Changes in cerebral blood flow and vasoreactivity in response to acetazolamide in patients with transient global amnesia

Yasuo Sakashita, Masanobu Kanai, Tatsuho Sugimoto, Suzuka Taki, Masaharu Takamori

Abstract

Objective—Previous reports about changes in cerebral blood flow (CBF) in transient global amnesia disclosed decreased flow in some parts of the brain. However, CBF analyses in most reports were qualitative but not quantitative. The purpose of this study was to determine changes in CBF in transient global amnesia.

Methods—The CBF was measured and the vasoreactive response to acetazolamide was evaluated in six patients with transient global amnesia using technetium-99m hexamethylpropylene amine oxime single-photon emission computed tomography (SPECT). The CBF was measured during an attack in two patients and soon after an attack in the other four. About one month later, CBF was re-evaluated in each patient.

Results—Two patients examined during an attack and one patient examined five hours after an attack had increased blood flow in the occipital cortex and cerebel- lum. Three patients examined at six to 10 hours after an attack had decreased blood flow in the thalamus, cerebellum, or putamen. These abnormalities of blood flow almost disappeared in all patients one month after onset. The vasodilatory response to acetazolamide, which was evaluated initially using SPECT, was poor in areas of increased blood flow. By the second evaluation of CBF with acetazolamide, the vasodilatory response had returned to normal.

Conclusions—In a patient with transient global amnesia, CBF increased in the vertebrobasilar territory during the attack and decreased afterwards. The vasodilatory response to acetazolamide may be impaired in the parts of the brain with increased blood flow. It is suggested that transient global amnesia is distinct from migraine but may share the same underlying mechanism.

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Keywords: amnesia; migraine; cerebrovascular circulation; physiopathology; acetazolamide

Transient global amnesia is an episodic dysfunction of declarative memory for recent events without neurological signs or symp-
flow and oxygen metabolism may be transient in patients with transient global amnesia.

Acetazolamide is a potent carbonic anhydrase inhibitor that produces a physiological inhibition of carbonic anhydrase in the red blood cells within one minute of the rapid intravenous injection of 1 g of the drug. The intravenous injection of acetazolamide to normal subjects increases cerebral as well as cerebellar blood flow within minutes. Acetazolamide has been used to test cerebral vasodilatory capacity. However, vasoreactivity to acetazolamide in patients with transient global amnesia has not been reported.

We report the quantitative analyses of changes in CBF and vasoreactivity with acetazolamide in six patients with pure transient global amnesia studied with technetium-99m (99mTc) hexamethylpropylene amine oxide (HMPAO) SPECT.

Patients and methods

Patients

We evaluated six Japanese patients with transient global amnesia, one man and five women, age range 56 to 63 years, mean 58.5 years (table 1). All had profound memory disturbances for recent events without neurological signs or symptoms. The amnesia was transient and the patients recovered from amnesia completely. All were right handed. No lesions in the brain were found in any patient by CT or MRI.

Measurements of cerebral blood flow with SPECT

Measurements of CBF using 99mTc HMPAO without and with acetazolamide stress were performed twice in each patient. The first application of SPECT was during the attack in patients 1 and 2 and soon after the attack (after five to 10 hours) in the other four patients. The second SPECT was done 24 to 36 days after the onset of the attack. The SPECT system consisted of a rotating gamma camera (GCA-901, Toshiba, Tokyo, Japan) and an image processing minicomputer (GMS-550U, Toshiba). 99mTc HMPAO SPECT both with and without acetazolamide stress was done according to the following procedure. For measurement of CBF without acetazolamide, acquisition of projection data was begun 15 minutes after the intravenous injection of 740 MBq 99mTc HMPAO. Data were collected for 60 angles (6° step, 360°) with 30 seconds per angle. Data were reconstructed by filtered back projection using Butterworth filters. After the data acquisition, 1 g acetazolamide was parenterally injected and after 10 minutes an additional 740 MBq 99mTc HMPAO was injected. Data accumulation for acetazolamide stressed CBF measurement was started 15 minutes later. Quantitative measurements of regional blood flow were performed using the method reported by Matsuda et al, which employed Lassen's correction algorithm for the linearisation of a curvilinear relation between the radioactivity in the brain and blood flow as seen with SPECT images. This quantitative method is non-invasive and does not require any blood sampling.

For quantification of CBF in each patient, regions of interest were drawn over the bilateral superior frontal, middle frontal, inferior frontal, superior temporal, inferior temporal, superior parietal cortices, inferior parietal, and occipital cortices, thalam, putamen, hippocampi, and parahippocampal gyri, and cerebellar cortices.

Results

Regional CBF measurement by SPECT without acetazolamide stress

Figure 1 shows the results of measurement of CBF without acetazolamide stress in the first and second applications of SPECT. Normal regional CBF values were obtained from age matched normal subjects. When the regional CBF was more or less than the mean ± 3 SD, it was judged to be abnormal. In the first application of SPECT, patients 1 and 2, who were examined during the attack, and patient 3, who was examined five hours after the attack, showed increased blood flow in some regions. Regional blood flow in the occipital cortex and cerebellum was increased in these three patients. Patients 2 and 3 also showed increased flow in the frontal, temporal, and parietal cortices. These abnormalities had almost returned to normal on application of follow up SPECT. In patients 4, 5, and 6, who were examined six to 10 hours after the amnesic period, there were some regions that showed decreased blood flow. Blood flow was decreased in the putamens in patient 4, in the bilateral cerebellum and right thalamus in patient 5, and in the bilateral temporal cortices and right hippocampus and parahippocampal gyrus in patient 6. These abnormalities had also returned to normal on follow up SPECT.

Regional CBF measurement by SPECT with acetazolamide stress

Figure 1 shows the results of regional CBF measurement at baseline and after acetazolamide injection. We considered that vasoreactivity to acetazolamide was impaired when a percentage increase was less than 10%. In the first application of SPECT in patients 1, 2, and 3, the regional blood flow was increased in the occipital cortices and cerebellum, and the vasoreactivity to acetazolamide was impaired in these regions. The superior temporal cortex in patient 1, the bilateral occipital cortices and left cerebellum in patient 2, and the bilateral thalam, bilateral hippocampi and parahippocampal gyrus, left cerebellar cortex, and left middle frontal cortex in patient 3 also had both increased blood flow and impaired vasoreactivity. In the other three patients, examined six to...
**Figure 1** Results of regional CBF (rCBF) measurements in the first and second applications of SPECT in patients with transient global amnesia. Normal values were obtained from age matched normal subjects and shaded areas show mean (3 SD) rCBF in each region. Open squares indicate rCBF in the left hemisphere and open circles indicate rCBF in the right hemisphere in the first application of SPECT. Closed squares indicate rCBF in the left hemisphere and closed circles indicate rCBF in the right hemisphere in the second application of SPECT. * indicates a percentage increase of rCBF <10% from baseline after acetazolamide injection. (-) without acetazolamide injection; (+) with acetazolamide injection. Cx=cortex; parahipp. gy=parahippocampal gyrus.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Frontal Cx</th>
<th>Temporal Cx</th>
<th>Parietal Cx</th>
<th>Occipital Cx</th>
<th>Thalamus</th>
<th>Putamen</th>
<th>Hippocampus and parahipp. Gy</th>
<th>Cerebellum</th>
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<tbody>
<tr>
<td></td>
<td>Superior</td>
<td>Middle</td>
<td>Inferior</td>
<td>Superior</td>
<td>Inferior</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patient 1</td>
<td>120</td>
<td>100</td>
<td>80</td>
<td>90</td>
<td>70</td>
<td>60</td>
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<td>140</td>
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<td>Patient 2</td>
<td>140</td>
<td>120</td>
<td>100</td>
<td>110</td>
<td>90</td>
<td>80</td>
<td></td>
<td>140</td>
</tr>
<tr>
<td>Patient 3</td>
<td>160</td>
<td>140</td>
<td>120</td>
<td>130</td>
<td>110</td>
<td>100</td>
<td></td>
<td>160</td>
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<tr>
<td>Patient 4</td>
<td>180</td>
<td>160</td>
<td>140</td>
<td>150</td>
<td>130</td>
<td>120</td>
<td></td>
<td>180</td>
</tr>
<tr>
<td>Patient 5</td>
<td>200</td>
<td>180</td>
<td>160</td>
<td>170</td>
<td>150</td>
<td>140</td>
<td></td>
<td>200</td>
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<tr>
<td>Patient 6</td>
<td>220</td>
<td>200</td>
<td>180</td>
<td>190</td>
<td>170</td>
<td>160</td>
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<td>220</td>
</tr>
</tbody>
</table>

Acetazolamide: (-) without acetazolamide injection; (+) with acetazolamide injection.
10 hours after the amnesic period, the regional blood flow was not increased in any regions, and vasoreactivities to acetazolamide stress were normal in the first application of SPECT. In the second application, vasoreactivities to acetazolamide stress were normal in all regions of all patients.

Case report (patient 1)
The patient was a 57 year old right handed housewife with no relevant medical history. On 1 March 1994, she gardened until 11:00 am and returned home for lunch. After lunch she began to ask family members why she was there and what she was doing there. Despite an answer to her questions, she repeated the questions. She could not recall what she had eaten for lunch an hour before. Her husband brought her to our hospital two hours after the onset of the disorder. The patient seemed very anxious and repeatedly asked why she was there. Her blood pressure was 124/78 mm Hg and her pulse was regular at 68 beats per minute. Neurological examination was normal except for severe memory impairment. Her ability to retain new information was severely impaired. Verbal expression, comprehension, and immediate repetition of sentences and words were normal. Brain MRI was normal. Measurement of CBF using $^{99m}$Tc HMPAO was done three hours after the onset of the attack. In the six hours after the onset of amnesia, the patient regained her ability to retain new information and recovered completely. The results of CBF measurement showed abnormally high blood flow in the bilateral occipital cortices and cerebellar cortices. A follow up study done 28 days after onset showed that blood flow in the bilateral occipital cortices and cerebellar cortices had returned to normal. Figure 2 shows the SPECT images.

Discussion
The two patients examined during an attack and one patient examined five hours after recovery from amnesia showed increased CBF and three patients who were examined six to 10 hours after amnesic periods had decreased blood flow in some areas of the brain. These abnormalities in CBF, both increased and decreased, were transient and almost disappeared on application of follow up SPECT. Table 2 shows a review of previous reports concerning location and nature of the blood flow studies with SPECT or PET. Regional CBF during transient global amnesia has usually been reported to be decreased in the temporal lobe, thalamus, and frontal lobe. Reports of increased regional CBF during an attack have been rare. However, most studies used qualitative methods, with quantitative CBF studies being rare. In our quantitative study, the common regions that showed increased blood flow during an attack were the occipital cortex and cerebellum. There has been no report of changes in blood flow in the occipital cortex or the cerebellum during an attack by quantitative CBF measurement. Tanabe et al reported hypoperfusion in the posterior cerebral artery territory by $^{[123I]}$I$\text{[\(\pm\)]}$N-isopropyl-p-iodoamphetamine (IMP) distribution; however, the distribution of IMP seemed to be higher in the cerebellum during the attack than five months later. Evans et al reported hypoperfusion in the bilateral medial temporal lobes; however, their data, presented in a figure, also seemed to suggest hyperperfusion in the bilateral occipital cortices during an attack. Although none of these reports included quantitative measurements of CBF, it is possible that CBF is increased in the cerebellum and occipital lobe during an attack. Our results indicate that CBF in the cerebellum and occipital cortices is increased during the attack, then gradually decreases after an amnesic spell. The blood flows in the hippocampus and parahippocampal gyrus were normal during an attack. The occipital lobe, the cerebellum, and the medial aspects of the temporal lobe receive blood from the verteobasilar system, which is called the posterior circulation. Therefore, it is possible that the hippocampus and parahippocampal gyrus receive relatively decreased blood flow during an attack when compared to the increased blood flow in the cerebellum and occipital cortex. After an amnesic period, the changes in blood flow are transient and gradually disappear. Previous reports suggest there may also be a period of decreased CBF in the medial aspects of the temporal lobe soon after an onset of transient global amnesia. Therefore, it is possible that blood flow in the hippocampus and parahippocampal gyrus of patients with transient global amnesia may initially decrease at
Cerebral blood flow in transient global amnesia

Table 2: Location and nature of the blood flow studies (SPECT and PET) in patients with transient global amnesia during or soon after an attack

<table>
<thead>
<tr>
<th>Author</th>
<th>Timing of acquisition</th>
<th>Technique</th>
<th>Regional CBF reactivity to acetazolamide</th>
<th>Follow-up</th>
<th>Regional CBF changes in the first examination</th>
<th>Regional CBF changes in the follow-up examination</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silbert et al.</td>
<td>7 h (during attack)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>5 m</td>
<td>Left rostral temporal region</td>
<td>—</td>
<td>Left thalamus.</td>
</tr>
<tr>
<td>Tanabe et al.</td>
<td>6 h (during attack)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>5 m</td>
<td>Left inferior temporal region</td>
<td>—</td>
<td>Bilateral temporal lobes.</td>
</tr>
<tr>
<td>Goldenberg et al.</td>
<td>4 h (during attack)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>5 m</td>
<td>Right superior temporal cortex</td>
<td>—</td>
<td>Bilateral temporal lobes.</td>
</tr>
<tr>
<td>Matsuda et al.</td>
<td>3 h (during attack)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>3 m</td>
<td>Bilateral parietal and occipital cortices</td>
<td>—</td>
<td>Bilateral occipital cortices.</td>
</tr>
<tr>
<td>Olesen et al.</td>
<td>24 h (5 h after ictus)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>29 days</td>
<td>Bilateral frontal cortices</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Jung et al.</td>
<td>6 h (during attack)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>5 days</td>
<td>Bilateral temporal and occipital cortices</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Baron et al.</td>
<td>23 h (7 h after ictus)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>29 days</td>
<td>Bilateral frontal cortices</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Our patients</td>
<td>28 h (5 h after ictus)</td>
<td>HMPAO SPECT</td>
<td>Normalised</td>
<td>36 days</td>
<td>Bilateral parietal and occipital cortices</td>
<td>—</td>
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</table>

Some authors suggested that cortical spreading depression plays an important part in the underlying mechanism of migraine aura. Cortical spreading depression is a transient phenomenon that induces remarkable cerebralvascular disturbances including an initial hyperaemia with dilatation of pial arterioles followed by a long lasting hypoperfusion. It impairs autoregulation of cortical blood flow both transiently and reversibly. There are some similarities between blood flow changes in cortical spreading depression and the results of our study in transient global amnesia. Olesen et al. hypothesised that transient global amnesia could be explained by the cortical spreading depression. Colonna et al. reported that nitric oxide promoted arteriolar dilatation during cortical spreading depression. Cortical spreading depression and an increase in nitric oxide seem to be promising candidates for the underlying mechanism of transient global amnesia; however, there is no direct evidence to support the hypothesis. Caplan proposed the concept of “acute arterial dyscontrol,” postulating that such dyscontrol causes transient global amnesia by a transient self limited alteration of vascular tone in the posterior circulation. Our results seem to support Caplan’s theory but the true mechanism of the dyscontrol remains unclear.

Regional CBF reactivity to acetazolamide is considered to represent an index of vascular reserve, because the extent of increase in regional CBF is determined by the condition of the vasculature. Our results showed that two...
patients examined during an attack had increased regional blood flow in the occipital cortex and cerebellum and that the vaso-reactive response to acetazolamide was impaired in these regions. In the first examination of patient 3, the regional blood flow in the thalamus, hippocampus, and parahippocampal gyrus was decreased after the injection of acetazolamide, which suggested a steal phenomenon caused by impaired vasoreactivity in these regions. The cause of this finding was not an arteriosclerotic change because the vasoreactivity examined one month after onset showed no abnormality. We therefore suggest that vasoreactivity in the posterior circulation may be impaired during an attack. Although the mechanism for the impaired response to acetazolamide during an attack is not known, it is possible that a transient change that abolished the response to acetazolamide had occurred in the vertebrobasilar system, or that additional vasodilation was not possible, because remarkable vasodilation had occurred during the attack.

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