Deep Cerebral Infarcts Extending to the Subinsular Region

Edward H. Wong, MB, ChB; Patrick M. Pullicino, MD, PhD; Ralph Benedict, PhD

Background and Purpose—We sought to determine the clinical and radiological features and pathogenesis of deep cerebral infarcts extending to the subinsular region (DCIs).

Methods—We defined DCIs as subcortical infarcts extending between the lateral ventricle and the subinsular region with a paraventricular extent >1.5 cm and a subinsular extent of at least one third of the anteroposterior extent of the insula. We identified patients by review of imaging records and noted the clinical information, risk factors, and investigations. We compared risk factors and clinical features between DCIs and “internal border zone” infarcts restricted to the paraventricular region.

Results—Eight patients were studied. The typical clinical features of DCIs were hemiparesis, aphasia, dysarthria, and dysphagia. Aphasia was seen in 3 of 5 patients with left-sided infarcts. Six of 8 patients (75%) had hypoperfusion as a possible pathogenetic factor (carotid occlusion in 4, surgical clipping of MCA in 1, low ejection fraction in 1), and 3 patients (38%) had cardioembolism as a possible pathogenetic factor (atrial fibrillation in 2, low ejection fraction in 1). One patient (12%) had no cause for stroke. Clinical features were similar to those for paraventricular infarcts. Carotid occlusion was more frequent (P=0.04), and there was a trend toward a higher frequency of hypertension (P<0.1) and smoking with DCIs than with paraventricular infarcts. DCIs were located in a deep vascular border zone.

Conclusions—The clinical features and pathogenesis of DCIs overlap with those of internal border zone paraventricular infarcts. Hypoperfusion may give rise to DCIs since large-artery occlusion is their main risk factor. The larger size of DCIs compared with paraventricular infarcts may relate to a poorer collateral blood supply. (Stroke. 2001;32:2272-2277.)

Key Words: carotid artery occlusion ■ cerebral infarction ■ hypoperfusion

In 1990, Angeloni et al1 described 7 patients with infarcts secondary to acute distal middle cerebral artery (MCA) embolic occlusions. They illustrated their report with a cranial CT scan showing a large subcortical infarct, which extended from the paraventricular region to the subinsular region, but no clinical data were given. Despite the embolic etiology, they used the term internal border zone infarct because it appeared to lie in a deep vascular border zone.

The term internal border zone (watershed) infarct is more frequently used to describe a type of subcortical infarct that is restricted to a paraventricular location.2-6 The pathogenesis of these paraventricular infarcts appears to be distinct from lacunar infarcts, with hypoperfusion, secondary to large-vessel occlusive disease, thought to be the major factor. They are located in the distal ramifications of the lenticulostriate arteries (rather than along the course of the lenticulostriate arteries, as are lacunar infarcts) and frequently are associated with ipsilateral high-grade carotid stenosis and exhausted perfusion reserve.⁷ ⁸ Brains with paraventricular infarcts have shown demyelination and astrogliosis (so-called ischemic rarefaction⁹ on pathology, suggesting that, unlike lacunes, some of these lesions are not true cavitory infarcts. Bladin and Chambers² divided paraventricular infarcts into confluent and partial infarcts on the basis of their radiological appearance and size.

Subinsular infarcts¹⁰ extend linearly subjacent to the insular cortex but do not extend to the paraventricular region. The pathogenesis of these infarcts may include hypoperfusion since they are located in a border zone between small insular cortical penetrating branches of the MCA and the lenticulostriate arteries.¹¹ Infarcts restricted to the subinsular region appear to be rare, and their clinical features have not been described apart from a single report of a patient with bilateral subinsular infarction, who had the opercular syndrome.¹¹

Infarcts in the paraventricular region constitute approximately 3% of infarcts.⁶ Infarcts that extend from the paraventricular region to the subinsular region appear to be less frequent, and we have found only a single clinical case description in the literature of a patient with a sensorimotor stroke and dysphasia.¹² Little is known about the pathogenesis and clinical features of these infarcts and whether they differ from infarcts that are localized to the paraventricular region. We here review the clinical features, imaging findings, and pathogenesis of a series of infarcts that involve and
extend between the paraventricular white matter and the subinsular region. We have called these deep cerebral infarcts extending to the subinsular region (DCIs).

Subjects and Methods
We defined DCIs as subcortical infarcts with
(1) a paraventricular component, appearing as a confluent low-attenuation area on CT scan or a hypointensity on T2-weighted MRI of >1.5 cm in diameter, and
(2) a linear subinsular component, appearing as a low-attenuation area on CT or T2-weighted MRI hyperintensity extending parallel and subjacent to the insular cortex, seen on axial or coronal images and extending for at least one third of the anteroposterior extent of the insula. The subinsular component has to be continuous with the paraventricular component, and the infarct should not primarily involve the insular cortex.

We reviewed MRI and CT scans of stroke unit patients seen by one of the authors (P.M.P.) over a period of 4 years to identify patients with these features. We obtained information from the patient, the medical records, or the patient’s physician on clinical presentation, past medical history, and outcome. We reviewed available investigations (in particular, complete blood count, coagulation studies, glucose level, lipid profile, echocardiogram, carotid ultrasound, and MR angiography). We prospectively studied 2 patients: one (patient 6) with single-photon emission CT (SPECT) and transcranial Doppler sonography and another (patient 1) with full neuropsychological testing. Details of patient 7 are also given and transcranial Doppler sonography and another (patient 1) with full ultrasound, and MR angiography). We prospectively studied 2 groups. A value of P<0.05 was used for statistical significance.

Microangiography was performed in 1 postmortem brain to outline the small arterial territories according to standard techniques.15

Results
We identified 8 patients with DCI over a 5-year period. Their risk factors and clinical findings and pertinent investigations are presented in Table 1. Six patients were scanned because of acute stroke. One patient was scanned as part of the investigation of bilateral carotid bruits and another as part of the workup of parkinsonism. Both of these patients had a history of stroke.

Patient Characteristics and Risk Factors
The group included 4 women and 4 men, with an age range from 49 to 75 years (mean age, 62.8±9.3 years) (Table 2). Seven patients (87%) had a history of hypertension, and 7 patients (87%) were current smokers or ex-smokers. Six patients (75%) had hypoperfusion as a possible pathogenetic factor: 1 developed a postoperative DCI ipsilateral to an MCA that was temporarily clipped during aneurysm surgery, 4 had ipsilateral internal carotid artery occlusions (1 of whom also had a low cardiac ejection fraction), and another patient had a low cardiac ejection fraction. Three patients (38%) had cardioembolism as a possible pathogenetic factor: 2 had atrial fibrillation, and 1 had low ejection fraction. One patient (13%) had no obvious cause for stroke.

MRI Findings
The infarcts were smaller in their subinsular portion than in their paraventricular portion (Figure 1). Patient 3 had bilateral infarcts. Two patients (patients 2 and 4) had associated

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TABLE 1. Characteristics of 8 Patients With DCIs

<table>
<thead>
<tr>
<th>Pt/Age, y/Race/Sex</th>
<th>Risk Factors for Stroke</th>
<th>Clinical Findings</th>
<th>Arterial/Cardiac Disease on Doppler/MRA/Cerebral Angiography</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/61/W/M</td>
<td>Smoker, hypercholesterolemia</td>
<td>R hemiparesis, aphasia, dysarthria, hemisensory loss</td>
<td>Occluded L carotid</td>
<td>Persistent hemiplegia, aphasia</td>
</tr>
<tr>
<td>2/71/W/F</td>
<td>HTN, DM, CAD, smoker</td>
<td>L hemiplegia, dysarthria, dysphagia</td>
<td>Occluded R ICA; 50% stenosis L ICA; EF 39%</td>
<td>Persistent hemiplegia; died 2 y later</td>
</tr>
<tr>
<td>3/52/W/F</td>
<td>HTN, CAD, AF</td>
<td>1981: transient aphasia, R hemiparesis, micrographia; 1991: fall, mutism, then hypophonia</td>
<td>Normal intracranial and carotid MRA</td>
<td>Persistent mild hemiparesis, hypophonia, parkinsonism 2 y later</td>
</tr>
<tr>
<td>4/58/W/M</td>
<td>HTN, hypercholesterolemia, ex-smoker</td>
<td>R hemiparesis (leg&gt;arm and face) and hemisensory deficit, dysarthria</td>
<td>Occluded L ICA</td>
<td>Good recovery, mild leg paresis 2 y later</td>
</tr>
<tr>
<td>5/75/W/F</td>
<td>HTN, hypercholesterolemia, smoker</td>
<td>L hemiparesis (arm&gt;leg)</td>
<td>Occluded R ICA; 40–50% stenosis L ICA</td>
<td>Good recovery</td>
</tr>
<tr>
<td>6/67/W/M</td>
<td>HTN, CHF, smoker, hypercholesterolemia, ♦ hematocrit</td>
<td>Collapse ×2, R hemiparesis, dysarthria, dysphagia</td>
<td>Normal carotid, intracranial MRA; EF 20%</td>
<td>Good recovery, mild residual leg weakness</td>
</tr>
<tr>
<td>7/49/W/M</td>
<td>HTN, smoker, AF</td>
<td>R hemiparesis, hemianopia, aphasia, dysphagia</td>
<td>Occluded R ICA; L MCA clipped</td>
<td>Hemiplegic, mild aphasia 5 y later</td>
</tr>
<tr>
<td>8/69/B/F</td>
<td>HTN, smoker, hypercholesterolemia</td>
<td>L facial weakness and numbness, dysarthria, dysphagia</td>
<td>Normal intracranial and carotid MRA</td>
<td>Good recovery</td>
</tr>
</tbody>
</table>

Pt indicates patient; MRA, MR angiography; W, white; B, black; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; AF, atrial fibrillation; CHF, congestive heart failure; R, right; L, left; ICA, internal carotid artery; EF, ejection fraction.
Partial and Confluent Paraventricular Infarcts

TABLE 2. Demographic Factors and Risk Factors of DCIs and Partial and Confluent Paraventricular Infarcts

<table>
<thead>
<tr>
<th></th>
<th>DCIs (n = 8)</th>
<th>CPVI$^2$ (n = 6)</th>
<th>PPVI$^2$ (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>62.8 ± 9.3</td>
<td>69.2 ± 4.0</td>
<td>75.0 ± 8.5</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>4:4</td>
<td>5:1</td>
<td>11:1</td>
</tr>
<tr>
<td>Bilateral infarcts</td>
<td>1 (13)</td>
<td>4 (67)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>7 (87)</td>
<td>5 (83)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Diabetes/hyperglycemia†</td>
<td>1 (13)</td>
<td>4 (67)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (25)</td>
<td>5 (83)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Smoker/ex-smoker§</td>
<td>7 (87)</td>
<td>3 (50)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Hypercholesterolemia‡</td>
<td>4 (50)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>ICA/MCA occlusion§</td>
<td>5 (63)</td>
<td>3 (50)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (25)</td>
<td>1 (17)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Low ejection fraction</td>
<td>2 (25)</td>
<td>0</td>
<td>3 (25)¶</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. CPVI indicates confluent paraventricular infarcts; PPVI, partial paraventricular infarcts; ICA, internal carotid artery; and N/A, not available.

* Trend (P = 0.1) to increase in frequency across 3 groups.
† Random glucose > 200 mg/dL.
‡ Cholesterol > 250 mg/dL.
§ Significant (P = 0.04) increase in frequency across 3 groups.
¶ Poor left ventricular function on echocardiogram.

TABLE 3. Clinical Features

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Patients (n = 8)</th>
<th>Other groups (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Posterior watershed infarcts</strong> affecting the trigonal region or overlying cortex**</td>
<td>In 3 patients (patients 1, 3, and 4) the MRI abnormality extended into the white matter above the lateral ventricle (Figure 1), with the signal characteristics in the white matter suggesting ischemic rarefaction of the white matter rather than cavitary infarction.</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>The clinical features are listed in Table 3.</strong></td>
<td></td>
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<tr>
<td>Seven patients (86%) had hemiparesis. Patient 8 had a partial opercular syndrome with left facial and tongue weakness with dysarthria and dysphasia but no limb weakness, and 5 other patients had a combination of dysphasia and dysarthria, suggesting a partial opercular syndrome. Three patients had sensory loss. Patient 3 had transient aphasia and hemiparesis after a left DCI at the age of 52 years. Ten years later she had a second right DCI with transient mutism and persisting hypophonia and developed parkinsonism. Four patients (50%) regained functional independence, and 3 had severe residual deficits.</td>
<td></td>
<td></td>
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<tr>
<td><strong>Representative Cases</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>A 61-year-old man with a 60-pack-year history of smoking and hypercholesterolemia developed sudden right-sided weakness and garbled speech. On examination he had a dense right hemiparesis and tongue deviation to the right and had severe motor aphasia with dysarthria. Sensation was decreased on the right side. His blood pressure was 130/70 mm Hg. Carotid Doppler examination revealed a left carotid occlusion. A CT scan showed an acute infarct involving the left subinsular and paraventricular regions. After prolonged rehabilitation he was able to ambulate with a quadripod cane but had right hemiplegia and aphasia. Five years later he had persisting hemiplegia and aphasia and was able to walk only a few steps with support. MRI scan of the brain showed a chronic infarct in the left subinsular region extending up to the lateral ventricle, with left lateral ventriculomegaly. His clinical presentation was marked by nonfluent, telegraphic speech, with occasional, literal paraphasic errors and frequent perseverations. He had no difficulty in repeating medium-length phrases or responding accurately to yes/no questions. He performed 2-step but not 3-step commands accurately. He was keenly aware of his defect and disturbed by it. Objective testing was remarkable for severe deficiencies on the Spontaneous Speech, Sequential Commands, and Object Naming scales from the Western Aphasia Battery (WAB). Profound defects were also encountered on tests emphasizing generative fluency, visual naming, and verbal learning. Finger tapping in the left hand was preserved, as was performance on tests of spatial ability. Impairment was found on the WAB Repetition scale, although the degree of impairment was far less than that of the Spontaneous Speech scale. Comprehension on the Yes/No Questions and Auditory Word Recognition scales of the WAB was preserved. Moreover, on the generative fluency task, the patient failed to produce a single word in 3 successive 60-second trials. This pattern of normal comprehension, relatively preserved repetition, and very profound impairment in conversational and generative fluency is congruent with a transcortical motor aphasia type I disorder.</td>
<td></td>
<td></td>
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<tr>
<td><strong>Patient 7</strong></td>
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</tbody>
</table>
| A 49-year-old man with a history of hypertension, smoking, atrial fibrillation, and peripheral vascular disease presented with recurrent episodes of a right ocular visual disturbance. MR and cerebral angiograms revealed a right internal carotid artery origin occlusion and left MCA bifurcation aneurysm. Transesophageal echocardiography showed no embolic
source and a normal ejection fraction. During elective clipping of the aneurysm, a small tear occurred, and the left MCA was clipped for 9 minutes. Postoperatively the patient was severely dysphasic, with dysphagia, a right homonymous hemianopia, and a right hemiplegia. Sensory examination was normal. A CT scan showed a left paraventricular infarct, which extended into the subinsular region. Five years later the patient needed a walker to ambulate and had mild aphasia.

### Comparison With Internal Border Zone Paraventricular Infarcts

Table 2 shows that patients with DCIs were younger than patients with partial internal border zone paraventricular infarcts \( (P<0.005) \) and tended to be younger than patients with confluent paraventricular infarcts \( (P<0.01) \). Large-artery occlusion was more frequent in patients with DCIs than in patients with partial or confluent paraventricular infarcts \( (P=0.04) \), and hypertension and smoking tended to be more frequent in patients with DCIs than in patients with partial or confluent paraventricular infarcts \( (P<0.1) \). Outcome for DCIs was similar to that for confluent paraventricular infarcts (50% independent) and worse than that for partial paraventricular infarcts (83% independent).

### Location of Infarcts in Relation to Vascular Territories

On superimposition of the location of the infarct seen on the coronal scan of patient 2 and a coronal postmortem microangiogram, DCIs were found to lie in a deep vascular border.
zone (Figure 2). The subinsular part of the infarct lay in a border zone between small insular penetrating arteries and branches of the lenticulostriate arteries. The paraventricular part of the infarct lay in a border zone between the terminal ramifications of long cortical penetrating arteries and the terminal branches of the lenticulostriate arteries or within the terminal ramifications of these cortical and basal penetrating arteries.

**Discussion**

DCIs appear to be a subtype of internal border zone infarction for the following reasons: (1) DCIs are located in a deep vascular border zone between small insular penetrating arteries and branches of the lenticulostriate arteries. Border zone infarcts confined to the paraventricular region are located near the upper ventricular end of this border zone, and infarcts confined to the subinsular region are located at the lower insular end. (2) DCIs have clinical features and risk factors that overlap with those of internal border zone infarcts restricted to the paraventricular region. (3) Hypoperfusion, particularly secondary to ipsilateral carotid occlusion, appears to be a risk factor for DCIs. Infarcts coinciding with deep vascular border zones have been described in several other locations, including the cerebellum, midbrain, subinsular region, and probably the white matter as well. For this reason it is important to qualify the term *internal border zone/watershed infarct* with the location of the infarct and not confine its use to infarcts restricted to the paraventricular region.

Hypoperfusion appears to be important for the development of DCIs. Not only did the majority of our patients have a potential cause for hypoperfusion, but in one case temporary occlusion of the MCA directly resulted in a DCI. The efficiency of pial collaterals or the presence of stenosis of small arteries may dictate whether hypoperfusion secondary to carotid occlusion results in an infarct that is localized to the paraventricular region or the subinsular region or involves both regions, resulting in a DCI. Our finding of a trend of a higher frequency of hypertension and smoking in DCIs than in infarcts localized to the paraventricular region suggests that hypertension may be a cause of reduced collateral efficiency in DCIs. In patient 6, who had no large-artery occlusion, compromise of vascular reserve beyond the location of the infarct shown on SPECT also suggests that flow to the MCA territory was compromised by poor pial collaterals or small-artery disease.

Cardioembolism was a potential cause of DCIs in 3 patients. This is in agreement with the report of 7 patients with internal border zone infarction secondary to distal MCA embolism. Multiple small emboli in the distal cortical branches of the MCA may reduce collateral flow to the insular region and result in a perisylvian area of decreased perfusion reserve and vulnerability to hypoperfusion injury.

The clinical findings in our patients reflect the 2 main anatomic locations involved by DCIs: the subinsular region and the corona radiata. Although the clinical presentation of subinsular infarcts is unknown, infarction of the insula is known to produce dysphagia, speech articulation difficulties, and aphasia, all of which were clinical features in our patients. We have described a patient with bilateral subinsular infarcts who had the opercular syndrome, and a unilateral subcortical infarct has also produced the opercular syndrome. Two of our patients with DCIs had a complete or partial opercular syndrome, suggesting that subinsular infarcts may produce the same symptoms as infarctions of the insula. The combination of dysarthria and dysphagia is typical of pseudobulbar palsy and is a component of the opercular syndrome secondary to infarction of the insula. It was seen in 5 of our patients, suggesting that the subinsular infarct may have been responsible for these symptoms. These patients may also have had language disorders, but they were not subjected to neuropsychological testing as was patient 1 in our series.
Three of our patients and 1 from the literature 12 who had aphasia had either a left-sided DCI or bilateral DCIs. Patient 1 had a severe persistent transcortical motor aphasia with an infarct that did not involve the cortex or frontal lobe (apart from some frontostriate semiovale white matter rarefaction). Larger confluent internal border zone infarcts localized to the paraventricular region may give rise to aphasia, 3 but subcortical infarcts do not usually give rise to the typical aphasia syndromes. 28, 29 Transcortical motor aphasia is thought to arise from a disruption of connections between the supplementary motor area and the perisylvian speech zone, 30 although cases have been described after damage to premotor cortex and the operculum. 31 The infarct in patient 1 most likely involved connections between the perisylvian speech zone and the insular cortex and possibly premotor regions and is unlikely to have damaged connections to the supplementary motor area. Involvement of the subinsular arcuate fasciculus has been linked to conduction aphasia but not transcortical motor aphasia. Transcortical aphasia is occasionally seen with subcortical infarcts 32 but Taubner et al 31 have suggested that injury to the opercular primary motor cortex or to its efferent projections may result in “phonemic disintegration.” Clinically this results in a nonfluent aphasia with intact comprehension and may be the variant of transcortical motor aphasia seen in our patients and in patients with DCIs.

References

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