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

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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 hexamethylene propylene 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 cerebellum. 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 symptoms. The patient cannot recall the verbal or non-verbal materials presented only minutes before, and he often repeats the same question many times. Whereas there are numerous studies on the aetiology of transient global amnesia, results are conflicting. The disagreement seems to result from three major investigative drawbacks. Firstly, the reported clinical syndromes were heterogeneous. Some authors included patients who had neurological symptoms or signs other than transient memory disturbances. The patient with pure transient global amnesia almost always displays an episode of temporary isolated amnesia and amnestic syndromes must be differentiated from pure transient global amnesia for further investigation. Absence of associated neurological deficits, such as aphasia, visual field defect, eye movement abnormalities or hemiparesis, is an essential criterion. There must be no evidence of head trauma, seizure, loss of consciousness, or overdose of some types of drugs. There should be no evidence of transient vertebrobasilar hypoperfusion caused by cardiac arrhythmia, coronary angiography, or cerebral angiography. Secondly, the intervals between the onset of transient global amnesia to the performance of diagnostic neuroimaging procedures were varied. The amnesia in transient global amnesia is, by definition, transient, and the prognosis is good.

Table 1  Profile of patients

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Anterograde amnesia (h)</th>
<th>Retrograde amnesia (h)</th>
<th>From onset to first application of SPECT (h)</th>
<th>From onset to second application of SPECT (days)</th>
<th>Relevant medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>6</td>
<td>15</td>
<td>3</td>
<td>28</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>F</td>
<td>16</td>
<td>3</td>
<td>12</td>
<td>24</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>21</td>
<td>3</td>
<td>26</td>
<td>29</td>
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</tr>
<tr>
<td>4</td>
<td>53</td>
<td>F</td>
<td>14</td>
<td>3</td>
<td>20</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>F</td>
<td>16</td>
<td>5</td>
<td>23</td>
<td>29</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>F</td>
<td>13</td>
<td>3</td>
<td>23</td>
<td>36</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

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 oxime (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, thalami, putamen, hippocampus, and parahippocampal gyrus, 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 amnestic period, there were some regions that showed decreased blood flow. Blood flow was decreased in the putamen 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 thalami, 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 Gyr=parahippocampal gyrus.
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 amnesia. His pulse was regular at 68 beats per minute. 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 $^{123}$I-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
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>Timing of examination</th>
<th>Regional CBF changes to acetazolamide</th>
<th>Authors</th>
<th>Technique</th>
<th>Analysis</th>
<th>Follow-up</th>
<th>Regional CBF changes in the first examination</th>
<th>Authors</th>
<th>Technique</th>
<th>Analysis</th>
<th>Follow-up</th>
<th>Regional CBF changes in the first examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Followup</td>
<td>Increased CBF in the left temporal lobe and thalamus</td>
<td>Increased CBF in the left temporal lobe and thalamus</td>
<td>Matsuda et al.</td>
<td>HMPAOSPECT Quantitative</td>
<td>15h (3hafter ictus)</td>
<td>Left inferiortemporal region, normalised</td>
<td>Our patients</td>
<td>HMPAOSPECT Quantitative</td>
<td>26h (5hafter ictus)</td>
<td>29days</td>
<td>Bilateraltemporal and occipital cortices, decreased CBF in the left inferiortemporal cortex</td>
</tr>
<tr>
<td>Followup</td>
<td>Slightly decreased CBF in the left hippocampus</td>
<td>Slightly decreased CBF in the left hippocampus</td>
<td>Olesen et al.</td>
<td>HMPAOSPECT Quantitative</td>
<td>10h (6hafter ictus)</td>
<td>Bilateralfrontal, temporal, and parietal lobes, increased CBF in the bilateral thalami and hippocampi</td>
<td>Olesen et al.</td>
<td>HMPAOSPECT Quantitative</td>
<td>10h (6hafter ictus)</td>
<td>29days</td>
<td>Bilateraltemporal and occipital cortices, decreased CBF in the left inferiortemporal cortex</td>
</tr>
<tr>
<td>Timing of examination</td>
<td>Regional CBF reactivity to acetazolamide</td>
<td>Regional CBF reactivity to acetazolamide</td>
<td>Olesen et al.</td>
<td>HMPAOSPECT Quantitative</td>
<td>5h (7hafter ictus)</td>
<td>Left inferiortemporal cortex and thalamus</td>
<td>Olesen et al.</td>
<td>HMPAOSPECT Quantitative</td>
<td>5h (7hafter ictus)</td>
<td>29days</td>
<td>Bilateraltemporal and occipital cortices, decreased CBF in the left inferiortemporal cortex</td>
</tr>
</tbody>
</table>

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.34 35 It impairs autoregulation of cortical blood flow both transiently and reversibly.36 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 attractive 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.37 Our results showed that two
patients examined during an attack had increased regional blood flow in the occipital cortex and cerebellum and that the vasoactive 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 vasoactivity in these regions. The cause of this finding was not an arteriosclerotic change because the vasoactivity examined one month after onset showed no abnormality. We therefore suggest that vasoactivity 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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