for albumin was also higher in patients with extensive infarctions on CT scans (p < 0.05; Wilcoxon signed rank test, fig. 6). Only 5 of 19 patients with a volume of hypodensity exceeding 30 ml had normal CSF serum quotients for albumin, as compared to 9 of 15 patients with a volume of less than 30 ml.

A correlation was also established between severity of the BCB disturbance on the 3rd day after the stroke and prognosis for the regression of neurological symptoms: In 7 of 19 patients observed over a 4-week period, only slight or no improvement of neurological symptoms was noted. On the whole, the CSF-serum quotient for albumin was higher in these patients than

TABLE 2

<table>
<thead>
<tr>
<th>CSFserum albumin ratio</th>
<th>3rd day n = 34</th>
<th>14th day n = 25</th>
<th>21st day n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0076</td>
<td>13 38.2</td>
<td>13 52</td>
<td>9 50</td>
</tr>
<tr>
<td>0.0077 &lt; 0.0100</td>
<td>7 20.6</td>
<td>4 16</td>
<td>3 16.7</td>
</tr>
<tr>
<td>0.0100 &lt; 0.0150</td>
<td>7 20.6</td>
<td>5 20</td>
<td>5 27.7</td>
</tr>
<tr>
<td>0.0150 &lt; 0.0200</td>
<td>6 17.7</td>
<td>1 4</td>
<td>0 0</td>
</tr>
<tr>
<td>0.0200</td>
<td>1 2.9</td>
<td>2 8</td>
<td>1 5.6</td>
</tr>
</tbody>
</table>
CT Contrast Enhancement and BCB Disturbances

A correlation exists between CT contrast enhancement and BCB-disturbance for albumin only when the enhancement appears in the 1st week after the stroke. The late appearance of enhancements in the 2nd and 3rd week is unrelated to the severity of the BCB disturbance. Early contrast enhancement in the 1st week appeared predominantly in patients with severely impaired BCB functions; impaired BCB function, however, was no longer demonstrable in late enhancements in the 2nd and 3rd week (fig. 8). In addition, CSF-serum quotients for albumin were significantly higher on the 3rd and 14th day in patients with contrast enhancement in the 1st week than in patients with late enhancement (p < 0.05; Wilcoxon signed rank test, fig. 9).

Discussion

The frequency of CT contrast enhancement in a brain infarction has been reported to be anywhere from 26% to 95%. Most authors found enhancement in approximately 60% of their patients, usually in the 2nd and 3rd week after the stroke {2-4, 8-13}. We observed contrast enhancement in 72% of our patients, especially during the 2nd and 3rd week.

In agreement with other authors,12,26 contrast enhancement also appeared in a few of our cases during the 1st week. In contrast to those showing late enhancement, brain infarctions with early enhancement were extensive on CT scans and showed severely impaired BCB function. These relationships and the time when the enhancement appeared suggest that infarctions with early enhancement are infarctions with diapedesis from necrotic capillaries, which can not be reliably detected on CT scans.14,15 Diapedesis is more frequent in extensive infarctions than in small ones: leakage of blood into the extracellular space may therefore be the consequence of BCB disturbance. Infarctions with early enhancement have been frequently recognized at a later time on the CT scan as being hemorrhagic.16

Petechiae in brain infarctions was found at necropsy of animals that showed contrast enhancement of the infarcted region during the first week.17 Radionuclide brain scans with technetium, obtained in the early phase of secondary hemorrhagic cerebral infarctions, also showed isotope accumulation at the site of the
infarction. This radionuclide uptake is comparable to early CT enhancement because iodinated contrast medium and technetium have a similar spatial and temporal distribution. Histologic assessment made to coincide with the time of early contrast enhancement reveals tissue necrosis extending into the capillary endothelium and, consequently, diapedesis. Leakage of protein tracers into necrotic zones has been observed in animal experiments of cerebral ischemia with restored blood supply. The bleeding, however, is non-uniform, perhaps because of variations in severity of capillary necrosis and glial swelling with compression of capillaries caused by edema. This may explain why an early enhancement does not exist in all cases.

The increase of the CSF albumin level up to the 3rd day in relation to the BCB disturbance can be explained by serum leakage associated with diapedesis. Since the incidence of diapedesis is higher in extensive infarctions, BCB function is more likely to be more severely impaired. Our CT studies show that the volume of the hypodensity reaches its maximum around the 3rd day. Impaired BCB function then gradually normalizes over a period of 4 weeks during which the endothelial cells regenerate. Some authors reported that initial impairment in function is due to defective tight junctions; most agree that vigorous pinocytosis can be observed at this time. Pinocytosis is rarely found as transport mechanism for macromolecules in normal cerebral capillary endothelial cells. The pinocytotic rate of endothelial cells not irreversibly injured by ischemia is probably higher than that of normal endothelium owing to metabolic changes. The resulting blood-brain barrier defect can be demonstrated in animal experiments by the increased passage of protein tracers through the endothelium.

Late CT contrast enhancement in the 2nd and 3rd week after the stroke is attributed to an impairment of blood-brain barrier function that may be conjecturally ascribed to increased pinocytosis. Increased pinocytosis...
ic rate, however, can be caused by the contrast medium alone. Early enhancement is attributed to diapedesis caused by capillary necrosis, primarily in extensive infarctions. Increased pinocytosis forming the basis of late enhancement is postulated in endothelial cells with reversible damage. For this reason, no correlation could be established between infarction size and frequency of CT contrast enhancement in the 2nd or 3rd week after the stroke.

The amount of protein crossing the blood-brain barrier as a result of pinocytosis is far less than that reaching the extracellular fluid and the CSF through defective tight junctions and diapedesis. Pinocytosis may only account for a very slight increase of albumin in CSF. No significant correlation could be established between late CT contrast enhancement and severity of BCB impairment.

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