Effects of Capsular or Thalamic Stroke on Metabolism in the Cortex and Cerebellum: A Positron Tomography Study

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We used positron emission tomography to study the cortical and cerebellar metabolic rates in 21 strictly selected patients with pure internal capsular infarct (n=8), thalamocapsular hemorrhage (n=6), or pure thalamic stroke (n=7). Significant diffuse ipsilateral cortical hypometabolism relative to 62 controls free of cerebrovascular risk factors was frequently, although not consistently, found in the 13 patients with thalamocapsular or thalamic lesions and neuropsychological impairment but was absent from the eight patients with pure internal capsule infarct and free of neuropsychological deficit. These data suggest that damage to the thalamus or the thalamocortical projections is important in the development of ipsilateral cortical hypometabolism and that the latter may underlie the associated neuropsychological impairment. Significant contralateral cerebellar hypometabolism relative to 49 controls was found in three of six patients with pure internal capsule infarct, suggesting a pathogenetic role for the corticopontocerebellar system. However, the occurrence of hypometabolism in two of six patients with thalamic lesions indicates that this phenomenon may also result either from damage to the ascending cerebello-thalamocortical system or indirectly from hypofunction of the cerebral cortex. No systematic association was observed between crossed cerebellar hypometabolism and ipsilateral ataxia. (Stroke 1990;21:519-524)

Reduction of metabolic activity in distant brain structures, diaschisis,1-2 may be implicated in both the clinical expression of and the functional recovery from stroke. Subcortical stroke is especially prone to induce diaschisis in the ipsilateral cortical and contralateral cerebellar cortex (ipsilateral cortical hypometabolism [ICH] and contralateral cerebellar hypometabolism [CH], respectively).3-5 Although damage to the thalamocortical system may explain the development of ICH after thalamic or thalamocapsular lesions of a hemorrhagic or ischemic nature,6-8 ICH has also been described after lesions in the internal capsule or striatum.9-15 Likewise, although neuropsychological impairment has been associated with ICH,5,8,12 exceptions have been reported.5,12 With respect to CH, conflicting opinions as to its mechanism, whether anterograde (via the corticopontocerebellar system) or retrograde (via the dentatothalmocortical pathway) still prevail.3,4,13,16-18

Subjects and Methods

Twenty-one patients with first stroke took part in our study. All 21 were evaluated with computed tomography (CT), and magnetic resonance imaging (MRI) was performed in 10. The patients were selected on the basis of strict clinical and CT/MRI criteria as having a pure internal capsular infarction (group I: a small internal capsule infarct was seen on CT scan in the posterior limb and the patient had pure motor or ataxic hemiparesis as defined by Fisher21 but no neuropsychological or sensory
impairment), a thalamocapsular hemorrhage (group II: a thalamocapsular hemorrhage was seen on CT scan and the patient had both a sensorimotor deficit and neuropsychological disturbances such as aphasia, neglect, or memory impairment), or a pure thalamic stroke (group III: an infarct or a hemorrhage apparently limited to the thalamus was seen on CT scan and the patient had a neuropsychological deficit without significant hemiparesis at time of PET study). Neuropsychological impairment was assessed by standard neurologic and neuropsychological examination; in those patients with significant impairment, a more detailed neuropsychological evaluation was carried out. Criteria for exclusion from the study were hemodynamically significant arterial disease by cervical Doppler ultrasonography and previous strokes on CT/MRI and/or clinical grounds. Finally, time since the onset of stroke ranged from 10 to 65 days to avoid as much as possible acute (e.g., edema) as well as chronic (e.g., metabolic recovery) effects. We used 67 persons free from cerebrovascular risk factors or history of central nervous system disorder as controls.

PET studies of the regional cerebral metabolic rates for oxygen (CMRO₂) and glucose (CMRglu), which are similarly reduced in deafferented areas, were performed using the C⁰¹⁸Ο₂–⁰¹⁸Ο₂ continuous inhalation technique (which allows measurement of cerebral blood flow [CBF] as well) and the [⁰¹⁸F]fluoro-2-deoxy-D-glucose ([⁰¹⁸F]FDG) method in 15 patients and 43 controls and in six patients and 19 controls, respectively. The methods applied in our center have been described in detail elsewhere. First, to match the regional metabolic rates for oxygen (CMRO₂) and glucose (CMRglu) have been justified because CMRO₂ and CMRglu have been shown to be quantitatively correlated in deafferented areas; also, the metabolic values obtained in the controls by the two cameras did not differ significantly (unpublished data). A similar procedure was applied for the cerebellar metabolic values (ECAT CMRO₂, n=18; LETI CMRO₂, n=15; ECAT CMRglu, n=4; LETI CMRglu, n=12; and ECAT CBF, n=18). We analyzed the normalized cortical metabolic rates (NCoMRs) using two-way analysis of variance (ANOVA) with two fixed factors (a group factor with four levels [controls, group I, group II, and group III] and a side factor with two levels [unaffected side and affected side]) assuming repeated measurement of the side factor and a possible group x side interaction. If ANOVA showed significant variation, group means were compared using t tests with Bonferroni correction. We used the same ANOVA procedure to compare the normalized cerebellar metabolic rates (NCeMRs) of the four groups. This statistical method was designed to assess ICH and CCH in the entire patient sample; however, this method is not suited for assessing individual patients because of the variability in global metabolic rates.

To analyze individual patients we used relative values as side-to-side indexes of metabolic asymmetry. An individual asymmetry index was derived as [(affected−unaffected)+unaffected]×100% using the NCoMRs and as [(contralateral−ipsilateral)+ipsilateral]×100% using the NCeMRs. The values so obtained were compared with the corresponding 95% individual prediction limits determined in the controls as [(right−left)+left]×100% using appropriate t values. This comparison was feasible since no significant differences between the right and left normalized metabolic rates were found in the analysis of the control data (n=62, p=0.59 in the cortex; n=67, p=0.10 in the cerebellum t test compared to zero).

Results

There were eight patients in group I, six in group II, and seven in group III. Chronic arterial hyperten-
sion was present in six, six, and three patients, respectively. The individual clinical and radiologic data are reported in Table 1.

At the cortical level, ANOVA revealed significant group and side effects ($p<0.012$ and $p<0.00001$, respectively; Figure 1). There was also a significant group×side interaction ($p=0.0001$). The group effect is characterized as a significantly lower NCoMR in group I patients with respect to the controls (Figure 3). Ataxia indexes were found in one of five group II patients and in two of four patients without ipsilateral ataxia (Table 2). Significant individual cerebellar asymmetry indexes were found in one of five group II patients and in two of six group III patients (Figure 2).

ANOVA of NCoMRs revealed a significant side effect ($p<0.0001$) with no group effect, but a significant group×side interaction ($p<0.01$, Figure 3). Intergroup comparisons demonstrate that these effects are explained by a significant difference between contralateral and ipsilateral NCoMRs of group I patients (contralateral<ipsilateral, $p<0.05$) with respect to the controls (Figure 3).

Significant cerebellar metabolic asymmetry was detected in three of six group I patients (Figure 2). Asymmetry was present in one of two patients with and in two of four patients without ipsilateral ataxia (Table 2). Significant individual cerebellar asymmetry indexes were found in one of five group II patients and in two of six group III patients (Figure 2).

### Discussion

Our results show that diffuse ICH is absent from patients with lesions limited to the posterior limb of the internal capsule and not causing neuropsychological impairment (group I), whereas significant ICH was detected in neuropsychologically impaired patients with thalamocapsular or thalamic lesions (groups II and III).

Hence, a lesion limited to the posterior limb of the internal capsule is apparently unable to induce metabolic depression of the overlying cortical mantle.
FIGURE 1. Mean (±SD) normalized cortical metabolic rates for right (○) and left (△) hemispheres of 62 controls and individual and mean ±SD rates for affected (●) and unaffected (○) sides of 21 patients, eight with pure internal capsule infarction (group I), six with thalamocapsular hemorrhage (group II), and seven with pure thalamic stroke (group III). †Significant group effect (ANOVA, p = 0.012) due to group III < controls (t test with Bonferroni’s correction, p < 0.05). ‡Significant side effect (ANOVA, p < 0.00001) due to affected < unaffected in groups II and III compared with controls (t test with Bonferroni’s correction, p < 0.01 and p < 0.05, respectively).

Only a few reports about the effects of “capsular stroke” on cortical metabolism or blood flow are available.9–11,15,27 A reduction in or a lack of activation of ipsilateral cortical blood flow has been reported.10,11,27 Likewise, left frontal cortical hypometabolism was observed in an intellectually impaired patient with a left capsular infarct involving the genu and anterior limb.9 Discrepancies with our results presumably reflect differences in patient selection in terms of clinical characteristics and location/size of the lesion. Hence, the presence of sensory impairment,10 aphasia-apraxia,27 or intellectual impairment9 in these previously published cases suggest that the thalamus and/or the thalamocortical radiations (e.g., in the anterior limb) were actually damaged, resulting in ICH. Our results concur with those of Olsen et al.,15 who found no significant ipsilateral cortical hypoperfusion in three patients

TABLE 2. Relation Between Contralateral Cerebellar Hypometabolism and Ataxia in Six Patients With Pure Internal Capsule Infarction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ataxia ipsilateral to hemiparesis</th>
<th>Cerebellar asymmetry index (Δ%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>−19.9*</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>−13.6f</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>−1.4</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>−10.3</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>−16.7*</td>
</tr>
</tbody>
</table>

1, present; 0, absent.  
*tp < 0.01, 0.05, respectively, relative to controls (see Figure 2).
with capsular lesions and apparently isolated hemiparesis or ataxic hemiparesis, while hypoperfusion was present in patients with larger lesions and aphasia.

The high combined incidence (54%) of ICH in the patients of groups II and III and the results of ANOVA concur with the results of earlier studies. Moreover, the occurrence of ICH in three patients with apparently pure thalamic lesions agrees with previous human and experimental studies. Hence, the evidence suggests that damage to either the thalamus itself or to a sufficient part of the thalamocortical projection plays a key role in the occurrence of ICH. However, striatal stroke may also induce ICH, as shown by Metter et al, Perani et al, Rousseaux et al, and Olsen et al, although damage to neighboring thalamic radiations cannot be easily excluded.

Taken as a whole, our data further support the previously reported association between ICH and the neuropsychological sequelae of thalamic stroke. However, significant individual metabolic asymmetry was lacking in six of our 13 patients with thalamic involvement and cognitive impairment. To explain this discrepancy, four factors of marginal importance can be mentioned. First, lesion size presumably influences the degree of ICH. Second, in a given patient, a mild neuropsychological deficit may be associated with minor, statistically nonsignificant, cortical metabolic asymmetry. Third, based on previous evidence, our study addressed diffuse ICH only, and we may have overlooked any focal cortical effect of thalamic stroke. Fourth, contralateral thalamic lesions may have gone unnoticed, although five of the 13 patients were subjected to detailed MRI, which confirmed unilaterality. Two additional factors, however, appear to be of much greater importance. First, ANOVA indicates that metabolic depression of the contralateral cerebral cortex—an effect already known to result from unilateral thalamic lesions—could have blunted the metabolic asymmetry measured. Second, recovery from bilateral cortical hypometabolism could have interfered with the assessment of metabolic asymmetry; however, our selection criteria required a relatively short interval from stroke onset to evaluation to limit this problem, and the six patients without significant individual metabolic asymmetry were not studied particularly late compared with the seven other patients.

Our data indicate that the contralateral cerebellar effects of subcortical stroke were essentially evenly distributed among the three patient groups, although compared with the controls, a significant effect was found only in group I.

We know of only two case reports showing CCH in patients with "capsular stroke," one with an anterior choroidal artery infarct and another with a left capsular infarct. The presence of aphasia and sensory impairment in both patients, however, suggests that the lesions may not have been purely capsular.

The occurrence of CCH in patients with pure thalamic stroke has not been specifically investigated previously. CCH has been reported in four of 20 and in two of two patients with thalamic stroke, but whether the internal capsule was involved was not mentioned. The preferential occurrence of CCH in our patients with pure capsular lesions suggests that damage at this site could be an important factor. However, CCH was also present in two (20 and 21) of our six patients with apparently pure thalamic lesions, suggesting a role for the thalamus as well. It must be noted, though, that a transient pyramidal deficit was present at the clinical onset in five of these six patients, indicating that some damage to the internal capsule may have occurred. In addition, we found no significant CCH and no cerebellar metabolic alterations in five hemiparkinsonian patients investigated by PET before and after stereotactic thalamotomy (unpublished data).

The hypothesis that damage to the corticopontocerebellar system plays a fundamental role in the development of CCH is supported by the occurrence of CCH in our patients with pure capsular stroke since part of the frontopontine bundle passes through the posterior limb of the internal capsule. An alternative mechanism must be considered for the significant CCH found in our two patients with apparently pure thalamic lesions. A retrograde (transneuronal) mechanism could be involved since human postmortem studies have shown that frontal and/or thalamic lesions may rarely result in retrograde contralateral dentate nucleus atrophy. A wholly different interpretation is that CCH in patients with thalamic stroke may result indirectly from hypofunction of the cerebral cortex, that is, from ICH. Hence, an association between parietal cortex hypometabolism and CCH has been demonstrated, while in aphasic patients CCH was associated with left frontal, parietal, caudate, and thalamic hypometabolism. Also, crossed cerebellar hypoperfusion has been reported in three patients with internal carotid artery occlusion, normal CT scans, and cortical hypoperfusion. Similarly, transient CCH has been reported in one patient with carotid transient ischemic attacks and during barbiturate-induced unilateral cerebral neuronal depression (Wada test). Finally, a positive correlation between cortical and contralateral cerebellar metabolic asymmetries has been reported recently in healthy subjects. Although we found no such correlation in our patient sample, the above arguments do suggest that cortical hypofunction could indirectly induce CCH.

Although previous studies have reported that CCH is well correlated with the presence and/or the severity of hemiparesis, only anecdotal reports have addressed its links with ipsilateral cerebellar ataxia, a more straightforward clinical correlate. This association has been reported in one patient with an internal capsule (posterior limb) infarct and in another with a pontine infarct. However, only one of our two patients with ataxic hemiparesis (contrasted to two of the four without ataxia) had significant CCH (ataxia could not be evaluated in severely hemiparetic patients). A specifically designed study is required to resolve this issue.
References


Key Words • diaschisis • cerebrovascular disorders • metabolism • thalamus
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