Metabolic neuroimaging of the cervical spinal cord in patients with compressive myelopathy: a high-resolution positron emission tomography study


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Object. The authors conducted a study to examine whether high-resolution [18F]fluorodeoxyglucose (FDG)–positron emission tomography (PET) could be used to visualize deterioration of cervical spinal cord function associated with various degrees of compression and to determine its potential usefulness during assessment of compressive myelopathy.

Methods. In 23 patients requiring decompressive surgery for myelopathy FDG-PET was performed. The preoperative findings of high-resolution FDG-PET were compared with the neurological scores and magnetic resonance (MR) imaging findings. The preoperative standardized uptake value (SUV) of FDG utilization rate of the cervical cord correlated with the pre- (r = 0.497, p = 0.016) and postoperative neurological scores (r = 0.595, p = 0.003), as well as with the rate of neurological improvement postoperatively (r = 0.538, p = 0.008). The FDG utilization rate did not correlate with the high signal intensity on T2-weighted MR images.

Conclusions. Analysis of these results indicates that high-resolution FDG-PET imaging provides useful qualitative and quantitative estimates of impaired metabolic activity of the compromised cervical cord that correlate closely with the severity of neurological dysfunction.

KEY WORDS • positron emission tomography • [18F]fluorodeoxyglucose • cervical myelopathy • spinal cord

Clinical Material and Methods

Patient Population and Neurological Assessment

The study population consisted of 23 patients (13 men...
High-resolution FDG-PET for cervical myelopathy

and 10 women), who were approached at random to volunteer for the study prior to undergoing decompressive surgery for osteocartilaginous impingement of the cervical spinal cord at one or two vertebral levels. The mean age at surgery was 54 years (range 32–71 years). Cervical spondylosis was present in 11 patients, cervical disc herniation in nine, and OPLL in three; the compressive lesion was located in the mid–cervical area between C-3 and C-7. Sixteen patients required anterior decompression and interbody fusion whereas seven underwent posterior en bloc laminoplasty in which established surgical techniques were used.1,3,5 Patients presented with a wide spectrum of clinical myelopathic features. The mean duration of symptoms was 8.7 months (range 3–36 months). Patients with diabetes mellitus were excluded from the study. The mean follow-up period was 2.2 years (range 1.8–2.6 years). Neurological status was assessed using the JOA scoring system (Table 1);11,18 clinical condition was scored preoperatively and at follow-up examination, and the rate of neurological improvement was calculated as follows:

\[
\text{Rate (\%)} = \frac{(\text{postoperative score} - \text{preoperative score})}{(17 - \text{preoperative score})} \times 100.
\]

Both PET and MR imaging studies were performed according to the Ethical Committee Guidelines of our university, and written informed consent was obtained from each patient.

**Magnetic Resonance Imaging**

Neuroimaging workup included routine MR imaging to evaluate the extent and degree of cervical spinal cord damage caused by the compressive lesion(s). On T₂-weighted MR images, changes in signal intensity27,31 within the cervical cord around the level(s) of compression were carefully viewed using a high-resolution 1.5-tesla imager (Signa; General Electric Medical Systems, Milwaukee, WI).

**Tracer Technique and PET**

The tracer technique for PET scanning was followed using the GE Advance system (General Electric Medical Systems). The physical characteristics of this scanner have been described previously by DeGrado, et al.,3 and our group.6,21 The system allows the simultaneous acquisition of 35 transverse slices with 4.25-mm interstice spacing with septa (two-dimensional mode). Images were reconstructed to a full width at half maximum of 4.2 mm in both transaxial and axial directions. The field of view and pixel size of reconstructed images were 256 and 2 mm, respectively. Individuals were studied during a period of fasting for at least 4 hours. Transmission scans were obtained during a 10-minute interval by a standard pin source of ⁶⁸Ge/⁶⁷Ga for attenuation correction of the emission images. A dose of 244–488 MBq of FDG was injected into the antecubital vein for 10 seconds. Dynamic scans were obtained up to 60 minutes postinjection with arterial sampling. Arterial blood was sampled from the distal artery contralateral to the injection site, after which 2-ml blood samples were obtained every 15 seconds in the first 2 minutes, and then at 2.5, 3, 5, 10, 15, 20, 30, 45, and 60 minutes postinjection. Plasma radioactivity was measured using the scintillation counter against which the PET camera was cross-calibrated, using a cylindrical phantom filled with FDG solution. The image was processed using Doctor View software (Asahikasei, Nobeoka, Japan) on a SPARC 20 workstation (Sun Microsystems, Mountain View, CA).

For quantitative analysis, the circulatory metabolic rate of glucose was calculated on pixel-by-pixel basis using the Sokoloff three-compartment model28,33 and an autoradiographic method with the following equation as well as a priori estimates of the rate constants and lumped constant of normal cerebral gray matter:16

\[
\text{CMrGlc} = \frac{\text{CP}}{\text{LC}} \cdot \left[ \frac{\frac{k_1}{\alpha_2 - \alpha_4} \cdot (k_4 - \alpha_4)e^{-\alpha_4 t} + (\alpha_2 - k_4)e^{-\alpha_4 t} \otimes \text{Cp}(t)}{k_2 + k_3} \cdot (e^{-\alpha_2 t} - e^{-\alpha_2 t}) \otimes \text{Cp}(t) \right]
\]

\[
\alpha_1 = \frac{1}{2} \left( k_2 + k_3 + k_4 - \frac{1}{4} (k_2 + k_3 + k_4)^2 - 4k_3k_4 \right)
\]

\[
\alpha_2 = \frac{1}{2} \left( k_2 + k_3 + k_4 - \frac{1}{4} (k_2 + k_3 + k_4)^2 - 4k_3k_4 \right)
\]

where CMrGlc is the circulatory metabolic rate of glucose, Cp is the serum glucose level (mg/dl), LC is the lumped constant, which indicates the ratio of FDG uptake to glucose uptake, Ci(T) is radioactivity of FDG in the brain at time T, and \( \otimes \text{Cp}(t) \) denotes the convolution of plasma activity of FDG. The \( k \) values were fixed as follows (\( k_1 \) in ml/min/g; \( k_2, k_3 \), and \( k_4 \) in min⁻¹): \( k_1 = 0.102, k_2 = 0.13, k_3 = 0.062, k_4 = 0.0068 \).

The normal range of the circulatory metabolic rate of glucose of the cervical cord has not been measured precisely. After injection of FDG, Kamoto, et al.,21 measured glucose metabolism of the normal spinal cord by using a camera similar to that used in the present study. They reported that the normal glucose metabolic rate of the cervical spinal cord was 1.93 ± 0.37 mg/100 g/min g of brain (mean age 65.5 ± 8.5 years), which was consistent with the rate reported earlier by Di Chiro, et al.,10 of 1.7 ± 0.6 mg/100 g/min g of brain, taking into consideration the difference of the spatial resolution of the different PET cameras. The SUV is the tissue activity normalized with the injected dose per body weight (mg/ml).21 The SUV is linearly related to the metabolic rate of glucose with the assumption of a negligible \( k_4 \) value:20

\[
\text{MrGlc} = \frac{\text{Cp} \cdot \text{Ki}}{\text{LC}}
\]

\[
\text{Ki} = \frac{\text{KpVo}}{\text{SUV}}
\]

where MrGlc is the metabolic rate of glucose, Ki is the net influx constant \( k_1 \cdot k_3 / (k_2 + k_3) \), Kp is the mean plasma clearance rate of FDG up to the imaging time (uptake period), and Vo is the initial distribution volume of FDG. The Kp and Vo are known to be relatively constant across individuals.29 Hence, SUV reflects the MrGlc, and with euglycemic conditions and constant uptake period, quantitative comparison across individuals is possible. In the present study, we tentatively used the SUV to report the level of glucose utilization in the cervical cord, similar to the studies of Mazziotta and colleagues,25,26 Kim, et al.,24 and Shields, et al.20
To determine the aforementioned parameters of cervical cord glucose metabolism, round ROIs, each 10.3 mm in diameter (21 pixels), were placed on the spinal cord in every transaxial slice (Fig. 1), and sagittal images were used as an “on-line” reference to place ROI. During placement of ROI, a sagittal MR image served as reference to match the level of the ROI placed with the entire cervical spinal cord. The maximal count in the ROI was then adopted as the tissue radioactivity to eliminate the partial volume effect caused by the slightly larger size of the ROI than the diameter of the spinal cord.12,15,19,23 The ROI values at all levels of the cervical cord were averaged to calculate the mean SUV. These values represented the metabolic activity of the cervical spinal cord as a whole.

Statistical Analysis

We then examined the correlation between ages, duration of symptoms, JOA scores, and mean SUV by using the Spearman correlation test running the SPSS11.0J program (SPSS, Inc., Chicago, IL) with the level of significance set at a probability value less than 0.05. The relationships between high signal intensity on T2-weighted MR images and other clinical data were examined using the Mann–Whitney U-test.

Results

Summary of Clinical and Neuroimaging Data

Table 2 provides a summary of data obtained in all 23 patients included in the study. Symptoms and signs of myelopathy exhibited in all patients with a mean JOA score of 13.5 ± 2.3 preoperatively (range 8–16). Neurological improvement was observed postoperatively in all patients, and the mean follow-up score increased to 15.5 ± 1.8 (range 10–17). Thus, the rate of postoperative neurological improvement was 67.6 ± 25.6% (range 22.2–100%). The mean metabolic rate of glucose of the compressed cervical cord was 2.14 ± 0.41 mg/100 g/min (range 1.52–3.08 mg/ml). On preoperative T2-weighted MR images, focal high intensity areas within the cord at and around the level of compressive lesions were demonstrated in 12 patients.

Correlation Between Mean SUV and Other Parameters

Figure 2 provides a preoperative T2-weighted midsagittal MR image, a midsagittal PET image, and the SUV values at various cervical vertebral levels in a representative patient (Case 15). The preoperative SUV value averaged across the entire cervical spinal cord in this patient was higher than the mean value calculated for all patients. In Case 15, pre- and postoperative neurological scores were 14 and 17, respectively, and the surgery-related outcome was excellent (rate of neurological improvement 100%).

Figure 3 provides a preoperative T2-weighted midsagittal MR image, a midsagittal PET image, and the SUV values at various cervical vertebral levels obtained in another patient (Case 7). The preoperative SUV value averaged across the entire cervical spinal cord was low relative to the mean value calculated in all patients. In Case 7, preoperative neurological scores were 10 and 12, respectively, and the surgery-related outcome was fair (rate of neurological improvement 28.5%).

The estimated SUV at the affected vertebral level did not show a consistent pattern relative to that of unaffected segments in most patients. There was no significant correlation between the mean SUV in patients with myelopathy and age (r = −0.107, p = 0.626), nor duration of symptoms (r = 0.036, p = 0.869). The mean SUV in patients with myelopathy correlated significantly with JOA scores (r = 0.497, p = 0.016) measured preoperatively (Fig. 4A). Although there was a trend for an increased JOA score postoperatively with high SUV, the correlation was significant (r = 0.595, p = 0.003, Fig. 4B). The mean SUV correlated significantly with the rate of neurological improvement postoperatively (r = 0.538, p = 0.008 [Fig. 4C]).

Correlation of High-Intensity Areas on MR Imaging and Other Parameters

The presence of a high-intensity area on T2-weighted MR imaging did not correlate with age at surgery, duration of symptoms, preoperative JOA score, postoperative JOA score, and the mean SUV (Table 3).

Discussion

The capacity of the damaged spinal cord to recover functionally is a subject of great interest. Many attempts...
have been made neuroradiologically to understand the reversibility of neurological dysfunction of the spinal cord. Because profound paresis reflects serious spinal cord damage, we have been interested in correlating this neurological symptom, as well as surgery-related outcome, with MR imaging abnormalities. In this regard, Weirich, et al., correlated changes in MR signal with the histopathological changes in a model of acute spinal cord compression. These signal intensity changes, however, do not always reflect cord function or neurological prognosis, particularly in chronic cases with progressive OPLL. At present, we believe that MR imaging is the most valuable tool for assessing the extent and degree of the compressive lesion impinging on the spinal cord, although not for investigating spinal cord function itself. In this regard, we agree with Budinger and Taylor that PET imaging may be useful for examining the functional activity of the damaged tissue, including the spinal cord.

To our knowledge, Di Chiro, et al., were the first group to demonstrate and quantitate the FDG utilization rate of the cervical cord in 34 healthy volunteers and patients by using a high-resolution PET scanner (Neuro-PET; National Institutes of Health, Bethesda, MD), with a maximum resolution of 6 mm. In their reports, the mean glucose utilization of apparently normal upper cervical cord was 1.7 ± 0.6 mg/100 g/min. They also described asymmetrical utilization of glucose in patients with high- or low-grade neoplasm of the spinal cord. More recently, Higano and coworkers used [11C]methylionine–PET scanning to identify the pathological viability of a cervical intramedullary ependymoma, and they stressed the potential usefulness of PET for assessing spinal cord function. Although our FDG-PET results may be of a preliminary nature, we derived important information regarding circulatory glucose utilization. In patients with profound myelopathy, low glucose utilization rates tended to be present compared with healthy individuals. These findings might reflect reduced metabolic activity of the cervical cord or motor neurons. Furthermore, the preoperative glucose utilization rate also tended to correlate with the postoperative neurological score. The mean SUV in patients with myelopathy also correlated significantly with the rate of neurological improvement postoperatively. Analysis of these findings indicates that PET scanning may be useful for evaluating neurological prognosis—that is, the preoperative glucose utilization rate can probably be used to predict the neurological outcome after surgery. Admittedly, our results showed some degree of overlap in the mean SUV despite the presence of similar neurological features of myelopathy. The exact mechanism of such variability in glucose utilization rate is unclear. During the early stages of the disease, spinal cord compression may result in increased neuropeptide metabolic activity in neurons and glial cells in response to external pressure stimulation, possibly increasing glucose utilization. This notion is based on recent studies performed in our laboratory. Using a specific murine (twy/twy) model of spinal cord mechanical compression, our group also found a significant increase in the total area of somatic bodies as well as the number and length of dendrites of cervical cord motor neurons in response to compression. In 24-week-old twy mice with severe compression, the expression levels of neurotrophins were significantly higher at the rostral and caudal sites immediately adjacent to the compression injury.

![Image](image_url)
to the maximal compression site. Such neuronal response may also occur in human cervical cord in the presence of a variable level of compression, which may explain the increased SUV. It has also been postulated that a diminished number of anterior and/or posterior gray horn cells, in response to necrosis- and, possibly, neural apoptosis–induced injurious stimuli, may also influence glucose use. We have recently described a significant decrease in the number of anterior gray horn cells that correlated linearly with a reduction in the transverse area of the cervical cord. Unlike the cerebrum and cerebellum, the transverse area of the cervical cord is small, and thus the effect of object size on quantification during PET imaging must be carefully considered. As Di Chiro, et al., have acknowledged, the hindrance to accurate measurement of glucose use in this comparatively small structure is the poor resolution of the PET scans. Thus, the use of a high-resolution scanner, similar to that in our study, is essential to compensate for the reduced volume. In the present study, data acquisition was performed using two-dimensional image analysis software, resulting in a reduced sensitivity. Perhaps refinement of the analysis software will improve the measurement of glucose utilization values. Furthermore, placement of ROIs on multiple transverse slices of PET images is another significant concern. Referring to the morphometric data in normal cadavers described by Kameyama, et al., the transverse area of the cervical spinal cord in Japanese individuals ranged from 51.2 ± 1.2 mm² at C-8 to 58.5 ± 7.2 mm² at C-6, whereas that of the gray matter ranged from 7.2 ± 1.2 mm² at C-3 to 10.7 ± 1.3 mm² at C-7. In a clinical study, we recently demonstrated that the transverse area of the cervical spinal cord in patients with compressive myelopathy is reduced by approximately two thirds relative to that measured in uncompressed control conditions. On the other hand, Fukushima, et al., demonstrated a significant re-

### TABLE 2

**Summary of clinical status and radiographic data***

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Duration of Symptoms (mos)</th>
<th>Disease</th>
<th>Affected Level(s)</th>
<th>Surgical Procedure</th>
<th>JOA Scores (before/after surgery)</th>
<th>Extent of Improvement (%)</th>
<th>MrGlc (mg/100 g/min)</th>
<th>SUV (mg/ml)</th>
<th>Intensity High/T2 Signal†</th>
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* ant = anterior decompression (Robinson procedure); CDH = cervical disc herniation; CSM = cervical spondylotic myelopathy; MrGlc = metabolic rate of glucose; OPLL = ossification of the posterior longitudinal ligament; post = C3–7 laminoplasty; Subt = subtotal spondylectomy.† High-intensity area demonstrated on MR imaging.
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Fig. 2. Case 15. A preoperative T₂-weighted MR image (TR 1580 msec, TE 80 msec; A) and PET image (B) in a 42-year-old woman with OPLL at C-5 and C-6. The pre- and postoperative neurological assessment scores were 14 and 17, respectively (100% neurological improvement). C: The mean preoperative SUV was $2.7 \pm 0.13$ mg/ml.

Fig. 3. Case 7. Preoperative T₂-weighted MR image (TR 4000 msec, TE 100 msec; A) and PET image (B) in a 53-year-old man with centrally protruded spondylosis at C3–4. The pre- and postoperative neurological assessment scores were 10 and 12, respectively (28.5% neurological improvement). C: The mean preoperative SUV was $1.67 \pm 0.13$ mg/ml.
duction in cervical cord function when the transverse area of the cord measured directly on MR images was less than 45 mm². Bearing these morphometric descriptions in mind, one should be extremely careful when placing an ROI during FDG-PET scanning, particularly in conditions associated with a considerable reduction in transaxial area of the spinal cord or any other similar deformation.

We conclude that using FDG-PET imaging can provide qualitative and quantitative measures of diminished metabolic activity of the compromised cervical cord in patients with compressive myelopathy, and that these values correlate with the score of neurological deficit. Although many aspects of this technique remain to be resolved to optimize the procedure, this PET scanning technique is expected to be of value in assessing the metabolic activity of the compressed cervical cord.

Conclusions

We conclude that FDG-PET scanning provides qualitative and quantitative measurement of reduced metabolic activity of the compromised cervical spinal cord in patients with compressive myelopathy. Examination of the current results indicates that PET imaging is potentially useful for the assessment of metabolic activity of the compromised cervical spinal cord, which is impossible when using other conventional neurodiagnostic modalities.

References

High-resolution FDG-PET for cervical myelopathy


Manuscript received November 11, 2003.
This work was supported in part by grants from the Japanese Orthopaedics and Traumatology Foundation Incorporated (Grant no. 0082, Maruho Award, 1996), and the Investigation Committee on Ossification of the Spinal Ligaments, Public Health Bureau of the Japanese Ministry of Health and Welfare (2000–2002).
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