Crossed Cerebellar Diaschisis in Patients With Cortical Infarction

Logistic Regression Analysis to Control for Confounding Effects

Yuichi Komaba, MD; Masahiro Mishina, MD; Kouichi Utsumi, MD; Yasuo Katayama, MD; Shiro Kobayashi, MD; Osamu Mori, MD

Background and Purpose—Crossed cerebellar diaschisis (CCD) refers to reduced metabolism and blood flow in the cerebellar hemisphere contralateral to a cerebral lesion. Many cortical areas have been reported to cause CCD without consideration of confounding factors. We performed single-photon emission computed tomography (SPECT) in patients with cortical infarction to identify regions independently related to CCD, controlling for possible confounding effects.

Methods—Patients with unilateral cortical infarction (n=113; 75 male, 38 female; mean±SD age, 66±13 years) underwent SPECT of the brain with N-isopropyl-p-[¹²³I]iodoamphetamine (¹²³I-IMP). Regional cerebral blood flow was measured autoradiographically. Asymmetry indices (AIs) were calculated on the basis of ratios representing symmetrical regional cerebral blood flow in the cerebellum and 16 cerebral regions. CCD was defined as AI for cerebellum < 0.1. AIs for 16 cortical regions were considered for both dichotomous and continuous variables for analysis of CCD occurrence by means of backward logistic regression.

Results—For dichotomized variables, hypoperfusion of postcentral (odds ratio [OR]=7.607; 95% CI, 2.299 to 25.174) and supramarginal (OR=3.916; 95% CI, 1.394 to 11.003) regions independently influenced CCD. For continuous variables, hypoperfusion of postcentral (OR=1.044; 95% CI, 1.019 to 1.068) and supramarginal (OR=1.021; 95% CI, 1.001 to 1.041) regions (and, as a negative factor, medial occipital regions; OR=0.942; 95% CI, 0.895 to 0.991) independently influenced CCD.

Conclusions—Many cortical areas apparently do not contribute to CCD. Correspondence of CCD between dichotomized and continuous analyses suggests that location of a lesion, not severity, is the main determinant of CCD. (Stroke. 2004; 35:472-476.)

Key Words: cerebellar diseases ■ neural pathways ■ radiopharmaceuticals ■ tomography, emission computed, single-photon

Crossed cerebellar diaschisis (CCD) is defined as a reduction in metabolism and blood flow in the cerebellar hemisphere contralateral to a destructive cerebral lesion. This phenomenon often is demonstrated in images obtained by single-photon emission computed tomography (SPECT) 1,2 or positron emission tomography (PET). 3,4 Using PET, Baron et al 3 first demonstrated CCD in patients with cerebral infarcts, showing decreased cerebral blood flow (CBF) and cerebral metabolic rate for oxygen in contralateral cerebellum. Involvement of the cerebropontine-cerebellar pathway is thought to result in CCD. Previous PET or SPECT studies have concluded that lesions in a variety of cortical areas can cause CCD. However, few of these analyses have taken account of confounding factors. When CCD is observed, regional cerebral blood flow (rCBF) decreases in the cortical area causing CCD but also frequently decreases in neighboring regions, creating a false impression that dysfunction in the neighboring regions is causing CCD. Logistic regression analysis can control for this confounding effect. We studied rCBF in 113 patients with cerebral cortical infarction using SPECT to investigate relationships between location of cerebral cortical lesions and CCD, by backward stepwise logistic regression analysis.

Subjects and Methods

Patients

We performed retrospective analysis on clinical data for patients with cerebral infarction. From among consecutive patients who underwent N-isopropyl-p-[¹²³I]iodoamphetamine (¹²³I-IMP) SPECT from January 5, 1994, to May 21, 1999, we selected the 113 patients who met the following criteria: (1) a unilateral cortical infarct confirmed on MRI and/or CT obtained within 1 month before CBF measurement; (2) no lacunes in the thalamus, basal ganglia, or deep

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Figure 1. ROI setting. Circular ROIs, 13 and 22 mm in diameter, were placed over cerebral cortex and cerebellum in the SPECT images of each patient, respectively.

white matter; (3) no infarct in the brain stem or cerebellum; (4) no history of intracranial tumor, head trauma, subarachnoid hemorrhage, arteriovenous malformation alcoholism, epilepsy, or brain surgery; and (5) no disturbance of consciousness. Of these patients, 75 were male, and 38 were female; their mean ± SD age was 66.9 ± 13.7 years (range, 26 to 91 years). Fully informed consent to SPECT examination was obtained from all patients.

SPECT Procedures

The patients underwent measurement of rCBF at rest by $^{123}$I-IMP autoradiographic SPECT. Earplugs were not used, but the eyes were closed. The SPECT scanner was a Headetone-SET080 (Shimadzu), which has a ring collimator consisting of 96 rectangular NaI detectors. Spatial resolution at the center of view was 8.5 mm in full width at half maximum activity. Slice thickness was 5 mm. Distribution volume values were obtained by the table look-up method. Single-point radioactivity in arterial blood collected from the left brachial artery 10 minutes after the start of injection and the radioactivity of 222 MBq of $^{123}$I-IMP were measured with a scintillation counter. Scanning was initiated 25 minutes after injection of $^{123}$I-IMP, and scanning continued for 30 minutes. The images were acquired as a 128×128 matrix. A Butterworth filter of order 4 was used with a cutoff frequency of 2.2 cycles cm$^{-1}$ and a ramp. Scatter correction was not performed. For the attenuation correction, an elliptical brain outline approximating a circle was assumed.

Region of Interest

CBF images were obtained parallel to the orbitomeatal plane (OM) for 6 slices of brain (OM+20, OM+30, OM+40, OM+50, OM+65, and OM+80 mm) in 128×128 mode. Placements of regions of interest (ROIs) were the same as in previous studies. Circular ROIs, each 22 mm in diameter, were positioned in each cerebellar hemisphere, with 56 circular ROIs approximately 13 mm in diameter being placed in the various cerebral cortical areas (Figure 1). Mean rCBF values in the anterior superior frontal, posterior superior frontal, anterior midfrontal, posterior midfrontal, inferior frontal, anterior cingulate, precentral, postcentral, supramarginal, angular, superior temporal, midtemporal, inferior temporal, medial temporal, lateral occipital, and medial occipital regions were obtained in each patient.

Image Analysis

From the absolute rCBF value, we calculated asymmetry indices (AIs) for each region except the cerebellum according to the following formula: $A1 = (\text{rCBF on Healthy Side} - \text{rCBF on Cerebral Lesion Side})/((1/2) \times (\text{rCBF on Healthy Side} + \text{rCBF on Cerebral Lesion Side}))$. AI for the cerebellum ($A_{\text{cerebellum}}$) was calculated similarly from the equation, as follows: $A_{\text{cerebellum}} = (\text{Cerebellar rCBF on Cerebral Lesion Side} - \text{Cerebellar rCBF on Cerebral Healthy Side})/((1/2) \times (\text{Cerebellar rCBF on Cerebral Lesion Side} + \text{Cerebellar rCBF on Cerebral Healthy Side}))$. CCD was considered present when $A_{\text{cerebellum}}$ was $>0.1$. We performed 2 different kinds of statistical analysis representing comparisons made with or without consideration of severity of cortical hypoperfusion. In the first analysis, hypoperfusion of each cortical region on the lesion side was considered present when AI was $>0.1$ without consideration of severity of cortical hypoperfusion. Patients were divided into 2 groups depending on the presence or absence of CCD. We used $\chi^2$ analysis to compare differences in presence or absence of hypoperfusion in each cerebral cortical area between these 2 groups. Backward stepwise multiple logistic analysis was performed to identify regions where hypoperfusion was independently and significantly related to CCD. In the logistic model, the presence or absence of CCD, coded as presence $=1$ or absence $=0$, was the dependent variable. Categorical variables, ie, presence or absence of hypoperfusion in each region, were coded as presence $=1$ or absence $=0$ (total, 16 variables). All variables were entered into the model initially, with the least significant variables removed 1 at a time until only significant variables associated with values of $P<0.05$ remained. Regression results were also presented as odds ratios (ORs) and their respective 95% CIs after determination of remaining variables.

In the second analysis, which considered severity of cortical hypoperfusion, cerebral AIs were not dichotomized; the actual values of AI were analyzed as continuous variables. We used the Mann-Whitney test for trends to compare differences between the 2 CCD-defined groups instead of $\chi^2$ analysis. Stepwise logistic regression was performed with the use of the continuous variables.

Data were analyzed with StatView version 5.0 (SAS Institute Inc), implemented in Macintosh OS 9.2.2 (Apple Computer).

Results

Of 113 patients with cerebral cortical infarcts, 45 (39.8%) also exhibited CCD. Mean ages of those with and without CCD [CCD (+) and CCD (−) groups, respectively] were 66.9 years (SD, 11.4) and 65.8 years (SD, 14.0), respectively. Thus, no significant age difference existed between the 2 groups ($t=0.434$, $P=0.6654$). The CCD (+) group included 16 female (35.6%) and 29 male (64.4%) subjects, compared with 22 female (32.4%) and 46 male (67.6%) subjects in the CCD (−) group (no significant sex difference between groups; $\chi^2=0.124$, $P=0.7243$).

Dichotomized univariate associations between the 16 potential determinants and CCD according to $\chi^2$ statistics are presented in Table 1. On dichotomized univariate analysis, CCD was significantly associated with hypoperfusion of inferior frontal (57.8% versus 25%; $P=0.0004$), anterior midfrontal (53.3% versus 26.5%; $P=0.0038$), posterior midfrontal (73.3% versus 41.2%; $P=0.0008$), posterior superior frontal (60.0% versus 38.2%; $P=0.0232$), precentral (84.4% versus 45.6%; $P<0.0001$), inferior temporal (60.0% versus 36.8%; $P=0.0153$), midtemporal (64.4% versus 27.9%; $P=0.0001$), superior temporal (77.8% versus 41.2%; $P<0.0001$), postcentral (91.1% versus 44.1%; $P<0.0001$), supramarginal (84.4% versus 41.2%; $P<0.0001$), and angular (71.1% versus 48.5%; $P=0.0174$) regions.

We used backward stepwise logistic regression to confirm independent relationships between cerebral hypoperfusion and CCD, categorizing hypoperfusion as dichotomized codes without consideration of magnitude of cortical hypoperfusion. As shown in Table 2, hypoperfusion of postcentral and supramarginal regions remained significantly and indepen-
TABLE 2. Backward Stepwise Multivariate Logistic Regression Model: Retained Dichotomized Determinants for Crossed Cerebellar Diaschisis

<table>
<thead>
<tr>
<th>Hypoperfusion</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcentral</td>
<td>3.67</td>
<td>1.01–12.56</td>
<td>0.0467</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>1.01</td>
<td>0.34–3.17</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

CCD indicates crossed cerebellar diaschisis; AI, asymmetry index.

Table 4 shows a backward stepwise logistic regression model for CCD, with actual values of AI entered. In this model, hypoperfusion of postcentral and supramarginal regions was each significantly and independently associated with CCD, while medial occipital hypoperfusion was an inhibitory determinant. The OR for CCD according to hypoperfusion of the postcentral region was 1.044 (per 1 AI; 95% CI, 1.019 to 1.068). The OR for CCD according to hypoperfusion of the supramarginal region was 1.021 (per 1 AI; 95% CI, 1.001 to 1.041). The OR for CCD according to hypoperfusion of the medial occipital region was 0.942 (per 1 AI; 95% CI, 0.895 to 0.991). Dichotomized variables removed from the model in consequence were hypoperfusion of inferior frontal, anterior midfrontal, posterior midfrontal, anterior superior frontal, posterior superior frontal, anterior cingulate, inferior temporal, midtemporal, superior temporal, medial temporal, precentral, angular, lateral occipital, and medial occipital regions.

TABLE 4. Backward Stepwise Multivariable Logistic Regression Model: Retained Continuous Determinants for Crossed Cerebellar Diaschisis

<table>
<thead>
<tr>
<th>Hypoperfusion</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Postcentral</td>
<td>1.044</td>
<td>1.019–1.068</td>
<td>0.0004</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>1.021</td>
<td>1.001–1.041</td>
<td>0.0442</td>
</tr>
<tr>
<td>Medial occipital</td>
<td>0.942</td>
<td>0.895–0.991</td>
<td>0.0219</td>
</tr>
</tbody>
</table>

Values are mean±SD. CCD indicates crossed cerebellar diaschisis; AI, asymmetry index.

Main Findings
Only 2 regions of hypoperfusion, postcentral and supramarginal, were independent determinants of occurrence of CCD after controlling for possible confounding effects.

CCD and Size of Infarction
Although a number of hypoperfused regions were associated with occurrence of CCD in our univariate analysis (Tables 1

Discussion

Representative cases are shown in Figure 2.

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and 3), many of these areas no longer appeared to contribute to occurrence of CCD after controlling by multivariate analysis for possible confounding effects (Tables 2 and 4). Many hypoperfused regions apparently associated with occurrence of CCD on univariate analysis may not actually be concerned with occurrence of CCD. Several studies have demonstrated that CCD is more frequent with large lesions. However, a recent study demonstrated that the size of an infarct did not correlate with occurrence of CCD. The anatomic location of the lesion rather than its size may be the decisive factor for occurrence of CCD.

**Relationship of CCD and Magnitude of Cortical Hypoperfusion**

Without consideration of magnitude of cortical hypoperfusion, the present study showed that hypoperfusion in postcentral and supramarginal regions was independently associated with occurrence of CCD in patients with cerebral infarction (Table 2). Moreover, our results demonstrated that when magnitude of cortical hypoperfusion was considered, the hypoperfusion in postcentral and supramarginal regions again was associated with occurrence of CCD, while hypoperfusion in the medial occipital region was an inhibitory determinant for occurrence of CCD (Table 4). The positive correspondence for the first 2 regions, whether or not severity was considered, indicated that the anatomic location of the lesion rather than its magnitude may be the main determinant for occurrence of CCD. Previous studies demonstrated that magnitude of cortical hypoperfusion was correlated with magnitude of CCD, but a recent report concluded that severity of cerebral hypoperfusion does not correlate with occurrence of CCD.

We do not know why hypoperfusion in the medial occipital region was an inhibitory factor for occurrence of CCD. When AI was considered a continuous variable, AI was especially low in the medial occipital region. When AI was regarded as a categorical variable, an AI < 0.1 was simply dichotomized as absence of hypoperfusion. Thus, a particularly low medial occipital AI could have influenced the present results of the continuous variable analysis.

**CCD and Location of Cortical Hypoperfusion**

The present study shows that hypoperfusion of postcentral and supramarginal regions is significantly and independently associated with CCD (Table 2). Involvement of the cerebropontine-cerebellar pathway is thought to result in CCD. The cerebropontine tract, derived from extensive areas of the cerebral cortex, projects to the ipsilateral pontine nuclei located ventral to the medial lemniscus via the ipsilateral cerebral peduncle, ie, the frontopontine, parietopontine, temporopontine, and occipitopontine tracts. The pontine nuclei send axons to the contralateral cerebellar cortex, traversing the anterior pons as the transverse pontine fibers.
Electrophysiological study demonstrated SI and SII from 25% of neurons in the pontine nuclei, suggesting that responses evoked by peripheral stimuli may be mediated by the transcortical pathway rather than via direct or indirect spino-pontine projections. Anatomic study also indicated that the cerebellar hemispheres receive strong connections from somatosensory areas via the pontine nuclei, presumably sending somatosensory movement–related information to the cerebellum. On the other hand, even though much of the cerebropontine-cerebellar pathway is also derived from the precentral area, this area was not independently associated with CCD in the present study. CCD is frequent in stroke patients with hemiparesis, but it also occurs in a considerable number of patients without hemiparesis and is not seen in all hemiparetic patients. Even a lesion in the primary motor area may not always participate in occurrence of CCD. The inferior parietal lobule, including the supramarginal region, is associated with initial stages of motor planning, facial recognition, and language. With respect to language, Desmond et al proposed a model of a cerebropontine-cerebellar circuit involved in verbal working memory that includes the supramarginal region, pontine nuclei, and cerebellum. A part of this hypothesized circuit is the part of the cerebropontine-cerebellar pathway projecting from the supramarginal region, an important site of phonological storage in the model. The present result that hypoperfusion of supramarginal regions is associated with CCD may reflect the large cortical expanse of the inferior parietal lobule related to the development of human cognitive and language abilities.

CCD and Duration After Infarction
We did not examine the effects of duration after infarction on CCD because onset data were unreliable in some patients. While recovery from CCD in patients with stroke has been reported, other authors reported unchanged or even exaggerated CCD in patients with old stroke as opposed to acute stroke. Therefore, the influence of duration after infarction on CCD is not established either generally or according to region.

Summary
Many cortical areas apparently do not contribute to CCD. Correspondence of CCD between dichotomized and continuous analyses suggests that location of a lesion, not severity, is the main determinant of CCD. It is important to be aware of these results regarding CCD for the clinical reading of images, whether or not actual ischemia in cerebellum is present.

References
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