Metabolic Characterization of Spinocerebellar Ataxia Type 6

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Background: Spinocerebellar ataxia type 6 (SCA6) is a neurodegenerative disorder characterized by slowly progressive ataxia and dysarthria. The mutational basis is an expanded CAG repeat sequence within the coding regions of the CACNL1A4 gene. Basic clinical, neuroimaging, and pathological, and epidemiological features have been described in the literature. However, the metabolic features of SCA6 have not been elucidated.

Objective: To investigate the metabolic features of SCA6.

Patients and Methods: Seven patients with SCA6 and 7 healthy individuals underwent positron emission tomography using fluorodeoxyglucose F 18.

Results: Cerebral glucose utilization in the 7 patients with SCA6 was characterized by significant hypometabolism in widespread structures, including cortical regions and basal ganglia, as well as the cerebellar hemispheres and brainstem.

Conclusions: The results of the multiple-regional brain hypometabolism suggest that brain dysfunction associated with SCA6 may not be limited to the cerebellum and inferior olive, as previously suggested by the results of other pathologic studies.

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DOMINANTLY inherited spinocerebellar ataxia (SCA) consists of a clinically, pathologically, and genetically heterogeneous group of neurodegenerative disorders that share clinical characteristics of progressive deterioration in gait and balance (due to degeneration of the cerebellum and its pathways) and various combinations of cerebral, extrapyramidal, bulbar, spinal, and peripheral nervous system involvement. Classification of dominant SCAs on the basis of clinical symptoms has been quite controversial because of the overlap in the clinical presentations. The genes causing 8 of these diseases, ie, SCA type 1 (SCA1), SCA2 (SCA2), Machado-Joseph disease and SCA3 (MJD/SCA3), SCA6 (SCA6), SCA7 (SCA7), SCA8 (SCA8), SCA12 (SCA12), and dentatorubral-pallidoluysian atrophy (DRPLA), have been identified. The mutational basis for all of the disorders except that of SCA8 is expanded CAG repeat sequences within the coding regions of the involved genes. Detection of these trinucleotide repeat mutations has enabled the classification of dominant SCAs on the basis of molecular analyses.

Spinocerebellar ataxia type 6 (Online Mendelian Inheritance in Man 183086) was originally identified using the expansion of polymorphic CAG repeats at the 3' end of the human $\alpha_{1A}$ voltage-dependent calcium channel subunit gene (CACNL1A4), which is known to be important for Purkinje cell function and survival. In the same gene, 4 missense mutations that cause familial hemiplegic migraine and 2 mutations that disrupt the reading frame responsible for episodic ataxia type 2 have also been identified.

Clinically, SCA6 has been characterized as a “pure” cerebellar syndrome belonging to autosomal dominant cerebellar ataxia type 3. Magnetic resonance imaging of the brain in patients with SCA6 has demonstrated cerebellar atrophy with no evidence of brainstem involvement. Single-photon emission tomography has shown moderately decreased tracer uptake in the cerebellum. Neuro-pathological study results have shown marked cerebellar atrophy and very mild atrophy of the brainstem. Microscopic examination results have revealed severe loss...
SUBJECTS AND METHODS

SUBJECTS

Seven healthy individuals (4 men and 3 women) and 7 patients (4 men and 3 women) with SCA6 underwent clinical evaluations by a board-certified neurologist (B.W.S.). Age at onset was provided by the patient or close relatives. Informed consent was obtained from all subjects before participation in the study.

MOLECULAR STUDIES

Genomic DNA was isolated from peripheral leukocytes as previously described.33 Polymerase chain reaction analysis was performed using the primers S-5-F1 and S-5-R1 for SCA6.34 The polymerase chain reaction condition was as described in the original report.35 Alleles were separated using electrophoresis on 6% polyacrylamide gels in parallel with an M13 sequencing ladder and were analyzed as previously described.29,33

PET STUDIES

The 7 patients with SCA6 (mean ± SD age, 51.7 ± 6.5 years), identified by the presence of expanded CAG repeats in the SCA6 gene, and the 7 healthy control subjects (mean ± SD age, 46.0 ± 10.3 years) underwent PET using FDG. All subjects were awake, taking no medication known to affect central nervous system function, and blindfolded during the examination. The imaging device was an 8-ring whole-body PET scanner (Scanditronix PC4096-15WB; Scanditronix, Uppsala, Sweden) with an axial resolution of 6 mm and an in-plane resolution of 8 mm at the center of the field of view. Twenty-two frames of dynamic PET images were acquired for 120 minutes after intravenous injection of 370 MBq of FDG. Arterial blood samples were drawn manually for use in obtaining the input function variables for modeling cerebral metabolic rate of glucose (CMRGlc). Thirty-one regions of interest (ROIs) were drawn manually for each patient in the cerebellar hemispheres, brainstem, thalami, basal ganglia, and frontal, parietal, temporal, and occipital cortices, and the corresponding time-activity curves were generated. The mean (± SD) size of the ROIs was 1.6 ± 0.4 cm² (range, 0.8-3.0 cm²). Extreme caution was exercised in the placement of ROIs to avoid potential signal contamination from adjacent anatomical structures. A modified Sokoloff 3 compartment model14-36 was used to describe and evaluate the CMRGlc in milligrams per minute per milliliter using the graphic method of Patlak et al.37,38 The physiological variable CMRGlc was defined as follows:

\[
\text{CMRGlc} = \frac{\text{Cp}}{\text{LC}} \times \text{K},
\]

where LC was the lumped constant that summarized the differences between FDG and glucose in transportation and phosphorylation, and was equivalent to 0.404 as previously reported39,40; Cp, the average glucose concentration in plasma from the blood samples during the last 30 minutes; and K, the slope of the Patlak plot.37,38

STATISTICAL ANALYSIS

Statistical analyses were performed using commercially available software (SAS; SAS Institute Inc, Cary, NC). The null hypothesis was rejected for \( P < .05 \). Group data were compared using the Wilcoxon rank sum test. The relationships between regional cerebral glucose metabolism and age at onset, age at the time of PET examination, and duration of SCA6 illness were assessed using Pearson correlation analysis.

RESULTS

CLINICAL FEATURES OF SCA6

The main clinical features of the 7 individuals with SCA6 in this study are summarized in Table 1.

PET STUDIES

Glucose metabolism rate was significantly lower not only in the cerebellar hemispheres, but also in the brainstem, basal ganglia, and frontal, temporal, and occipital cerebral cortices (Table 2 and Figure). However, the ages at onset and at the time of PET examination and duration of the illness did not correlate with CMRGlc.

COMMENT

The predominant clinical feature of our patients with SCA6 was cerebellar ataxia (loss of balance and dexterity of handwriting) with an onset late in adult life and a very slowly progressive disease course (Table 1). Although brisk deep tendon reflexes were frequently observed, plantar response was normal in all of our patients, indicating that the upper motor neurons were only slightly involved.31 Other noncerebellar features, eg, rigidity, gait disturbance, and sphincter disturbances, were rarely found in our patients with SCA6. Patient 1 had a partial right abducens palsy and exhibited a horizontal diplopia on looking toward the right side. Many of our patients also had exacerbation of the sense of imbalance in a visually “busy” environment, as has been previously reported by others with SCA6 (S. H. Subramony, MD, written communication, May 10, 1999). Clinical features associated with other disorders caused by mutations in the CACNL1A4 gene,37 ie, migraine, epi-
sodes of hemiplegia, or ataxia were checked for carefully but rarely found in our SCA6 cohort, which is consistent with the findings of Matsumura et al19 and Gomez et al.24 In all patients in this study, the disease had an indolent course, which rarely progressed to severe disability during the first 10 years.

The widespread reduction of glucose metabolism (Table 2 and Figure) ranged from 71% to 78% of the healthy controls in all structures except the brainstem, where metabolic rate was 66% of that for controls, and cerebellar hemisphere, where it was 63% of that for controls. These results were unexpected. We exercised extreme caution during the study and ruled out the possibility of a systematic error or a statistical phenomenon that might have caused low values. Positron emission tomography has been shown to be very sensitive in the detection of subtle subclinical abnormalities.26-32 The fact that hypometabolism was found in various brain regions does not imply widespread neuronal degeneration but could simply reflect subclinical neuropathological features, or metabolic dysfunction in structurally intact neurons. None of our patients manifested symptoms referable to the basal ganglion or cerebral cortices. Therefore, the clinical relevance of this observation is not clear. The findings of several previous studies might add insight to the mechanisms responsible for these discrepancies. First, a study of SCA1 transgenic mice demonstrated that considerable neuropathological changes occurred without the manifestation of a neuro-

### Table 1. Clinical Features of 7 Patients With SCA6*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedigree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Duration of illness, y†</td>
<td>13/23</td>
<td>13/23</td>
<td>14/23</td>
<td>13/23</td>
<td>13/23</td>
<td>14/23</td>
<td>14/23</td>
</tr>
<tr>
<td>CAG repeat units</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Saccadic pursuit</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decreased OKN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Brisk DTR</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ophthalmoparesis</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Extensor plantar response</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Migraine</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Episodic ataxia</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Ambulation</td>
<td>S</td>
<td>S</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>A</td>
<td>. . .</td>
</tr>
</tbody>
</table>

SCA6 indicates spinocerebellar ataxia type 6; ellipses, not applicable; OKN, optokinetic nystagmus; DTR, deep tendon reflex; S, support from another person needed when walking.

†Range, 39 to 55 years.

‡Range, 4 to 14 years.

### Table 2. Cerebral Glucose Metabolic Rate in Patients With SCA6 and Healthy Controls*

<table>
<thead>
<tr>
<th>Region, glucose metabolic rate‡</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Patients (n = 7)†</th>
<th>Controls (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>1.92</td>
<td>2.58</td>
<td>2.00</td>
<td>1.71</td>
<td>1.78</td>
<td>2.07</td>
<td>1.68</td>
<td>1.96 ± 0.31§</td>
<td>2.96 ± 0.44</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>2.10</td>
<td>3.06</td>
<td>2.07</td>
<td>1.72</td>
<td>1.83</td>
<td>2.97</td>
<td>1.90</td>
<td>2.23 ± 0.58§</td>
<td>3.54 ± 0.31</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>2.24</td>
<td>3.14</td>
<td>2.60</td>
<td>2.58</td>
<td>2.72</td>
<td>3.65</td>
<td>2.79</td>
<td>2.82 ± 0.49§</td>
<td>3.93 ± 0.46</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>2.57</td>
<td>3.75</td>
<td>2.75</td>
<td>2.78</td>
<td>3.30</td>
<td>3.95</td>
<td>3.20</td>
<td>3.32 ± 0.63§</td>
<td>4.46 ± 0.58</td>
</tr>
<tr>
<td>Thalamus</td>
<td>2.84</td>
<td>4.08</td>
<td>3.13</td>
<td>3.01</td>
<td>3.09</td>
<td>3.95</td>
<td>3.48</td>
<td>3.37 ± 0.53§</td>
<td>4.60 ± 0.49</td>
</tr>
<tr>
<td>Calcarine cortex</td>
<td>2.65</td>
<td>4.10</td>
<td>3.05</td>
<td>3.08</td>
<td>2.77</td>
<td>4.32</td>
<td>2.66</td>
<td>3.15 ± 0.74</td>
<td>4.02 ± 0.40</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>2.55</td>
<td>3.92</td>
<td>2.93</td>
<td>2.61</td>
<td>2.75</td>
<td>4.82</td>
<td>2.29</td>
<td>3.12 ± 0.89</td>
<td>4.26 ± 0.40</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>2.56</td>
<td>3.53</td>
<td>2.60</td>
<td>2.82</td>
<td>2.63</td>
<td>3.69</td>
<td>2.60</td>
<td>2.92 ± 0.50§</td>
<td>4.13 ± 0.50</td>
</tr>
<tr>
<td>Caudate</td>
<td>2.64</td>
<td>3.93</td>
<td>3.00</td>
<td>2.85</td>
<td>2.90</td>
<td>4.06</td>
<td>2.85</td>
<td>3.18 ± 0.60</td>
<td>4.19 ± 0.39</td>
</tr>
</tbody>
</table>

SCA6 indicates spinocerebellar ataxia type 6; ellipses, not applicable.

†Mean age at onset, 43.9 ± 5.7 years; mean duration of illness, 7.9 ± 4.3 years.

‡Given as milligrams per minute per milliliter.

§P < .01.
logic phenotype. Second, there have been precedents of minor pathologic abnormalities in clinically unexpected areas in other “pure system degenerations” such as hereditary spastic paraparesis. Previous study results have also shown that overt ataxia occurred in mice only after there was loss or dysfunction of a substantial number (50%-75%) of the Purkinje cells. Thus, it is likely that the absence of cerebral cortical and basal ganglia symptoms in our patients reflects that neuronal cell dysfunction progression in these patients occurred at an insufficiently rapid rate to cause symptoms during the course of our observations. Third, many structures in the cerebellum influence regional cerebral blood flow. Stimulation of the fastigial nucleus has been shown to increase neurogenically the mean carotid blood flow in primates. The cerebellar vermis projects by way of the fastigial nucleus to the cortical and brainstem regions. Hence, cerebellar vermal atrophy theoretically could alter the normal physiologic regulation of regional cerebral blood flow mediated by the fastigial nucleus, resulting in regional hypoperfusion and hypometabolism. Further studies are warranted to investigate the contribution of cerebellar structures to regional hypometabolism.

The calcium receptor subunit affected by the mutation has been known to be expressed ubiquitously in neurons of the entire brain, including the hippocampus, cerebral cortex, thalamus, hypothalamus, medulla, inferior olivary nucleus, and the horizontal cells of the retina. In patients with familial hemiplegic migraine, which is caused by point mutations in the CACNL1A4 gene, altered regional cerebral blood flow and a neuronal dysfunction have been well described. This finding might add to the evidence of the involvement of other cerebral structures in calcium channel dysfunction. Altered channel characteristics are expected to profoundly disturb the normal function of cerebral neurons. Further studies in transgenic mice expressing mutant alleles of the CACNL1A4 gene will enable determination of the pathogenic mechanism of SCA6.

CONCLUSIONS

Study of SCA6 by means of PET surprisingly indicated that significantly reduced glucose uptake was present not only in the cerebellum but also in other regions of the brain. Thus, SCA6 may not be a purely cerebellar syndrome. Future comparison of PET findings in different subtypes of SCA may reveal genotype-specific patterns of regional metabolic deficits in the brain, which might sharpen the distinction between these genetically characterized forms of SCA.

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REFERENCES


