IV. 7. Evaluation of TRH Therapy in a Patient with Spinocerebellar Degeneration by Measuring Glucose Metabolism with Positron Emission Tomography

Tanj H., Nagasawa H., Hayashi T., Onodera H., Ityama Y., Itoh M.*, and Ido T.*

Department of Neurology, Tohoku University School of Medicine
Cyclotron and Radioisotope Center, Tohoku University*

Introduction

Thyrotropin releasing hormone (TRH) has been used for treatment in patients with spinocerebellar degeneration (SCD). Positron emission tomographic (PET) study of SCD has revealed that the regional metabolic rate for glucose was decreased in the cerebellum\(^1\)-\(^3\)) and degree of hypometabolism was correlated to the clinical severity of SCD\(^2\)-\(^3\)). In the present study, we measured cerebral metabolic rate for glucose (CMRGlc) in a patient with SCD using 2-[\(^{18}\)F]fluoro-2-deoxy-D-glucose (\(^{18}\)FDG) and PET in order to evaluate the effect of TRH therapy.

Patient and method

PATIENT

A 56-year-old female developed slowly progressive gait instability and speech disturbance for 2 years. There was no remarkable past illness or family history of SCD. On admission in 1994, neurological examination revealed saccadic eye movement, horizontal nystagmus, ataxic speech, moderate truncal ataxia and marked incoordination in four limbs with no pyramidal and extra-pyramidal tract signs, but involuntary movement or dementia were not observed. The general laboratory data, thyroid function, tumor markers and cerebro-spinal fluid examination were normal. Nerve conduction velocities in four limbs and electroencephalogram were also normal. Gallium scintigraphy of the whole body showed no abnormality. MRI revealed marked atrophy in both cerebellar hemispheres and vermis, and slight atrophy in the brainstem (Figure 1).

METHOD

The patient was diagnosed as sporadic type of SCD by her clinical symptoms and MRI findings. For the treatment, 2.0 mg of TRH was administered intravenously everyday. Regional CMRGlc of the brain was measured by PET using \(^{18}\)FDG before and 3 weeks after the TRH treatment.
The study was approved by the Research Ethics Committee of the Tohoku University, School of medicine. The patient gave her written informed consent.

PET study was performed with a model PT-931 scanner (CTI Inc., USA), according to the FDG method\textsuperscript{4-5} at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan. Before the study, a short 21-gauge cannula was placed in a brachial artery under local anesthesia for arterial blood sampling. The patient was then positioned in the scanner, with the orbitomeatal (OM) line parallel to the detector ring. A cross of light was projected onto markes on her head from three dimensions, and the head was set at the standard points of 16, 63 and 110 mm above and parallel to the OM line. The study was conducted in a quiet, semi-darkened room. Before the emission scanning, a 15-min transmission scan using a $^{68}$Ge-$^{68}$Ga external ring source was performed. $^{18}$FDG was synthesized according to the method of Ido et al.\textsuperscript{6}. $^{18}$FDG (96.2 MBq 1st study, 115.4 MBq 2nd study) was injected as an intravenous bolus. Thirty to 60 min after the injection, a series of three emission scans was performed by using a PT-931 with an 8 mm axial and transaxial resolution at the center of each standard point. Each emission datum was simultaneously collected from seven contiguous axial sections. A total of 21 slices parallel to the OM line with a slice thickness of 6 mm, encompassing virtually the whole brain including the cerebellum, was analyzed. Twenty blood samples were collected from the brachial artery according to the following protocol; from injection to 2 minutes, one sample every 20 seconds, then samples at 2.5, 3, 4, 5, 7.5, 10, 15, 20, 25, 30, 40, 50, and 60 min after the intravenous administration of $^{18}$FDG. The blood plasma radioactivities of $^{18}$FDG were measured with a cross-calibrated well-counter.

Values of regional CMRGlc were calculated using the operational equation derived by Phelps et al.\textsuperscript{4} and Huang et al.\textsuperscript{7} from that of Sokoloff et al.\textsuperscript{8}.

A lot of regions of interest (ROIs) were placed in the cerebellum and the frontal cortex, and mean value of CMRGlc in each structure was calculated.

We also examined the sway of gravity center of her body unbalanced by truncal ataxia using stabilography at the 19th and 26th day of TRH treatment.

**Results**

Before the TRH treatment, CMRGlc was markedly decreased in the cerebellum. In the other regions of the brain, regional CMRGlc was almost normal and there was no difference between right and left hemispheres with focal abnormality (Figure 2). A marked decrease of CMRGlc in the cerebellum was also observed 3 weeks after the TRH treatment (Figure 3). The mean values of CMRGlc in the cerebellum were 4.92 and 4.90mg/100g/min, and the ratios of the cerebellum versus the frontal cortex were 0.50 and 0.51 before and after the TRH treatment, respectively (Table 1). There was not significant change of the CMRGlc in the cerebellum before and after the TRH treatment in this patient.
On the examination with stabilography, the degree of disequilibrium of her body when she was standing on the floor was less observed at 19th day of the TRH treatment, and such finding was further improved at 26th day of the treatment (Table 2).

**Discussion**

In the previous studies, values of CMRGlc were significantly reduced in the cerebellar hemispheres and vermis in patients with SCD\(^1-3\). However, marked atrophy was also observed in most of such patients by MRI, therefore these findings were speculated that hypometabolism in the cerebellum might be explained by partial volume effects. In some cases with slight atrophic change of the cerebellum, regional CMRGlc was reduced significantly\(^4\). It is suggested that the glucose hypometabolism of the cerebellum may not be explained only by the cerebellar atrophy but also by neuronal dysfunction of the cerebellum itself. In the present patient, the significant decrease of CMRGlc in the cerebellum was observed in accordance with previous reports. It may be due to both the cerebellar atrophy and the neuronal dysfunction of the cerebellum. TRH has been widely used for treatment in patients with SCD. It has been suggested that the mechanism of the effects of TRH may be related to improvement of abnormal noradrenaline metabolism in the cerebellum\(^9-10\), but the details are still unknown. A few reports using PET or SPECT described an increase of cerebellar blood flow immediately after intravenous TRH administration\(^11-12\), so cerebellar function might improve during short time after administration. However, the administrated TRH is rapidly metabolized in blood, and mechanisms of the chronic effects are unknown. In the present study, we tried to evaluate the chronic effects of TRH therapy and also investigate the mechanism by PET. In order to exclude the influence of cerebral blood flow, we calculated the ratios of the cerebellum versus the frontal cortex as a reference area, because TRH receptor binding sites are relatively low level in the frontal cortex\(^13\). Based on the present study, we concluded that TRH did not improve CMRGlc in the cerebellum, but evidently improved the sway of gravity center by stabilography with no significant changes of neurological findings. We speculate the reason why the effect of TRH was too small to improve glucose metabolism with PET. We also speculate the effect of TRH was not necessarily due to an improvement of cerebellar function, because TRH receptors are widely distributed throughout the central nervous system\(^13\). A further detailed study is needed to clarify the mechanism of pharmacological action of TRH in patients with SCD.
References


Table 1. The mean values of metabolic rate for glucose in the cerebellum and the frontal cortex, and the ratios of the cerebellum versus the frontal cortex before and after the TRH treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before TRH</th>
<th>After TRH</th>
<th>Control (n=6)</th>
</tr>
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<tbody>
<tr>
<td>Cerebellum</td>
<td>4.92</td>
<td>4.90</td>
<td>7.02±1.89 *</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>9.76</td>
<td>9.60</td>
<td></td>
</tr>
<tr>
<td>Cerebellum /</td>
<td>0.50</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Frontal cortex</td>
<td></td>
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* Control value is given as mean±SD (mg/100g/min) from six normal subjects

Table 2. The areas of sway of gravity center of the patient measured by stabilography before and after TRH treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before TRH</th>
<th>After TRH</th>
<th>Control (n=31)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>19th day</td>
<td>26th day</td>
</tr>
<tr>
<td>Envelop. Area</td>
<td>27.94</td>
<td>8.95</td>
<td>4.94</td>
</tr>
<tr>
<td>Rectangle Area</td>
<td>79.18</td>
<td>33.05</td>
<td>15.10</td>
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* Control values are given as means±SD (cm²) from 31 normal subjects
Fig. 1. MRI (T1-weighted image) revealed marked atrophy in both cerebellar hemispheres and vermis, and slight atrophy in the brainstem.

Fig. 2. Positron emission tomographic (PET) images of cerebral metabolic rate for glucose (CMRGlc) using 2-[18F]fluoro-2-deoxy-D-glucose (18FDG) before the TRH treatment. CMRGlc was markedly decreased in the cerebellum. In the other regions of the brain, regional CMRGlc was almost normal and there was no difference between right and left hemispheres with focal abnormality.
Fig. 3. PET images of CMRGlc using $^{18}$FDG 3 weeks after the TRH treatment. A marked decrease of CMRGlc in the cerebellum was also observed.