IV. 2. Brain Function Evaluated by $^{18}$F-FDG PET in Spinocerebellar Ataxia Type7


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Introduction

Hereditary spinocerebellar ataxia (SCA) is a clinically and genetically heterogeneous group of neurological disorders characterized by dysfunction of the cerebellum and its afferent and efferent connections. Aberrant expansions of coding sequence in trinucleotide repeat assays of genes on 6p22-23, 12q24.1, 14q32.1, 19p13 and 3p12-13 have been identified in type1, type2, type3 / Machado-Joseph disease (MJD), type6 and type7 respectively$^{1-5}$.

SCA7 is the first clinical entity in which the neurodegenerative process affects the macula and/or retina in addition to other brain structures. In a previous classification of inherited ataxia, this SCA is categorized as an autosomal dominant cerebellar ataxia (ADCA) typeII and as an olivopontocerebellar atrophy (OPCA) typeIII in which the clinical manifestation is cerebellar ataxia with progressive pigmentary macular dystrophy and/or retinal degeneration$^{6-9}$). Recently, the mutated gene of this SCA has been identified. Subsequent pathological studies have revealed that SCA7 is epitomized by the selective degeneration of Purkinje cells and the dentate nucleus in the cerebellum with the inferior olivary complex and the pontin nuclei. Immunohistochemical studies have shown that neuronal intranuclear inclusions are most frequent in atrophic brain regions. These inclusions were also observed in the cerebral cortex considered to be unaffected, suggesting that the observed distribution of neuronal intranuclear inclusions is unlikely to be found in the other ataxias$^{10}$.

Although the clinical, pathological and molecular features of SCA7 have been reported in several ethnic groups, these aspects of the Japanese patients have not been reported except our ophthalmologic report$^{11-14}$. Furthermore, the mechanisms underlying the neurological manifestations associated with this type of SCA are still unclear$^{17}$. Therefore, we described the clinical aspects of the two Japanese probands, then the brain function of the two probands was investigated by evaluating the cerebral metabolic rate for
glucose (CMRGlc).

**Subjects and methods**

**Patients:**

Proband of 117 Japanese families with autosomal dominant spinocerebellar ataxia (SCA) were recruited from clinics at Tohoku University. Among these probands, two patients (the proband 1 and 2) were diagnosed both clinically and genetically as SCA type7. The purpose and necessity for the genetic and the other studies were carefully explained, and informed consents were obtained from the patients and/or their families.

**Genetic studies:**

Gnomic DNA was isolated from fresh peripheral leukocytes of each subject. PCR products representing trinucleotide repeat coding regions were amplified from gnomic DNA with the primer pair 4U1024: 5'-TGTTACATTGTAGGAGCGGAA-3'/ 4U1716: 5'-CACGACTGTCCAGCATCT-3'. For PCR amplification and definition of the mutated gene bearing the aberrantly expanded CAG repeats, the same method was used as previously reported\(^6,10\).

**MRI study:**

Magnetom 1.5 teslar MRI (Magnetom Vision SIEMENS) scanning was performed to estimate morphological impairments of the brain for T1 and T2 weighted images of the axial, coronal and sagittal sections.

**PET scanning:**

PET study was performed with a model SET-2400W scanner (Shimazu, Japan) at the Cyclotron and Radioisotope Center, Tohoku University. The two age matched control groups consisted of healthy normal volunteers ranging in age from 18-27 years (n=11, mean±SD, 20.9±2.9) and 49 74 years (n=6, mean±SD, 63.5±9.0). They had no history of recent medical illness, neurological diseases, developmental disorders or substance abuse. MRIs of the brain were also normal.

CMRGlc was measured in the proband 1 and 2, then in 17 control members. Between 6 and 7mCi of \(^{18}\text{F}\) 2-fluoro-2-deoxy-D-glucose \((^{18}\text{F-FDG})\) was injected to each member as an intravenous bolus. Positron emission scans were performed at 45min after the injection. For the other conditions of this study and data analysis, the same method was used as previously reported\(^9\).
Results

The proband 1 and 2 clinical manifestations:

The proband 1 (age 26, male) with 47/10 heterozygous CAG repeats had an onset of
gate disturbance at 20 years of age. The development of the symptoms was very mild, then
slurred speech and slightly decreased visual acuity occurred subsequently at age 24.
Neurological findings at age 26 included slurred speech, mildly decreased visual acuity,
viscous eye movement, upward gaze palsy, mild ataxia and generalized hyperreflexia.
Neuropsychologically, he had mild naming difficulty and a moderately delayed verbal
memory disturbance. Laboratory analysis of the blood and cerebrospinal fluid indicated that
the data were within normal limits.

The proband 2 (age 48, female) with 48/10 heterozygous CAG repeats noticed
decreased visual acuity at 28 years of age. Since 40 years, she has subsequently been
affected by slurred speech and ataxic gate. These symptoms developed relatively more
aggressively than in the proband 1. Neurological findings at 46 years of age included
subcortical dementia, slurred speech, remarkably decreased visual acuity, prominently
viscous eye movement, upward gaze palsy, severe truncal and limb ataxia and generalized
hyperreflexia. Laboratory analysis of the blood and cerebrospinal fluid indicated that the
data were within normal ranges.

MRI studies and PET scanning:

Axial, coronal and sagittal images obtained by $^{18}$F-FDG PET from the proband 1 and
2 are shown in Fig.1 (A,B,C) with MRI at the levels of the corresponding brain slice. In the
proband 1, a prominent attenuation in $^{18}$F-FDG uptake of the inferior bi-temporal cortex and
the cerebello-brainstem was observed. In contrast, MRI studies showed no atrophic
changes in the temporal lobi but mild atrophy of the cerebello-brainstem was observed
(Fig.1B, C). In the brain of the proband 2, scattered reduction of $^{18}$F-FDG uptake was
observed in the fronto-parieto-temporal cortex and the cerebello-brainstem as well. In
contrast to this, MRI studies showed only mild atrophy of the bi temporal lobi in cerebrum,
while remarkable atrophic changes were observed in the cerebello-brainstem regions (Fig.1
A,B,C).

As shown in Table 1, CMRGlc values were tabulated in order to compare levels in
each of proband’s brain structures with those of age matched controls. In the proband 1, the
values in the inferior bi-temporal cortex and the bi-temporal pole were lower in comparison
with the normal controls. CMRGlc values in the brainstem and the cerebellum were also
lower than that of the controls. In the proband 2, scattered decrease in CMRGlc values was
observed in the fronto-parieto-temporal cortex. CMRGlc reduction was also observed in the
cerebello-brainstem region.

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Discussion

The clinical manifestations of SCA7 are characterized by cerebellar ataxia with pigmented macular and/or retinal degeneration. The clinical aspects of this SCA, including central and peripheral neural impairment, have been reported in several ethnic groups\textsuperscript{5,13-15}. However, due to the fact that there is a low prevalence of this SCA in Japan, Japanese cases have not been reported except our ophthalmologic report\textsuperscript{16,20}. To date, the reported symptoms are mental deterioration, visual impairment, slow eye movement, ophthalmoplegia, hearing impairment, facial myokymia, involuntary movement (such as chorea and dystonia), parkinsonian symptoms and sensory loss\textsuperscript{5,13-15}. It is likely that in other types of SCA, this constellation of clinical features are presented in varying degrees in members of the same family and/or at different times during the course of illness\textsuperscript{21}.

Recently, several pathogenetic findings related with these clinical aspects have been reported to provide insight into the pathogenesis of SCA7. Using SCA7 cDNA clones, the subcellular localization of ataxin-7 was examined in transfected COS-1 cells. The study demonstrated that ataxin-7 is the protein encoded from the SCA7 gene, and that this protein is distributed intranuclearly with a portion localizing in the nucleolus. Thus, it is speculated that the expanded ataxin-7 carries out its pathogenetic effect in the nucleus by altering a matrix-associated nuclear structure and/or by disrupting nucleolar function\textsuperscript{17}. In recent studies, two new immunohistological observations have been reported\textsuperscript{10,22}. First, ataxin-7 accumulates as a single nuclear inclusion in neuronal cells of the brain. Second, these intranuclear structures were shown to be most frequent in the neurons of the inferior olive, the lateral geniculate body and the substantia nigra, which are also regions of frequent degenerative changes. However, these inclusions were also observed in the cerebral cortex, a region that is normally considered to be an unaffected in this and the other types of SCA\textsuperscript{10}.

Taken together with these observations, our data suggests that investigating the role of mutant ataxin7 in neural impairments would be of great interest. In several brain regions including non-atrophic areas, an attenuation of glucose metabolism was observed. This observation raises the possibility that mutant ataxin7 might be associated with the deleterious effects on neurons that result in attenuation of the neural activity and hypometabolism of glucose in several brain regions.

Although we were not able to ascertain the specific pathological mechanism underlying SCA7, the present study suggests that attenuation of neural activity may occur in several non-atrophic brain regions and that these impairments may be associated with the diverse neurological manifestations characteristic of this neurodegenerative disorder.

Acknowledgments

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References


Table 1. In each structure of the brain, values of CMRGlc are shown in age matched controls and the two probands (mean±SD mg/100g/min). In the proband 1, the values in the inferior bi-temporal cortex and the 4-temporal pole are lower than the normal values. Remarkable reductions of the values are also shown in the cerebellum-brainstem region. In the proband 2, CMRGlc values decrease in both the fronto-parieto-temporal cortex and the cerebellum-brainstem.

<table>
<thead>
<tr>
<th>Control (n=11): Age 20.9±2.9</th>
<th>Proband 1: Age 26</th>
<th>Control (n=6): Age 63.5±9.0</th>
<th>Proband 2: Age 46</th>
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<tbody>
<tr>
<td>Frontal cortex</td>
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<tr>
<td>Superior frontal cortex</td>
<td>8.82±3.38</td>
<td>rt. 7.92</td>
<td>lt. 8.67±0.66</td>
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<td>Medial frontal cortex</td>
<td>10.63±3.46</td>
<td>7.63-7.32</td>
<td>8.63±0.97</td>
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<td>Medial mesial frontal cortex</td>
<td>10.52±2.31</td>
<td>7.86-8.10</td>
<td>8.53±1.10</td>
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<td>Inferior frontal cortex</td>
<td>10.43±2.92</td>
<td>7.42-7.30</td>
<td>8.72±1.31</td>
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<tr>
<td>Lateral frontal cortex</td>
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<td>7.60-7.31</td>
<td>8.16±1.30</td>
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<td>10.28±2.28</td>
<td>8.35-8.02</td>
<td>8.23±0.92</td>
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<td>Parietal cortex</td>
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<td>Primary motor and sensory cortex</td>
<td>10.29±2.37</td>
<td>8.15-8.12</td>
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<td>Posterior parietal cortex</td>
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<td>8.41-8.20</td>
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<td>7.46-7.71</td>
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<td>Temporal cortex</td>
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<tr>
<td>Superior temporal cortex</td>
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<td>7.06-7.30</td>
<td>8.70±0.88</td>
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<td>Temporal pole</td>
<td>10.45±2.53</td>
<td>4.49-4.33</td>
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<td>Occipital cortex</td>
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<td>Primary visual area</td>
<td>8.92±2.50</td>
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<td>8.74-8.98</td>
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<td>8.79±0.95</td>
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<td>Caudate nucleus</td>
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<td>9.59-9.42</td>
<td>9.13±0.88</td>
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<td>Putamen</td>
<td>11.50±3.11</td>
<td>11.01-10.42</td>
<td>8.67±0.88</td>
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<td>Brainstem</td>
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<td>5.20</td>
<td>7.06±0.46</td>
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<tr>
<td>Cerebellum</td>
<td>10.26±2.24</td>
<td>4.39-4.10</td>
<td>7.70±1.23</td>
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</tbody>
</table>

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Fig. 1. Representative images obtained by $^{18}$F-FDG positron emission tomography (PET) and MRI T1W.1 at the levels of corresponding brain slices in a normal control (age 52, male), the proband 1 and the proband 2. The color scale in the present study ranges from 0 to 12mg/100g/min. (A): Axial images (B): Coronal images (C): Sagittal images.