Quantitative Assessment of Cerebral Blood Flow in Genetically Confirmed Spinocerebellar Ataxia Type 6

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Background: Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant cerebellar ataxia caused by CAG trinucleotide expansion. The characteristics of regional cerebral blood flow (rCBF) in SCA6 patients have not been established, whereas it has been reported that decreased rCBF in the cerebrum seems to be a remote effect of cerebellar impairment in other cerebellar disorders.

Objective: To clarify the characteristics of rCBF, including cerebro-cerebellar relationship, and its correlation with clinical manifestations in patients with genetically confirmed SCA6 using quantitative assessment of rCBF by brain single-photon emission computed tomography (SPECT).

Design: Technetium Tc 99m ethyl cysteinate dimer SPECT study using a Patlak plot.

Patients: Hiroshima University Hospital, Hiroshima, Japan. Ten patients with SCA6 and 9 healthy controls.

Main Outcome Measure: The rCBF of the cerebellar vermis, cerebellar hemisphere, and frontal lobes.

Results: In SCA6 patients, rCBF was decreased only in the cerebellar vermis and hemisphere compared with healthy controls, and this was inversely correlated with duration of illness. The rCBF in the frontal lobes was slightly correlated with duration of illness without statistical significance. The rCBF in the vermis was inversely correlated with severity of dysarthria, but there was no significant correlation with CAG repeated expansions.

Conclusions: Decrease in rCBF was found only in the cerebellum and was associated with duration of illness, dysarthria and ataxia, and cerebellar atrophy. No remote effect of cerebellar hypoperfusion was found in the SCA6 patients.

Arch Neurol. 2004;61:933-937

Spinocerebellar Ataxia Type 6 (SCA6) is an autosomal dominant cerebellar atrophy caused by a CAG trinucleotide repeated expansion in the α 1A voltage-dependent calcium channel subunit gene (CACNA1A gene) on chromosome 19p13. This gene is important for the function and survival of Purkinje cells. Ataxia, gait disturbance, and dysarthria develop slowly in most SCA6 patients. Other neurologic signs often associated with other spinocerebellar degeneration (SCD) are seldom associated with SCA6, and SCA6 is characterized as pure cerebellar ataxia. Brain magnetic resonance (MR) imaging in SCA6 patients has demonstrated atrophy in the cerebellum without brainstem and cerebral involvement. Brain single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in SCD patients have been reported before genetic analysis became available. In recent studies of SCD, including SCA6, regional cerebral blood flow (rCBF) was not assessed compared with healthy controls, and the relationships between rCBF and other variables were not clarified. The SPECT, PET, and neuropsychological studies on other cerebellar diseases have revealed remote effects in regions besides the cerebellum, especially in the frontal lobes, a phenomenon known as crossed cerebelo-cerebral diaschisis (CCCD).

The SPECT using a Patlak plot with a technetium Tc 99m ethyl cysteinate dimer (99mTc-ECD) enables noninvasive quantitative assessment of rCBF, and it was already applied in the patients with Parkinson disease. We performed SPECT with 99mTc-ECD using a Patlak plot in genetically confirmed SCA6 patients. The goals of this study were to...
clarify the characteristics of rCBF, including assessment of CCCD, in SCA6 patients and to evaluate the relationships between rCBF and symptoms and brain MR imaging findings.

**METHODS**

**PARTICIPANTS**

Ten patients with SCA6 (5 men and 5 women; age range, 40-74 years; mean ± SD age, 59.9 ± 8.9 years; mean duration of illness, 9.4 ± 9.4 years; range of illness durations, 2-34 years; age at onset, 50.5 ± 9.3 years) and 9 age-matched, healthy controls (5 men and 4 women; mean ± SD age, 59.6 ± 8.5 years) were enrolled. The diagnosis of SCA6 was confirmed by cerebellar symptoms and signs and also by genetic analysis as described previously.13 The possibility of SCA8 coexpansion was excluded.14 All patients’ symptoms were assessed with 5 degrees for ataxia and 4 degrees for dysarthria (Table 1). None of the patients had any other neurologic disease that might affect the central nervous system and had the possibility of phenotypic heterogeneity of familial hemiplegic migraine from their symptoms. Informed consent for participation in the study was obtained from each participant.

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>CAG Repeat</th>
<th>Disease Duration, y</th>
<th>Age at Onset, y</th>
<th>Ataxia*</th>
<th>Dysarthria*</th>
<th>Cerebellar Vermis Atrophy†</th>
<th>Cerebellar Hemisphere Atrophy†</th>
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<tr>
<td>1/F/74</td>
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<td>57</td>
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<tr>
<td>8/F/55</td>
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<td>52</td>
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<tr>
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<td>48</td>
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<tr>
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<td>26/14</td>
<td>8</td>
<td>32</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
</tbody>
</table>

Average ± SD ... 9.4 ± 9.4 50.5 ± 9.3 1.7 ± 1.2 1.9 ± 0.9 1.9 ± 0.9 1.4 ± 0.5

*According to the grading scale of severity of ataxia (0, normal; 1, mild disturbance of gait; 2, moderate disturbance of gait; 3, walk with a cane; 4, use of a wheelchair) and dysarthria (0, normal; 1, mild; 2, moderate; 3, severe).

†According to the grading scale of atrophy (Figure 1).

**MR IMAGING STUDIES**

Axial spin-echo T1- and T2-weighted images and sagittal T1-weighted images were obtained using a 1.0- or 1.5-T machine. Images were assessed by 2 neuroradiologists (K.H. and T.O.) who were unaware of the severity of disease. Each neuroradiologist assessed the images independently, and agreement was reached by consensus in cases with differing opinions. Atrophy of the cerebellar vermis and hemisphere was visually estimated, and its severity was scored in 4 degrees for the vermis on sagittal images (Figure 1) and 3 degrees for the hemisphere on axial images (Figure 2). We referred to the previously reported method to analyze the vermis atrophy.

**rCBF MEASUREMENTS**

A total of 20 mCi (740 MBq) of 99mTc-ECD was injected intravenously. The passage of the tracer from the aortic arch to the brain was monitored using a rectangular gamma camera of a 3-head SPECT system (Multispect3; Siemens AG, Munich, Germany). Global cerebral blood flow values were obtained using graphic analysis as previously described by Imon et al.12 Five minutes after the injection, a SPECT scan was performed using a system equipped with high-resolution parallel-hole col-
The projection data were obtained in a 128 × 128 format for 24 angles in 120° increments at a rate of 40 seconds per angle. A Butterworth filter was used for image reconstruction. Attenuation correction was performed using the method described by Chang. 

To calculate rCBF and to correct for incomplete retention of 99mTc-ECD in the brain, the algorithm was applied as previously described.

ANALYSIS OF DATA

Three SPECT coronal images were selected to distinguish rCBF of the cerebellar vermis from that of the cerebellar hemisphere. Twelve regions of interest (ROIs) (128 pixels, square shaped) were placed manually with care taken to avoid the CSF (Figure 3). The ROIs were calculated twice and the reproducibility was confirmed. We calculated the average variables of the bilateral ROI counts in the cerebellar hemispheres; frontal, temporal, and parietal lobes; and thalamus. A difference of rCBFs between the SCA6 and control group was analyzed by the unpaired t test. We evaluated the association of rCBFs in the vermis with that in other regions by regression analysis. We assessed the relationships of rCBF in the cerebellar hemisphere and vermis atrophy in the patients using the Spearman correlation coefficient by rank. P < .05 was accepted as statistically significant.

RESULTS

Clinical features and degree of cerebellar atrophy on MR images obtained from the SCA6 patients are summarized in Table 1. There was a significant inverse correlation between CAG repeated lengths and age at onset (r = −0.87, P = .001). Table 2 gives the average values of rCBF in the SCA6 patients and the healthy controls. The mean rCBF values of the cerebellar hemispheres and vermis in the SCA6 patients were significantly lower than those in the healthy controls (P = .03 in the hemisphere, P = .006 in the vermis). In contrast, there was no significant decrease in rCBF in other areas in the SCA6 patients.

In the SCA6 group, there were significant correlations between age at onset and rCBFs in the vermis (r = 0.66, P = .04), cerebellar hemisphere (r = 0.71, P = .02), and frontal lobes (r = 0.82, P = .004). There were significant inverse correlations between duration of illness and rCBFs in the cerebellar hemisphere (r = −0.73, P = .02) and vermis (r = −0.67, P = .03), and a correlation without statistical significance was found between duration of illness and rCBF in the frontal lobes (r = −0.59, P = .07) (Figure 4). There was no significant correlation between CAG repeated expansions and rCBFs in the cerebellar hemisphere or vermis.
The severity of dysarthria had a significant inverse correlation with rCBF in the vermis \((P = .03)\), and the severity of ataxia was correlated with rCBF in the vermis without statistical significance \((P = .07)\). In contrast, the severity of each symptom had no correlation with rCBF in the cerebellar hemisphere (Figure 5) or in other regions.

Atrophy of the vermis was significantly correlated with rCBF in both the vermis \((P = .04)\) and the cerebellar hemisphere \((P = .01)\). Significant correlations were also found between atrophy of the cerebellar hemisphere and rCBF in the cerebellar hemisphere \((P = .01)\) and the vermis \((P = .04)\). There was a correlation between duration of illness and rCBF in the cerebellar hemisphere \((P = .01)\) and the vermis \((P = .04)\). Significant correlations were also found between duration of illness and rCBF in the cerebellar hemisphere, the vermis, and the frontal lobes \((P = .01)\) without statistical significance \((P = .07)\). In contrast, there was no decrease in rCBF in the cerebrum. We also found that rCBF decrease in the cerebellum was correlated with cerebellar atrophy and cerebellar symptoms. These results are in accordance with results of previous neuropathologic studies showing that lesions of SCA6 are restricted to the cerebellum, where abundant expression of P/Q-type calcium channels has been found.19 The number of Purkinje cells was markedly decreased in the vermis,20 and this coincides with the distribution of rCBF decrease in SCA6 patients. The MR imaging analysis of SCA6 patients demonstrated no abnormalities in the central nervous system except for cerebellar atrophy.4

Botez et al10 first reported CCCD. An experimental study21 has shown that it derived from the functional deactivation of the cerebello-ponto-thalamo-cerebral pathways. Impairment of a unilateral cerebellum would lead to reduced radioisotope uptake in the contralateral cerebellar hemisphere, and CCCD might be found also in patients with spinocerebellar ataxia type 6. There were significant inverse correlations between duration of illness and rCBFs in the cerebellar hemisphere \((P = .02)\) and the vermis \((P = .04)\). There was a correlation between duration of illness and rCBF in the frontal lobes without statistical significance \((P = .07)\).

We found that rCBF of the cerebellum was significantly lower in the genetically confirmed SCA6 patients than in the healthy controls. The degree of decrease in rCBF in the vermis was more severe than that in the cerebellar hemisphere. In contrast, there was no decrease in rCBF in the cerebrum. We also found that rCBF decrease in the cerebellum was correlated with cerebellar atrophy and cerebellar symptoms. These results are in accordance with results of previous neuropathologic studies showing that lesions of SCA6 are restricted to the cerebellum, where abundant expression of P/Q-type calcium channels has been found.19 The number of Purkinje cells was markedly decreased in the vermis,20 and this coincides with the distribution of rCBF decrease in SCA6 patients. The MR imaging analysis of SCA6 patients demonstrated no abnormalities in the central nervous system except for cerebellar atrophy.4

Table 2. Average Quantitative Values of Regional Cerebral Blood Flow (rCBF) in Patients With Spinocerebellar Ataxia Type 6 (SCA6) and Control Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>rCBF, mL/100 g per Minute</th>
<th>SCA6 (n = 10)</th>
<th>Control (n = 9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar hemisphere</td>
<td></td>
<td>49.3 ± 6.3</td>
<td>59.3 ± 11.3</td>
<td>.03*</td>
</tr>
<tr>
<td>Cerebral vermis</td>
<td></td>
<td>46.3 ± 6.3</td>
<td>60.3 ± 11.8</td>
<td>.006†</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td>54.2 ± 7.7</td>
<td>52.4 ± 8.0</td>
<td>.45</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td></td>
<td>55.7 ± 7.9</td>
<td>54.5 ± 11.3</td>
<td>.59</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
<td>44.8 ± 5.0</td>
<td>45.5 ± 11.3</td>
<td>.88</td>
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<tr>
<td>Occipital lobe</td>
<td></td>
<td>77.5 ± 9.6</td>
<td>73.5 ± 12.8</td>
<td>.62</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>52.8 ± 6.5</td>
<td>52.6 ± 10.6</td>
<td>.95</td>
</tr>
</tbody>
</table>

*Statistically significant, unpaired t test.
†Statistically significant, Bonferroni adjustment.

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SCA6 patients. CCCD has been established by PET and SPECT studies in the various cerebellar diseases.\textsuperscript{6,9,10} In contrast, some studies\textsuperscript{5,22} have shown no decrease in glucose metabolism or rCBF in the cerebral cortex in patients with SCDS.

Our study revealed that there was no decrease in rCBF in the cerebral hemisphere, and no CCCD was detected in SCA6 patients. This finding indicates that the cerebellum-ponto-thalamo-cerebral pathways are not impaired by only damage to Purkinje cells or are not impaired unless there is dysfunction or loss of a certain percentage of Purkinje cells. Previous studies\textsuperscript{3} showed that symptoms appear with 50% to 75% loss of Purkinje cells. To confirm the frontal lobe function, we performed the Wisconsin Card Sorting Test in all of our SCA6 patients but found no frontal lobe dysfunction (data not shown).

On the other hand, we found a correlation between rCBF decrease in the frontal lobes and duration of illness without statistical significance in the SCA6 patients. If rCBF is observed for a longer duration of illness, rCBF decreases in the frontal lobes, suggesting CCCD might be observed.

In our study, decrease in rCBF in the cerebellum was not correlated with the CAG repeated expansion. Other investigators have shown that there is no correlation between the CAG repeated expansion and clinical findings in SCA6 patients.\textsuperscript{2,3,23} This finding may be due to the small difference of CAG repeated expansion between healthy controls and SCA6 patients. In summary, we confirmed that decrease in rCBF is restricted to the cerebellum, and CCCD was not revealed by measurements of rCBF. This finding suggests that quantitative SPECT analysis is a useful tool to clarify the disease mechanism.

Accepted for publication January 19, 2004.

\textbf{Author contributions:} Study concept and design (Drs Honjo, Ohshita, and Imon); acquisition of data (Drs Kawakami, Maruyama, and Mimori); analysis and interpretation of data (Drs Honjo, Ohshita, Naka, and Imon); drafting of the manuscript (Drs Honjo, Ohshita, and Mimori); critical revision of the manuscript for important intellectual content (Dr Matsumoto); administrative, technical, and material support (Drs Ohshita, Naka, and Imon); study supervision (Dr Ohshita).

This work was supported by a grant-in-aid from the Research Committee for Ataxic Diseases of the Ministry of Health, Labor and Welfare of Japan (Dr Kawakami) and a Research Fellowship for Young Scientists of the Japan Society for the promotion of science (Dr Maruyama), Tokyo. We thank Shigenobu Nakamura, MD, PhD, Tatsuo Kohriyama, MD, PhD, Sadao Katayama, MD, PhD, Hiroshi Yamashita, MD, PhD, and Masaya Oda, MD, for providing samples, clinical information, and guidance. We also thank Kingo Taniguchi and Masao Kiguchi for their technical support on SPECT analysis.

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\textbf{REFERENCES}


