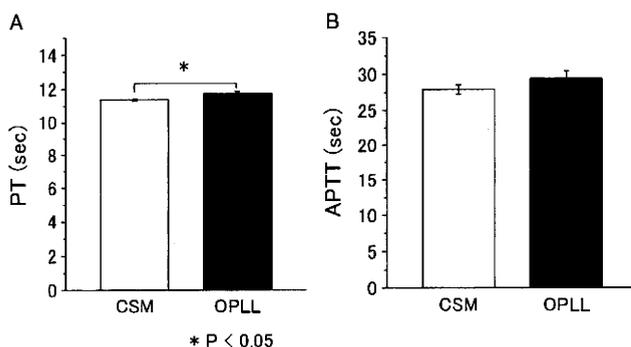


**FIGURE 6.** Bleeding time. Bleeding time was 1.5 ± 0.1 in CSM (n=23) and 1.6 ± 0.2 in OPLL (n=12). CSM indicates cervical spondylotic myelopathy; OPLL, ossification of the posterior longitudinal ligament.

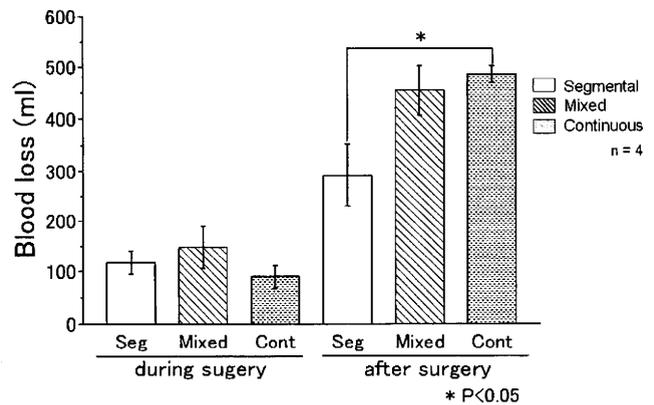
than that in patients with segmental type, but not significant (P = 0.08).

**DISCUSSION**

Spinal ligaments undergo hypertrophy, chondrification, and often ossification. Spine surgeons recognize 3 syndromes associated with this phenomenon, including (1) Forestier disease (involving anterior longitudinal ligaments) and more diffuse variants (exhibiting additional extra-axial features) being termed DISH, (2) OPLL, and (3) ossification of the vertebral arch ligaments. OPLL has been further classified into segmental type, continuous type, and mixed type. Progress in ossification compresses the spinal canal, resulting in various neurologic symptoms. However, this classification is anatomically and rather expedient. The etiologic difference between DISH and OPLL has still not been clear and the relationship between these types and



**FIGURE 7.** Coagulation factors assessed by prothrombin test (PT) and activated partial thromboplastin time (APTT). A, PT was 11.4 ± 0.1 in CSM (n=23) and 11.7 ± 0.1 in OPLL (n=12). B, APTT was 27.9 ± 0.7 in CSM (n=23) and 29.5 ± 1.0 in OPLL (n=12). CSM indicates cervical spondylotic myelopathy; OPLL, ossification of the posterior longitudinal ligament.



**FIGURE 8.** Blood loss of OPLL during and after surgery. (1) Blood loss during surgery was 117.5 ± 23.2 in segment type (n=4), 148.3 ± 42.0 in mixed type (n=4) and 90 ± 21.6 in continuous type (n=4). (2) Blood loss after surgery was 291.3 ± 61.0 in segment type (n=4), 455.0 ± 48.0 in mixed type (n=4) and 486.3 ± 17.0 (n=4) in continuous type. OPLL indicates ossification of the posterior longitudinal ligament.

tendency of ossification have not been elucidated. The systemic factors, which can distinguish them definitely, have been clinically requested.

Polymorphism of many genes and many growth factors or cytokines has been demonstrated in various histologic,<sup>18,19</sup> pathologic,<sup>20</sup> biologic<sup>21-29</sup> studies on OPLL. Local factors such as mechanical stress,<sup>21,22,29-31</sup> systemic factors (parathyroid hormone and insulin-like growth factor-I), and genetic factors [ColA1(6),<sup>23,26</sup> ColA2(11),<sup>32,33</sup> NPPS,<sup>34-37</sup> leptin receptor,<sup>35</sup> TGF-β1,<sup>25,38,39</sup> PLZF,<sup>27,28</sup> TSG-6,<sup>28</sup> CTGF,<sup>29</sup> PGI<sub>2</sub>,<sup>30</sup> etc] have been suggested to be candidates for causes of this disease. Several factors, including genetic background, have been postulated in the etiology of OPLL (multifactorial inheritance). Recent advances in molecular genetics have shown remarkable progress in the research for complex diseases. However, thus far, none of the genetic factors has been statistically linked to the disease state of OPLL, most likely owing to the complexity of the disease.

Parameters concerning the surgery (operation time and duration of drainage) were fairly equal between OPLL and CSM patient groups. In cardiovascular parameters, blood pressure before surgery and at 1 hour after surgery started and maximum blood pressure during surgery were almost the same between 2 patient groups. On the other hand, the coagulation factors assessed by PT were statistically high in OPLL compared with that in CSM; however, the difference was small and within normal limit. APTT, bleeding time, and blood loss during surgery showed increasing tendency in OPLL, but the difference was not significant. Only blood loss after surgery showed a significant difference. Interestingly, the value varied among OPLL types, that is, the value of patients with continuous type of ossification was significantly higher than of patients with segmental type of ossification, which was nearly equal to that of CSM

patients. In the case of mixed type of ossification, the value was the middle of segmental and continuous types. There was not significant difference in the surgery method (C3 laminectomy + C4-7 laminoplasty). These observations suggest a relation between the disease state of OPLL and microangiopathic dysfunction, that is, breeding tendency, which may be due to microangiogenic dysfunction but not an abnormality of the coagulation system. Furthermore, continuous and mixed types may have to be considered separately with a segmental type of OPLL.

Recent etiologic studies on ectopic bone formation, such as DISH and OPLL, suggest that its ossification occurs through the endochondral pathway.<sup>29,40-43</sup> In the physiologic endochondral ossification of bone tissue, invasion of blood vessels into cartilaginous template plays an indispensable role, because migration of osteoblasts and osteoclasts occurs through the vessel formed.<sup>29,40-43</sup> Our comprehensive study using microarrays indicates differences in the expression profiles of not only osteogenesis and chondrogenesis-related genes but also angiogenesis-related genes between OPLL patients and CSM patients.<sup>14</sup> Recently, blood loss during surgery have been reported to be the bleeding tendency in OPLL group; it was not significant.<sup>44,45</sup> Our results were not significant during surgery, too; but in this study, it was found that patients with continuous type of ossification show a tendency of breeding and significant blood loss after surgery compared to CSM patients. Therefore, some abnormality of angiogenesis in the OPLL lesion may play an important role in ectopic bone formation. Targeting the phenomena may be beneficial for advances in not only diagnosis but also the therapy of OPLL.

#### ACKNOWLEDGMENTS

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## Cervical myelopathy in patients with ossification of the posterior longitudinal ligament

### Clinical article

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**Object.** The authors assessed the clinical course in patients with a narrowed cervical spinal canal caused by ossification of the posterior longitudinal ligament (OPLL), but who have no or only mild myelopathy. Additionally, the authors analyzed the factors contributing to the development and aggravation of myelopathy in patients with OPLL-induced spinal canal stenosis.

**Methods.** Between 1997 and 2004, the authors selected treatments for patients with cervical OPLL in whom the residual space available for the spinal cord was  $\leq 12$  mm. Treatment decisions were based on the severity of myelopathy at presentation. Twenty-one patients with no or mild myelopathy (defined as a Japanese Orthopaedic Association [JOA] scale score  $\geq 14$  points) received conservative treatment, with a mean follow-up period of 4.5 years. In 20 patients with moderate or severe myelopathy (JOA scale score  $< 14$  points), the authors performed surgery via an anterior approach. The clinical course in these patients was assessed with the JOA scale and the OPLL types were classified. The authors evaluated the range of motion between C-1 and C-7, the developmental segmental sagittal diameter, the percentage of spinal canal diameter occupied by the OPLL (% ratio), and the residual space available for the spinal cord on cervical radiographs; T2-weighted MR images were examined for high signal changes (HSCs).

**Results.** In the conservative treatment group, 8 patients showed improvement, 12 remained unchanged, and 1 patient's condition became slightly worse during the observation period. Fifteen patients in this group had mixed-type, 3 had continuous-type, 2 had localized-type, and 1 had a segmental-type OPLL. In the surgically treated group, there were 12 patients with segmental-type, 10 patients with mixed-type, and 1 with localized-type OPLL. The mean range of motion at C1–7 was  $36.4^\circ$  in the conservatively treated group and  $46.5^\circ$  in the surgical group ( $p < 0.05$ ). No significant difference was seen between the groups in terms of developmental segmental sagittal diameter, % ratio, or residual space available for the cord. No HSCs were noted in the conservative group, while 17 patients in the surgical group had HSCs ( $p < 0.05$ ).

**Conclusions.** In the present study, the authors demonstrate that the mobility of the cervical spine and the type of OPLL are important factors contributing to the development and aggravation of myelopathy in patients with OPLL-induced spinal canal stenosis. The authors advocate conservative treatment in most patients with OPLLs who have no or only mild myelopathy, even in the presence of spinal canal narrowing. (DOI: 10.3171/2008.10.SPI08480)

**KEY WORDS** • myelopathy • ossification • posterior longitudinal ligament • stenosis

**I**N patients with OPLL of the cervical spine, the heterotopic ossified mass frequently occupies a considerable area of the spinal canal, resulting in a decrease in space available for the spinal cord (Fig. 1 upper). When compression myelopathy secondary to OPLL is

severe, most surgeons suggest surgical decompression of the spinal cord from an anterior and/or posterior approach.<sup>6</sup> The optimal treatment for patients with cervical OPLL and decreased space for the cord who have no or only mild myelopathy has been controversial, however. Some authors have advocated early surgery in patients with mild myelopathy,<sup>12</sup> and some have even suggested prophylactic surgery in patients without myelopathy.<sup>2</sup> In contrast, other authors have recommended conservative treatment.<sup>7</sup> In deciding on the best treatment for a particular patient with cervical OPLL who has no or only mild

Abbreviations used in this paper: DSSD = developmental segmental sagittal diameter; HSC = high signal change; JOA = Japanese Orthopaedic Association; OPLL = ossification of the posterior longitudinal ligament; ROM = range of motion.

## Cervical myelopathy in patients with OPLL

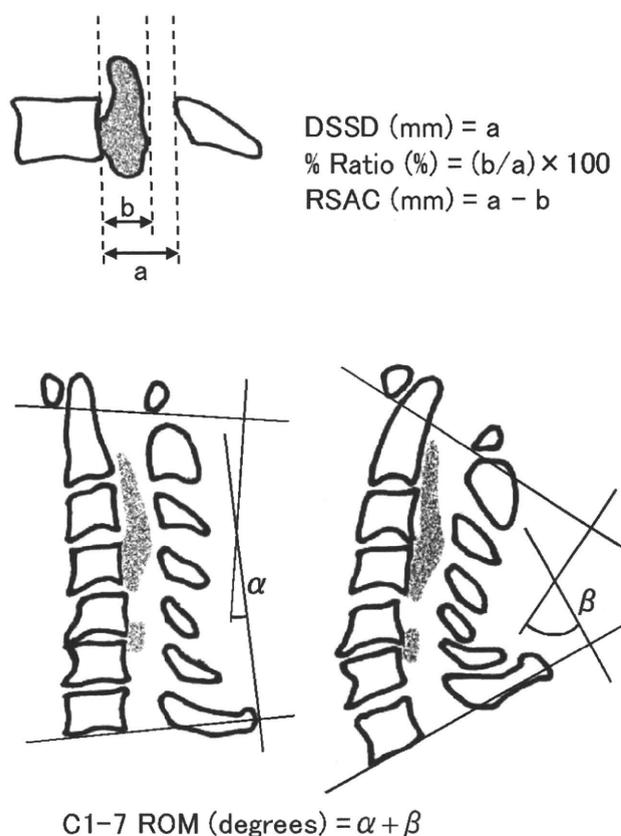


FIG. 1. Schematic drawings of radiographic parameters. In lateral cervical radiographs (upper), we measured the DSSD, % ratio, and the residual space available for the spinal cord (RSAC). In flexion and extension radiographs (lower), we evaluated the ROM between C-1 and C-7.

myelopathy, it is important to predict the neurological course as precisely as possible. To date, however, there have been only a few reports on neurological changes in patients who receive conservative management of their disease.<sup>10</sup> In addition, the factors that contribute to myelopathy in patients with cervical OPLL and spinal canal narrowing have yet to be fully established.

Since 1997, we have selected treatments for patients with cervical OPLL based principally on the severity of myelopathy at the initial consultation, regardless of the degree of residual space available for the cord. In patients with OPLL who have no or only mild myelopathy (cervical myelopathy JOA scale score  $\geq 14$  points), we have taken a conservative approach. In patients with moderate or severe myelopathy (JOA scale score  $< 14$  points), we have performed surgery via an anterior approach.

The purpose of the present study was to assess the clinical course in patients with spinal canal narrowing due to OPLL, but who have no or mild myelopathy. We also investigated the factors contributing to the development and aggravation of myelopathy in patients with OPLL-induced spinal canal stenosis. Based on our results, we discuss the appropriate timing of surgery in patients with cervical OPLLs.

TABLE 1: Clinical data\*

Characteristic	Conservative Tx Group (21 patients)	Surgical Tx Group (20 patients)
sex		
male	12	16
female	9	4
age at 1st visit (yrs)	61.1 $\pm$ 8.7 (48–75)	—
age at op (yrs)	—	59.4 $\pm$ 10.4 (42–74)
FU period (yrs)		
1st visit to final FU	4.2 $\pm$ 2.7 (1–10)	—
op to final FU	—	3.6 $\pm$ 0.8 (3–5)

\* Except as otherwise noted, values are expressed as the means  $\pm$  SDs with the range in parentheses. Abbreviation: FU = follow-up.

## Methods

### Patient Population

Between January 1997 and December 2004, 99 patients with cervical OPLLs in whom the residual space available for the cord at the cervical spine was  $\leq 12$  mm visited our institute for an initial consultation. We selected a treatment procedure for these patients based on extent of myelopathy: patients with no or mild myelopathy (JOA scale score  $\geq 14$  points) were followed up conservatively, and patients with moderate or severe myelopathy (JOA scale score  $< 14$  points) underwent surgical treatment.

Of our 99 patients, 21 had a JOA scale score  $\geq 14$  points at the initial consultation and received conservative treatment (Table 1). The conservative group included 12 men and 9 women, with a mean age at initial consultation of 61.1 years (range 48–75 years). The mean follow-up period from the first visit to the final examination was 4.2 years (range 1–10 years). Eleven patients underwent follow-up for  $< 5$  years and 10 patients for  $\geq 5$  years. Of the 99 patients, 78 had JOA scale scores  $< 14$  points; these patients underwent surgical treatment via an anterior approach. To match the 2 groups in terms of numbers, we specifically chose patients who underwent surgery between 2002 and 2004. Of these 24 patients, 20 patients attended follow-up for  $\geq 1$  year and were included in our final analysis. The surgery group included 16 men and 4 women with a mean age at surgery of 59.4 years (range 42–74 years). In all 20 patients, surgeries were performed with anterior excision of OPLL foci and placement of an arthrodesis with a strut autograft using either fibula or iliac crest. After surgery, these patients attended follow-up for a mean of 3.6 years (range 3–5 years).

### Clinical Assessment

The JOA scale was used to evaluate the severity of cervical myelopathy.<sup>6</sup> Patients with mild myelopathy who increased their JOA scale score by  $\geq 1$  point were said to have improved, and those with a decrease of  $\geq 1$  point

TABLE 2: Clinical results

Parameter	Conservative Tx Group (21 patients)	Surgical Tx Group (20 patients)
JOA scale score		
1st visit	15.6 ± 0.9 (14–17)	—
before op	—	10.2 ± 2.3 (6–13.5)
at FU	16.4 ± 1.0 (14.5–17)	15.1 ± 1.8 (10–17)
postop recovery ratio (%)	—	74.6 ± 20.6 (30.8–100)
outcome after conservative tx*		
improved (%)	8 (38.1)	—
unchanged (%)	12 (57.1)	—
worsened (%)	1 (4.8)	—

\* Improvement was defined as a ≥ 1-point gain in JOA scale score, unchanged status was gain or loss of < 1 point, and worsening was defined as the loss of > 1 point. Except as when otherwise noted, values are presented as means ± SDs with the range in parentheses.

were said to have worsened. When JOA scale scores increased or decreased by < 1 point, this was recorded as unchanged. In surgically treated patients, scores obtained before surgery and at the final follow-up examination were evaluated and a recovery rate was calculated.<sup>6</sup>

#### Radiographic Assessment

Using lateral cervical radiographs, we measured the DSSD, the percentage of the spinal canal diameter occupied by the OPLL (% ratio), and the residual space available for the cord (Fig. 1 upper). The types of OPLL were classified as continuous type, mixed type, segmental type, and localized type, according to the criteria of the Japanese Investigation Committee on the Ossification of the Spinal Ligaments.<sup>14</sup> We evaluated the ROM between C-1 and C-7 on flexion and extension radiographs (Fig. 1 lower), and spinal cord HSCs were assessed on T2-weighted MR images.

#### Statistical Analysis

The Mann-Whitney U-test and Fisher exact probability test were applied for statistical analyses. Probability values < 0.05 were considered significant; results are presented as the means ± SDs.

### Results

Of the 21 patients in the conservative treatment group, 6 showed no sign of myelopathy and 15 had mild myelopathy at the initial consultation. In the 6 patients without myelopathy, radiographs were originally obtained because the patients complained of neck stiffness or pain. All 6 remained neurologically unchanged during

TABLE 3: Radiographic data at the initial consultation\*

Parameter	Conservative Tx Group	Surgical Tx Group
OPLL type (no. of patients)		
continuous	3	0
mixed	15	7
segmental	1	12†
localized	2	1
DSSD (mm)		
mean ± SD	14.9 ± 1.3	15.0 ± 1.1
range	13–17	13–17
% ratio		
mean ± SD	46.6 ± 11	40.0 ± 12
range	25–63	25–61
RSAC (mm)		
mean ± SD	7.9 ± 1.5	9.3 ± 1.9
range	6–11	6–12
C1–7 ROM (°)		
mean ± SD	36.4 ± 14.0	46.5 ± 9.3†
range	15–62	26–64
ROM (no. of patients)		
≥35°	11	19†
<35°	10	1
HSC status (no. of patients)		
negative	21	3
positive	0	17†

\* RSAC = residual space available for cord.

† Indicates statistically significant difference compared to the conservative treatment group (p < 0.05).

the follow-up period. Of the 15 patients with myelopathy, 8 showed improvement, 6 remained unchanged, and in 1 patient the myelopathy worsened. The mean JOA scale score at the initial consultation in the conservatively treated group was 15.6 points (range 14–17 points), and 16.4 points at follow-up (range 14.5–17 points) (Table 2). In the surgical group, the mean preoperative JOA scale score was 10.2 points (range 6–13.5 points) and 15.1 points at the most recent follow-up (range 10–17 points). The mean recovery rate was 74.6% (range 30.8–100%).

Cervical radiographs and MR images obtained at the initial consultation were analyzed to clarify the morphological characteristics of the OPLLs. In the conservative treatment group, 15 patients had mixed-type, 3 had continuous-type, 2 had localized-type, and 1 had a segmental-type OPLL. In the surgical treatment group 12 patients had segmental-type, 7 had mixed-type, and 1 had a localized-type OPLL (Table 3). The incidence of segmental-type OPLL was significantly higher in the surgical than the conservative treatment group (p < 0.05).

The mean DSSD was 14.9 mm (range 13–17 mm) in the conservative group and 15 mm (range 13–17 mm) in the surgically treated group. The % ratio was 46.6%

## Cervical myelopathy in patients with OPLL

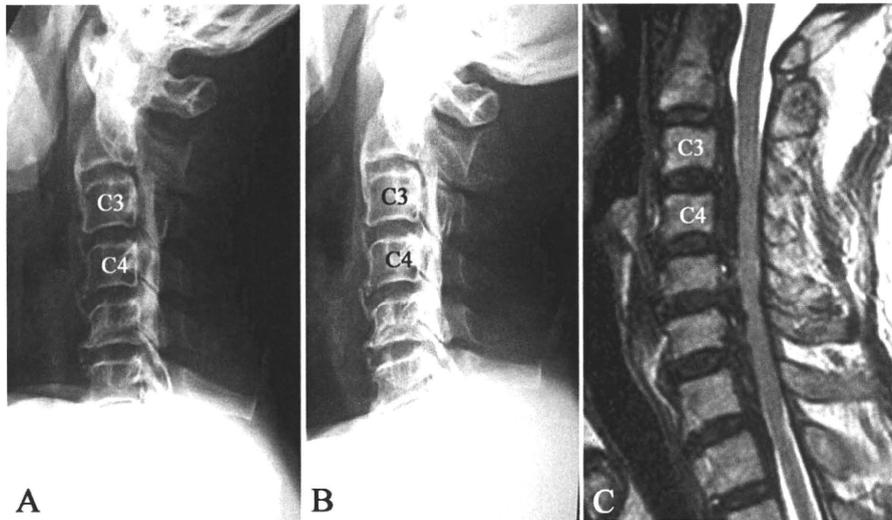


FIG. 2. Case 1. Flexion (A) and extension (B) cervical radiographs obtained at presentation in a patient with mixed-type OPLL. The residual space available for the cord is 7 mm at C3–4, and the C1–7 ROM is 23°. Anterior impingement of the spinal cord at several levels is visible on a T2-weighted, midsagittal MR image (C), but no HSCs are visible.

(range 25–63%) in the conservative group and 40% (range 25–61%) in the surgical group. The residual space available for the cord was 7.9 mm (range 6–11 mm) in the conservative group and 9.3 mm (range 6–12 mm) in the surgical group. No significant differences were seen on imaging data between the 2 groups.

The mean ROM at C1–7 at the initial consultation was 36.4° (range 15–62°) in the conservative treatment group and 46.5° (range 26–64°) in the surgical group. The mobility of the spinal column between C-1 and C-7 was therefore significantly greater in the surgical group ( $p < 0.05$ ). Nineteen of 20 patients in the surgical group had a C1–7 ROM  $\geq 35^\circ$ , whereas 11 of 21 patients in the conser-

vative treatment group had a C1–7 ROM  $\geq 35^\circ$  ( $p < 0.05$ ). The C1–7 ROM in the conservative group was measured until the most recent follow-up. The mean C1–7 ROM at the final follow-up examination was 33° (range 11–50°) in the conservative group, indicating that no significant changes had occurred since the initial consultation.

High signal changes on T2-weighted images were not seen in any patient in the conservative treatment group, whereas 17 patients in the surgical group had HSCs. Thus, the incidence of HSCs in the spinal cord was significantly higher among patients in the surgically treated group than in the conservative group ( $p < 0.05$ ). During the follow-up period, no HSCs developed in the conservative group.

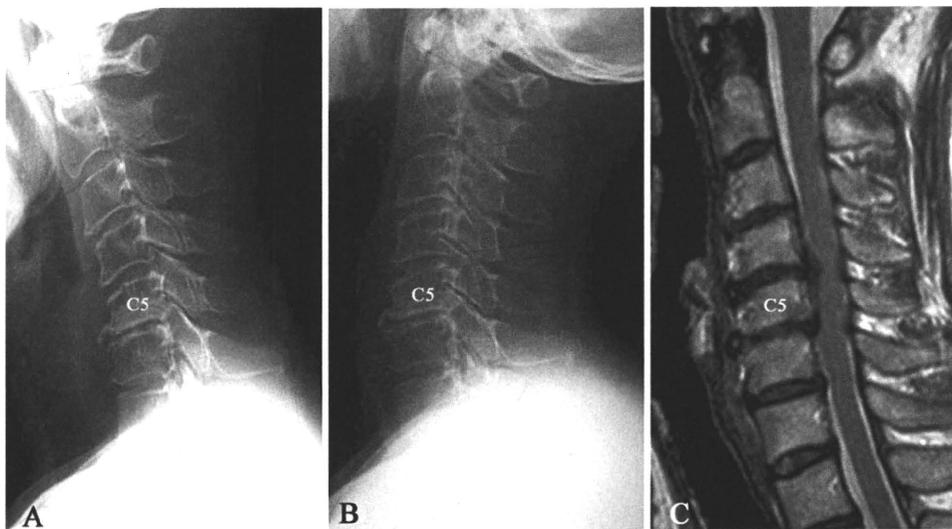


FIG. 3. Case 2. Flexion (A) and extension (B) cervical radiographs obtained at the initial visit in a patient with segmental-type OPLL. The residual space available for the cord is 9 mm at the C-5 level, and the C1–7 ROM is 52°. A T2-weighted midsagittal MR image obtained at presentation (C) indicates that impingement of the spinal cord at the C4–5 level is seen, but no HSCs are visible.

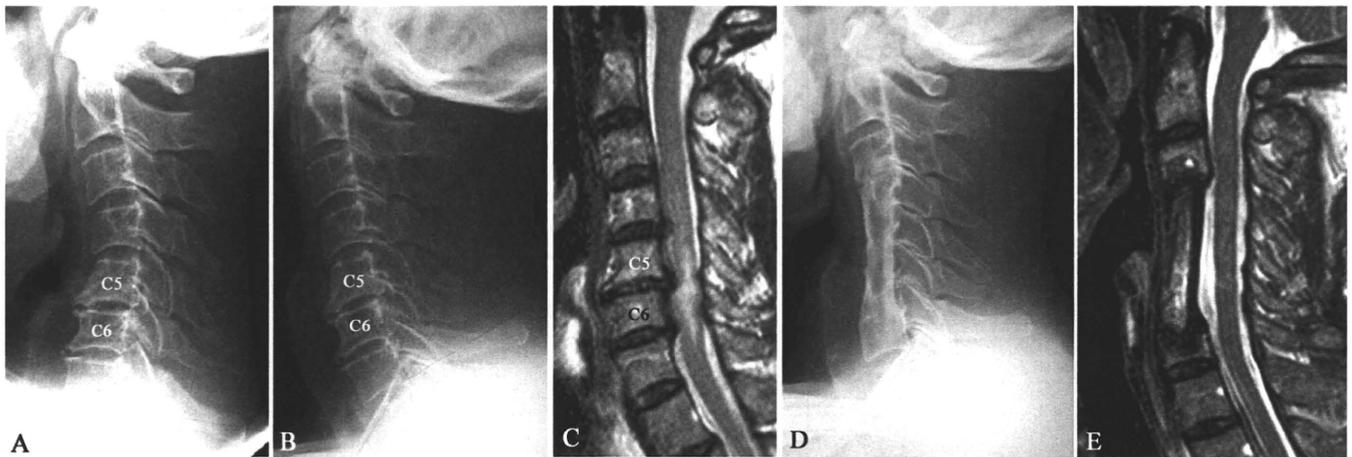


FIG. 4. Case 3. Flexion (A) and extension (B) cervical radiographs obtained at the initial visit in a patient with segmental-type OPLL. The residual space available for the cord was 10 mm at the C5–6 level, and the C1–7 ROM was 57°. A T2-weighted midsagittal MR image (C) obtained at presentation shows impingement on the spinal cord at multiple levels in both the anterior and posterior directions, and HSCs are evident in the spinal cord, especially at C5–6 and C6–7. Lateral cervical radiograph (D) obtained 2 years after surgery shows successful spinal fusion with fibula autograft. A T2-weighted midsagittal MR image obtained 1 year postoperatively (E) shows decompression and diminished cord HSCs.

### Illustrative Cases

#### Case 1: Patient in the Conservative Treatment Group Without Improvement

This 68-year-old man with mixed-type OPLL complained of neck stiffness for 20 years and was recommended for surgery. At the initial examination, he showed no sign of myelopathy and he had a JOA score of 17. A lateral cervical radiograph obtained at the first visit showed that the DSSD was 16 mm, % ratio was 56%, and the residual space available for the cord was 7 mm at the C3–4 level. Flexion and extension radiography revealed that the C1–7 ROM was 23°, indicating a relatively small amount of spinal mobility (Fig. 2A and B). Midsagittal T2-weighted MR images showed no HSCs in the spinal cord, although obstruction of the subarachnoid space with anterior impingement of the spinal cord was found at several levels (Fig. 2C). The patient was followed up conservatively. During the follow-up period of 2 years, his neck stiffness persisted but no myelopathy developed.

#### Case 2: Patient in the Conservative Treatment Group With Clinical Worsening

This 59-year-old woman presented with complaints of mild numbness in all of her fingers and bilateral clumsiness of her hands caused by segmental OPLL at C-5. Deep tendon reflexes were hyperactive in her lower extremities, but she did not have any gait disturbance; her JOA scale score was 15.5. A lateral cervical radiograph obtained at the first visit showed that the DSSD was 14.5 mm, % ratio was 38%, and residual space available for the cord was 9 mm at the C-5 level. Flexion and extension radiographs showed that the C1–7 ROM was 52°, indicating an extensive degree of spinal mobility (Fig. 3A and B). Midsagittal T2-weighted MR images showed impingement of the spinal cord at the C4–5 level from both

the anterior and posterior directions due to a thickened posterior longitudinal ligament and ligamentum flavum, but no signal change was seen in the spinal cord at this level (Fig. 3C). Over a 3-year follow-up period, the patient complained of increasing numbness and clumsiness, with a decreased JOA scale score of 14.5 points.

#### Case 3: Patient in the Surgical Treatment Group

This 58-year-old man presented with bilateral upper arm weakness and gait disturbance. A lateral cervical radiograph obtained at the first visit showed segmental type OPLL (C-4, C-5, C-6, and C-7) with a DSSD of 16 mm, % ratio of 37.5%, and 10-mm residual space for the cord at the level of C5–6. Flexion and extension radiographs demonstrated that the C1–7 ROM was 57°, an extensive degree of spinal mobility (Fig. 4A and B). Impingement of the spinal cord at multiple levels from both the anterior and posterior directions was shown on T2-weighted midsagittal MR imaging, and HSCs were evident in the spinal cord, especially at the C5–6 and C6–7 levels (Fig. 4C). The patient's preoperative JOA scale score was 11.5 points. He underwent anterior excision of OPLL and spinal fusion with fibula autograft. Postoperatively, the patient improved neurologically. Cervical radiographs obtained 2 years later revealed that spinal fusion was accomplished (Fig. 4D). Midsagittal T2-weighted MR images obtained 1 year postsurgery showed that the spinal cord was decompressed and the HSCs in the cord were diminished (Fig. 4E). At the final follow-up examination 3 years after surgery, the patient's JOA scale score was 16 points (recovery rate 81.8%).

### Discussion

In the present study, we assigned patients with cervical OPLL to treatment groups based on myelopathy se-

## Cervical myelopathy in patients with OPLL

verity and investigated the clinical course in patients with no or mild myelopathy despite the presence of OPLL-induced spinal canal narrowing. Of 21 patients with no or only mild myelopathy, newly developed myelopathy was not seen in any patient, and slight aggravation of preexisting myelopathy occurred in only 1 patient (4.8%). Thus, clinical symptoms were unchanged or improved in 95.2% of patients, although they had OPLL-induced spinal canal narrowing with  $\leq 12$  mm of residual space available for the spinal cord. These results suggest that our criterion for conservative treatment (a JOA scale score  $\geq 14$  points) is appropriate. On the basis of our findings in the present study, we suggest that decompression surgery at an early stage is not recommended in most patients with OPLL who have no or mild myelopathy, even in the presence of OPLL-induced spinal canal narrowing.

Regarding factors that influence the development of myelopathy in patients with cervical OPLL, several reports have demonstrated the importance of static compression factors, which are expressed in % ratios and measurements of the residual space available for the spinal cord.<sup>4,5,9,13</sup> In younger patients, such static compression factors preferentially contribute to the development and aggravation of myelopathy because of the presence of strong growth activity of the ossified mass.<sup>3</sup> In addition to static compression factors, recent reports have described dynamic factors, such as spinal column mobility, in the development of myelopathy in patients with a considerable degree of OPLL canal occupation.<sup>8,9,12</sup>

In the present study, the mobility of the cervical spine, which was analyzed as the C1–7 ROM, participated in the development of myelopathy in patients with OPLL-induced spinal canal narrowing, but the % ratio and the residual space available for the cord did not. In addition, our results indicate the contribution of the morphological subtypes of OPLL to the development of myelopathy. Patients with segmental-type OPLL generally have increased mobility of the cervical spine compared with patients with continuous-type OPLL. We speculate that when OPLL-induced canal stenosis develops in patients with segmental-type OPLL, the relatively larger cervical mobility is maintained and myelopathy will be more likely to occur than in patients with continuous-type OPLL. In the majority of patients who suffered from moderate and severe myelopathy and who underwent surgery, the C1–7 ROMs were  $\geq 35^\circ$  at the initial consultation. We therefore suggest that having a C1–7 ROM of  $\geq 35^\circ$  is a risk factor for the development or aggravation of myelopathy in patients with OPLL-induced canal stenosis. In support of this hypothesis is the fact that the only patient in the conservative treatment group (Case 2) who experienced clinical deterioration during the follow-up period had a  $52^\circ$  ROM at C1–7.

Previous studies have shown that high signal intensity in the spinal cord in T2-weighted MR images may correlate with some spinal cord disorders including attenuated venous circulation.<sup>1</sup> In the present study, the incidence of the HSCs was significantly higher in patients with moderate and severe myelopathy who underwent surgery. We suggest that increased myelopathy is more likely to occur in patients with cervical OPLL and spinal canal narrow-

ing who show high signal intensity on imaging at their initial presentation.

In view of our results and previous findings,<sup>9,11,12</sup> when we decide the treatment procedure for patients with OPLL-induced canal stenosis and no or mild myelopathy, conservative treatment is the first choice if 1) the C1–7 ROM is  $< 35^\circ$ ; 2) OPLL type is continuous; 3) the patient is older than 50 years of age; and 4) no HSCs are seen in the spinal cord on T2-weighted MR images. In contrast, surgical treatment is indicated if 1) the C1–7 ROM is  $\geq 35^\circ$ ; 2) OPLL type is segmental; 3) the patient is younger than 50 years of age and has activated growth activity of the ossified mass; and 4) a high signal intensity is seen in the spinal cord and there is a risk of myelopathy or aggravation of existing myelopathy. When we undertake surgery in patients with cervical OPLL and canal stenosis, we consider not only the need for spinal cord decompression but also the suppression of dynamic factors. Thus, we believe that complete excision of the ossified mass using an anterior approach in combination with the stabilization of the spine column with strut bone graft is theoretically the best procedure.

To the best of our knowledge, ours is the first study to base treatment in patients with cervical OPLL on the severity of myelopathy and to investigate the natural clinical course in patients with cervical OPLL and no or mild myelopathy. Our findings provide guidance for deciding on the appropriate timing of surgery in patients with cervical OPLL who have significant cord compression caused by OPLL and early myelopathy. Nevertheless, our retrospective study design and relatively small number of patients should be considered when interpreting the results.

## Conclusions

In the present study, we demonstrated that mobility of the cervical spine and morphological types of OPLL are important factors that can contribute to the development and aggravation of cervical myelopathy in patients with OPLL-induced canal stenosis. We advocate conservative treatment for most patients with OPLL and no or mild myelopathy, even in cases of spinal canal narrowing.

## Disclosure

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**141. Clinical application of MEG to mild cognitive impairments—Nobuyuki Nishitani (Fujita Neurological Clinic, Higashi-Osaka, Japan)**

Mechanisms of the dementia have gradually elucidated in aging society. Recently, there are many researches with MRI, SPECT, and PET focused on the mild cognitive impairments (MCI), for the establishment of the early diagnosis of MCI. However, it is a pivotal node to assess clinically the higher brain functions non-invasively and repetitively. We clarified the cognitive functions from normal subjects and subjects suffering from MCI with a whole head magnetoencephalography (MEG). Our studies showed the significantly decreased and delayed activities of the hippocampus of each hemisphere and the left posterior inferior frontal (PIF) area in the subjects with MCI, compared with the normal subjects. Both results were more significant in the subjects with Alzheimer's disease than MCI. Disorders of the cognitive processing in the left PIF area proposing the association with social communication suggest early cognitive impairments with social cognitive impairments. Based on these results, MEG is a useful method for early diagnosis of MCI as non-invasively neurophysiological clarification of the cognitive brain processing, and this method would produce precious information for clinical examination and basic brain researches of the cognitive disorders.

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**142. Brain functional monitoring in neonatal brain hypothermia—Masaki Shimizu (Neonatology, Saitama Children's Medical Center, Saitama, Japan)**

Neonatal brain hypothermia therapy (BHT) has been considered one of the therapeutic tools for hypoxic-ischemic encephalopathy (HIE), but BHT is insufficient to prevent basal ganglia injury in severe HIE. The efficacy and safety of neonatal BHT has not been established. Therefore, it has been considered to be the preliminary therapy for neonatal intensive care units in Japan. We must examine and monitor the brain function during BHT for strict managements of the infants. Electroencephalography, amplitude-integrated EEG (aEEG), and near infrared spectroscopy (NIRS) are available for non-invasive monitoring for the brain function during BHT. EEG and aEEG are useful for non-invasive neonatal brain functional monitoring to evaluate the real-time brain activity during BHT. Although EEG or aEEG play an important part in the prediction of neurodevelopmental outcome in severe HIE treated by BHT, the relation between EEG/aEEG and neurodevelopmental outcome have not been sufficiently evaluated. In the future, effective and safe method of BHT will be clarified about the cooling periods and re-warming rate on the basis of aEEG findings. NIRS is useful monitor of the cerebral blood perfusion during BHT. In the HIE, the cerebral blood perfusion and the oxygen consumption show abnormal findings on NIRS. Brain function monitoring with NIRS will be very important for the safe re-warming in BHT.

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**143. An trial of functional neuroimaging on the human spinal cord—Takefumi Ueno, Tatsunori Ikemoto, Takahiro Ushida, Toshikazu Tani (Kochi University and Kyushu University, Kochi and Fukuoka, Japan)**

Recent studies showed possibility of neuroimaging on the human spinal cord using functional MRI with EPI sequence (spiral sampling methods) or Spin Echo method. However, present general EPI method

was not suitably usable for the spinal (cervical) cord neuroimaging. Therefore, we tried to obtain EPI image by the modified protocol. Three healthy controls were recruited with written informed consent under the permission of Kochi University IRB committee. Participants were lied on the MRI scanner with closed eyes. The functional tasks consisted of 11 times pin prick stimulation about 1.2 Hz for 6 s and rest with the same duration (6 s). The parameters were following: FOV 16 × 16, TR 2000, TE 60, and BW 250 kHz. We obtained a relatively clear image and the activation area on the cervical cord with the general linear model by using Box-car curve. This study showed the possibility for the spinal cord neuroimaging.

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**144. Neuropsychological outcome of transsylvian selective amygdalohippocampectomy preserving the limen insula in patients with hippocampal sclerosis—Michiharu Morino<sup>1</sup>, Tsutomu Ichinose<sup>1</sup>, Satoko Ohfuji<sup>2</sup>, Kyoko Kondo<sup>2</sup>, Kenji Ohata<sup>1</sup> (<sup>1</sup>Department of Neurosurgery, Osaka City University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan)**

The present study was performed to investigate the effects of selective surgery on memory outcome in patients with hippocampal sclerosis treated by transsylvian selective amygdalohippocampectomy preserving the limen insula (TSA-PLI). The study population consisted of 70 patients who underwent left ( $n = 33$ ) or right ( $n = 37$ ) TSA-PLI. All patients underwent comprehensive neuropsychological testing before (preop.), 1-month (1MP), and 1-year (1YP) after unilateral TSA-PLI. Verbal memory I (VM-I), nonverbal memory I (NVM-I), total memory (TM), attention (AT), and delayed recall (DR) were assessed using WMS-R, while verbal memory II (VM-II), nonverbal memory II (NVM-II) were assessed using Miyake Verbal Retention Test, Benton Visual Retention Test. Separate repeated-measures multivariate analysis of variance (MANOVA) were performed for these intervals with memory scores. MANOVA indicated that right TSA-PLI showed significant improvements in VM-I (preop.-1MP~ $p < 0.0001$ ; preop.-1YP~ $p = 0.0002$ ), VM-II (preop.-1YP~ $p = 0.002$ ; 1MP-1YP~ $p = 0.037$ ), NVM-I (preop.-1MP~ $p = 0.0008$ ; preop.-1YP~ $p = 0.007$ ), TM (preop.-1MP~ $p < 0.0001$ ; preop.-1YP~ $p < 0.0001$ ) and DR (preop.-1MP~ $p = 0.006$ ; preop.-1YP~ $p = 0.01$ ) at both follow-ups. In the left TSA, VM-I&II were maintained at the same level 1-month after surgery, in addition, VM-II showed significant improvement 1-year after surgery ( $p = 0.04$ ). The present study indicated that left TSA-PLI tends to improve verbal memory function with preservation of other types of memory function. Moreover, right TSA-PLI can lead to significant improvement in memory function.

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**145. Alarm point of muscle evoked potentials after brain stimulation in intraoperative spinal cord monitoring—Kyohei Sakaki, Shigenori Kawabata, Atsushi Okawa, Yoshiyasu Arai, Tsuyoshi Kato, Kenichiro Sakai, Shoji Tomizawa, Ichiro Torigoe, Masaki Tomori, Senichi Ishii, Kenichi Shinomiya (Tokyo Medical and Dental University, Tokyo, Japan)**

Muscle evoked potential after brain stimulation (BR-MSEP) is widely used for intra-operative spinal cord monitoring, but critical point of BR-MSEP remains controversial. We reviewed critical point of BR-MSEP from our previous cases. he subject was a series of 394

operative cases that performed spinal cord monitoring using BR-MSEP. The alarm to surgeons consisted of disappearance of BR-MSEP wave, alteration of spinal cord evoked potential/SEP wave and surgical maneuver. Disappearance of wave form was shown in 50 cases. We alarmed in 15 cases among them. The postoperative neurological deficits developed in 3 cases: one case of medullary cone tumor whose wave form was not recovered after alarm, 2 cases that there was no disappearance of wave form. Those 3 cases showed segmental spinal disorder after decrease of amplitude below 30%. No postoperative neurological deficits due to long tract disorder were found in this study. Therefore we regard wave form disappearance as critical point of long tract disorder. We might be able to avoid segmental disorder by considering decline of amplitude below 30% as alarm point. However, a large number of false positive disturbs operation. We must distinguish the critical point of segmental disorder from that of long tract disorder.

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**146. Auditory brainstem responses (ABRs) in cerebellopontine angle tumors (CPAT)—Mikio Osawa, Takashi Maruyama, Hiroshi Sunose, Mutsumi Iijima, Ryosuke Ushijima, Shinichiro Uchiyama (Tokyo Women's Medical University, Tokyo, Japan)**

To determine whether there are any characteristic ABR findings in CPAT, ABRs were recorded in 45 patients with CPAT, including 28 with vestibular schwannoma, 10 with meningioma. ABRs ipsilateral to the stimulated ear were abnormal in 8 of the 45 patients, who did not show decreased hearing acuity ipsilateral to the CPAT. ABRs ipsilateral to the stimulation were abnormal in all patients with vestibular schwannoma ipsilateral to the stimulation. Among these patients, 9 of 11 (82%) patients showing no ABR components had tumors measuring 2 cm or more on brain MRI. ABRs contralateral to the stimulation were abnormal in 10 patients with vestibular schwannoma, 9 of whom had tumors measuring 2 cm or more. There was no significant correlation between the abnormality in II and/or the later components and the tumor size. Only one meningioma patient showed no ABR components. In conclusions, ABRs are sensitive to CPAT, especially vestibular schwannoma, even in patients without any clinically significant decrease in hearing acuity. The absence of all ABR components may indicate the presence of large CPAT measuring 2 cm or more and compression of the brainstem, which may evoke ABR abnormality contralateral to the stimulation.

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**147. Clinical applications of transcranial magnetic stimulation for the treatment of depression: How to determine the parameters of TMS based on the pathophysiology of depression—Shinsuke Kito (Kyorin University School of Medicine, Tokyo, Japan)**

Transcranial magnetic stimulation (TMS) is a noninvasive technique for stimulating the cerebral cortex and changing the cortical and subcortical functions. High-frequency TMS of the left dorsolateral prefrontal cortex and low-frequency TMS of the right dorsolateral prefrontal cortex have both been shown to have antidepressant effects, although its mechanism has still not been elucidated sufficiently. Recent brain functional imaging studies have revealed the several regions including the prefrontal, cingulate, orbitofrontal, and medial temporal regions involved in the pathophysiology of depression. For the treatment of depression, high-frequency TMS increases metabolism and cerebral blood flow in the

stimulation site as well as the remote regions via a neural pathway, and low-frequency TMS decreases metabolism and cerebral blood flow in the stimulation site as well as several broad regions. These findings raise the possibility that changes in neuroanatomical functions with improvements of depressive symptoms differ according to the site and frequency of the stimulation. We have investigated changes in regional cerebral blood flow by TMS using a SPECT study and biological features of depression associated with therapeutic efficacy, which contribute to how to determine to the parameters of TMS based on the pathophysiology of depression.

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**148. Comparison of the efficacy and safety between sine- and pulse-wave ECT methods—Sho Takahashi, Youichi Kawanishi, Fujita Toshiyuki Takafumi Hori, Nobutoshi Kawai, Fumihiko Yasuno, Katsuyoshi Mizukami, Takashi Asada (Psychiatry, University of Tsukuba, Ibaraki, Japan)**

Electroconvulsive therapy (ECT) is a popular therapy for psychiatric illness, and sine- and pulse-wave ECT methods are available at present. It has been said that the latter is superior to the former in the safety, however little evidence has been reported which compared efficacy and safety between the two methods. Therefore, we conducted such a comparison. The subjects are consecutive clinical cases that underwent pulse-wave ECT ( $n = 40$ ) between 2001 and 2005 and sine-wave ECT ( $n = 82$ ) between 2005 and 2007 at Tsukuba University Hospital. The efficacy of the sine- and the pulse-wave ECT for the patients with depressed mood was evaluated using the Hamilton rating scale for depression. The analysis revealed that the efficacy was similar between the two methods, and that sine-wave therapy had more occurrence rate for a variety of adverse events, while pulse-wave therapy did for blood pressure rise and tachycardia. In conclusion, even when we use a pulse-wave therapy, we must be cautious in such cardiovascular adverse events.

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**149. Electroencephalography neuroimaging of oscillatory activity in chronic interictal psychosis of epilepsy—Leonides Canuet, Ryouhei Ishii, Ryu Kurimoto, Masao Iwase, Koji Ikezawa, Michiyo Azechi, Hidetoshi Takahashi, Takayuki Nakahachi, Masatoshi Takeda (Department of Psychiatry, Osaka University, Suita City, Japan)**

Chronic interictal psychosis of epilepsy (CIPE) is an entity with unknown pathophysiological mechanisms. In this study we assessed brain oscillatory activity in patients with CIPE to help clarify the anatomical correlates of chronic psychotic symptoms in epilepsy. The electroencephalography (EEG) activity of 12 patients with temporal lobe epilepsy (TLE) and CIPE was compared to that of 17 non-psychotic TLE patients. Thirty-second artifact-free EEG epochs during awake, eye-closed state were analyzed using standardized Low-resolution Electromagnetic Tomography (sLORETA). Patients with CIPE showed significant increase in delta activity in the fusiform and anterior cingulate cortex. EEG sources of delta activity correlated with positive symptoms scores on the Brief Psychiatric Rating Scale. Our findings suggest that dysfunction in paralimbic areas might underlie chronic psychotic symptoms in epilepsy.

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# Prevalence of radiographic lumbar spondylosis and its association with low back pain in elderly subjects of population-based cohorts: the ROAD study

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## ABSTRACT

**Objectives:** Although lumbar spondylosis is a major cause of low back pain and disability in elderly people, few epidemiological studies have been performed. The prevalence of radiographic lumbar spondylosis was investigated in a large-scale population study and the association with low back pain was examined.

**Methods:** From a nationwide cohort study (Research on Osteoarthritis Against Disability; ROAD), 2288 participants aged  $\geq 60$  years (818 men and 1470 women) living in urban, mountainous and coastal communities were analysed. The radiographic severity at lumbar intervertebral levels from L1/2 to L5/S was determined by Kellgren/Lawrence (KL) grading.

**Results:** In the overall population the prevalence of radiographic spondylosis with  $KL \geq 2$  and  $\geq 3$  at the severest intervertebral level was 75.8% and 50.4%, respectively, and that of low back pain was 28.8%. Although  $KL \geq 2$  spondylosis was more prevalent in men,  $KL \geq 3$  spondylosis and low back pain were more prevalent in women. Age and body mass index were risk factors for both  $KL \geq 2$  and  $KL \geq 3$  spondylosis. Although  $KL = 2$  spondylosis was not significantly associated with low back pain compared with  $KL = 0$  or 1,  $KL \geq 3$  spondylosis was related to the pain only in women.

**Conclusions:** This cross-sectional study in a large population revealed a high prevalence of radiographic lumbar spondylosis in elderly subjects. Gender seems to be distinctly associated with  $KL \geq 2$  and  $KL \geq 3$  lumbar spondylosis, and disc space narrowing with or without osteophytosis in women may be a risk factor for low back pain.

Lumbar spondylosis is considered a major public health issue causing chronic disability of elderly people in most developed countries.<sup>1,2</sup> Despite the urgent need for strategies for the prevention and treatment of this condition, epidemiological data on lumbar spondylosis such as its prevalence and association with symptoms are sparse. With the goal of establishing epidemiological indices to evaluate clinical evidence for the development of disease-modifying treatment, we set up a large-scale nationwide cohort study for bone and joint disease called ROAD (Research on Osteoarthritis Against Disability) in 2005. We have to date created a baseline database with detailed clinical and genetic information on three population-based cohorts in urban, mountainous and coastal communities of Japan.

Lumbar spondylosis is characterised by disc degeneration and osteophytosis.<sup>2,3</sup> Although this

disorder has been widely studied in a clinical setting, few population-based radiological studies have been attempted.<sup>4-11</sup> The reported prevalence of radiographic lumbar spondylosis differs greatly in these reports from about 40% to 85%. This may be due to limitation of the sample size and variability in age. The present study therefore initially investigated the prevalence and distribution of this disorder according to age, gender and community using cohorts of 2288 participants aged  $\geq 60$  years in the baseline survey of the ROAD study.

The most popular grading system for the radiographic severity of osteoarthritis is the Kellgren/Lawrence (KL) system with classification into five grade scales (0-4) where  $KL \geq 2$  is the conventional standard of the diagnosis.<sup>12</sup> For lumbar spondylosis, KL grade 2 is defined as osteophyte formation and grade 3 as disc space narrowing in addition to osteophyte formation,<sup>12</sup> although few epidemiological studies have applied the KL system to evaluate the lumbar spine.<sup>5,6,9</sup> Hence, to assess osteophyte formation alone and disc space narrowing with or without osteophytosis separately, this study examined not only the prevalence of  $KL \geq 2$  spondylosis but also that of  $KL \geq 3$  spondylosis.

Although low back pain is believed to be the principal clinical symptom of lumbar spondylosis, its association with the radiographic severity remains unclear. The correlation was not as strong as one would expect, and there is often a disconnection between them.<sup>7,8</sup> In previous reports radiographic spondylosis was determined at the severest intervertebral level, but it is possible that other levels with milder spondylotic change might give rise to low back pain. This study therefore assessed the radiographic severity at all intervertebral levels of the lumbar spine by the KL system, and examined the association between radiographic severity and low back pain.

## METHODS

### Participants

The ROAD study is a nationwide prospective cohort study for bone and joint diseases consisting of population-based cohorts established in several communities in Japan. To date we have created a baseline database which includes clinical and genomic information of 3040 inhabitants (1061 men, 1979 women) in the age range 23-95 years (mean 70.6) in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in

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Taiji, Wakayama. Participants in the urban region were recruited from those of a cohort study<sup>13</sup> in which the participants were randomly drawn from the register database of Itabashi ward residents, with a response rate in the age group  $\geq 60$  years of 75.6%. Participants in the mountainous and coastal regions were recruited from resident registration lists, with response rates in the groups aged  $\geq 60$  years of 68.4% and 29.3%, respectively.

Participants completed an interviewer-administered questionnaire of 400 items which included lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables and health-related quality of life. Anthropometric measurements included height, weight, arm span, bilateral grip strength and body mass index (BMI,  $\text{kg}/\text{m}^2$ ). Medical information was taken by experienced orthopaedic surgeons (SM and HO) on systemic, local and mental status including information on low back, knee and hip pain, swelling and range of motion of the joints, and patellar and achilles tendon reflex. All participants were interviewed regarding low back pain by asking: "In the past month, have you had pain on most days lasting?", and those who answered yes were defined as having low back pain. Blood and urine samples were collected for biochemical and genetic examinations. Plain radiographs of the lumbar spine, knee and hip were taken for all participants. Participants were confirmed to be comparable to the Japanese general population according to the national nutrition survey by the Ministry of Health, Labour and Welfare (Japan). The height of the men and women in the ROAD study was 162.5 cm and 149.7 cm, respectively, compared with 162.6 cm and 149.9 cm in the Japanese general population. Weight was 61.3 kg and 51.8 kg, respectively, compared with 61.6 kg and 53.8 kg. The percentage of the men and women in the study population with a smoking habit was 26.4% and 3.2%, respectively, compared with 29.4% and 4.0% in the general population. From the baseline data of the overall participants, the present study analysed 2288 subjects (818 men and 1470 women) aged  $\geq 60$  years.

### Radiographic assessment

Plain radiographs of the lumbar spine were taken in the anteroposterior and lateral positions and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files to assess radiographic spondylosis. Contrast-adjusted images were used to detect osteophytes and intervertebral spaces when the original images were obscure. Osteophytes were analysed at endplates. The severity of lumbar spondylosis was determined according to the KL grading<sup>12</sup> at each intervertebral level from L1/2 to L5/S by a single experienced orthopaedic surgeon (SM) who was blind to

the background of the patients. To evaluate the intra-observer variability of the KL grading, 100 randomly selected radiographs of the lumbar spine were scored by the same observer more than 1 month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopaedic surgeons (SM and HO) using the same radiographic atlas for inter-observer variability. The intra- and inter-observer variabilities were evaluated by kappa analysis. The variability in KL grading of the lumbar radiographs was found to be sufficient for assessment (0.84 and 0.76, respectively).

### Statistical analysis

The non-paired *t* test was used to examine the difference in age and BMI between men and women. To compare the percentage of patients with radiographic spondylosis (KL $\geq 2$  or  $\geq 3$  at the severest level) and low back pain between men and women, logistic regression analysis was performed after adjustment for age and BMI. The differences in prevalence among the age groups were determined using one-way analysis of covariance and Scheffe's test after adjustment for BMI. The association of the variables such as age, BMI, gender and community with radiographic spondylosis and low back pain was evaluated by multivariate logistic regression analysis. The association of radiographic spondylosis at each intervertebral level with low back pain was determined by logistic regression analysis after adjustment for age and BMI. The association of the number of intervertebral level with KL $\geq 3$  with low back pain was determined by multiple regression analysis after adjustment for age and BMI. Data analyses were performed using SAS Version 9.0 (SAS Institute, North Carolina, USA).

### RESULTS

Table 1 shows the overall characteristics of the 2288 participants aged  $\geq 60$  years in the three cohorts of the ROAD study. Although the men were significantly older than the women in the overall population and in some communities, BMI was comparable between them.

Table 2 shows the prevalence of radiographic lumbar spondylosis and low back pain in the overall population and subgroups classified by gender and age strata. In the overall population the prevalence of radiographic spondylosis with KL $\geq 2$  and  $\geq 3$  at the severest intervertebral level was 75.8% and 50.4%, respectively, and that of low back pain was 28.8%. The prevalence of osteoporotic fracture at the lumbar spine was 10.7%. Logistic regression analysis after adjustment for age and BMI showed that the prevalence of radiographic spondylosis with KL $\geq 2$  was higher in men than in women, while the prevalence of KL $\geq 3$  radiographic spondylosis and low back pain was higher in women than in men. When the prevalence was

**Table 1** Characteristics of study participants

	Men				Women			
	Overall	Urban	Mountainous	Coastal	Overall	Urban	Mountainous	Coastal
No of subjects	818	397	266	155	1470	742	434	294
Age (years)	74.7 (6.1)	77.3 (4.1)	72.1 (6.2)	72.7 (7.4)	74.0 (6.4)*	76.4 (4.8)*	72.1 (7.1)	70.9 (6.8)*
Height (cm)	161.3 (6.3)	161.2 (5.9)	160.3 (6.6)	163.0 (6.1)	148.6 (6.2)	148.6 (5.8)	146.8 (6.4)	151.2 (5.9)
Weight (kg)	60.1 (9.9)	59.8 (8.3)	59.3 (11.4)	62.2 (10.6)	50.9 (9.0)	50.7 (8.4)	49.8 (9.8)	53.1 (8.8)
BMI ( $\text{kg}/\text{m}^2$ )	23.0 (3.2)	23.0 (2.7)	23.0 (3.8)	23.3 (3.3)	23.0 (3.7)	22.9 (3.4)	23.1 (4.2)	23.2 (3.5)
Current smoker (%)	24.6	25.2	26.3	20.0	3.1*	3.1*	4.4*	1.0*
Current drinker (%)	61.2	60.0	67.0	54.8	20.2*	21.0*	22.1*	15.3*

Data are mean (SD).

\* $p < 0.05$  vs men in the corresponding group by the non-paired *t* test.

BMI, body mass index.

**Table 2** Number (%) of participants with radiographic lumbar spondylosis and low back pain according to gender and age

		Radiographic lumbar spondylosis		Low back pain
		KL $\geq$ 2	KL $\geq$ 3	
Overall	2288	1728 (75.8)	1149 (50.4)	659 (28.8)
Men	818	688 (84.1)	383 (46.8)	201 (24.6)
<70	154	114 (74.0)	51 (33.1)	35 (22.7)
70–79	491	419 (85.3)*	232 (47.3)*	119 (24.2)
$\geq$ 80	173	155 (89.6)*	100 (57.8)*	47 (27.2)
Women	1470	1040 (70.7)†	766 (52.1)†	458 (31.2)†
<70	356	196 (55.1)	128 (36.0)	80 (22.5)
70–79	818	612 (74.8)*	456 (55.7)*	273 (33.4)*
$\geq$ 80	296	232 (78.3)*	182 (61.5)*	105 (35.5)*

Radiographic spondylosis was determined at the severest level among L1/2–L5/S1. \* $p < 0.05$  vs subjects aged <70 years by Scheffe's test after adjustment for body mass index.

There was no significant difference between ages 70–79 and  $\leq$ 80 in both genders. † $p < 0.05$  vs men by logistic regression analysis after adjustment for age and body mass index.

K/L, Kellgren/Lawrence grading.

compared among the generations, radiographic spondylosis (KL $\geq$ 2 and  $\geq$ 3) and low back pain tended to increase with age. Interestingly, the difference was greater between ages <70 and 70–79 years than between 70–79 and  $\geq$ 80 years.

To identify risk factors for the radiographic spondylosis and low back pain, we further performed the logistic regression analysis to estimate odds ratios and confidence intervals (table 3). Age and BMI were significantly associated with radiographic spondylosis. Male sex was confirmed to be a risk factor for KL $\geq$ 2 spondylosis while female sex was a risk factor for KL $\geq$ 3 and low back pain. Among the communities, residents of the mountainous area had a lower risk for KL $\geq$ 3 spondylosis than urban residents.

We then examined the association between radiographic spondylosis and low back pain. Considering that intervertebral levels other than the severest level of radiographic spondylosis might possibly cause low back pain, spondylosis at all intervertebral levels from L1/2 to L5/S1 was evaluated: KL $\geq$ 2 spondylosis was found to be comparably prevalent at L2/3, L3/4 and L4/5 while KL $\geq$ 3 spondylosis was remarkably prevalent at L4/5 in both men and women (table 4). In fact, among the five levels L4/5 was most frequently determined to be the severest level in both genders (men: L1/2 49.4%, L2/3 59.5%, L3/4 58.0%, L4/5 64.5%, L5/S1 48.3%; women: L1/2 49.5%, L2/3 58.0%, L3/4 58.6%, L4/5 65.5%, L5/S1 44.3%). We then looked at the percentage of subjects with low back pain in three groups: KL = 0 or 1, KL = 2, and KL $\geq$ 3, at each intervertebral level and

the severest level in the overall population and the three communities (fig 1). When odds ratios of KL = 2 and KL $\geq$ 3 spondylosis compared with KL = 0 or 1 for pain were estimated by logistic regression analysis after adjustment for age and BMI, KL = 2 spondylosis was not significantly associated with pain in either gender at any intervertebral level (table 5). However, KL $\geq$ 3 spondylosis was related at all levels in women while in none of the levels in men. Furthermore, the number of intervertebral levels with KL $\geq$ 3 spondylosis was significantly associated with low back pain in women ( $p < 0.01$ ) but not in men by multiple regression analysis after adjustment for age and BMI. The association between KL $\geq$ 3 spondylosis at the severest level and low back pain in women was evident at younger ages (<70 and 70–79 years; see table 1 in online supplement) and in the urban community (see table 2 in online supplement).

## DISCUSSION

This study showed that the prevalence of radiographic lumbar spondylosis with KL $\geq$ 2 and KL $\geq$ 3 in elderly people ( $\geq$ 60 years) was 75.8% and 50.4%, respectively, and that of low back pain was 28.8% in the overall population. Although KL $\geq$ 2 spondylosis was more prevalent in men (84.1%) than in women (70.7%), KL $\geq$ 3 spondylosis and low back pain were more prevalent in women. This study also showed that KL = 2 spondylosis was not significantly associated with low back pain compared with KL = 0 or 1, while KL $\geq$ 3 spondylosis was related to the pain only in women.

Most previous epidemiological studies on lumbar spondylosis focused on middle-aged or younger populations, reporting the prevalence to be 46.5–83.7%.<sup>4–8 10 11</sup> Our previous small-scale study on a younger population reported the prevalence to be 76.3% and 37.4%.<sup>9</sup> Interestingly, the subjects were living in a mountainous area in Japan, which was shown to have a lower risk for spondylosis in the present study. The variability may therefore be due to the differences in age, community, the sample size and ethnic variation. In fact, a study on elderly people ( $\geq$ 65 years) showed that the prevalence of KL $\geq$ 2 spondylosis was 84.8% and 70.6%, similar to the present results, although in a relatively small number of subjects.<sup>5</sup> We have reported a different prevalence of lumbar spondylosis in Japan and the UK in a small-scale comparative study,<sup>9</sup> which may in part relate to ethnic variation. It should be noted that this is the first population-based study to investigate the age-related prevalence of lumbar spondylosis in elderly people. Although KL $\geq$ 2 and KL $\geq$ 3 spondylosis tended to increase with age, a significant difference was detected between the 60s and the 70s, but not thereafter. However, this cross-sectional

**Table 3** Association of gender and community with radiographic lumbar spondylosis and low back pain

	Radiographic lumbar spondylosis		Low back pain
	KL $\geq$ 2	KL $\geq$ 3	
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (years)	1.07 (1.06 to 1.09)†	1.05 (1.04 to 1.07)†	1.02 (1.00 to 1.04)*
BMI (kg/m <sup>2</sup> )	1.06 (1.03 to 1.09)†	1.04 (1.01 to 1.06)†	1.02 (0.99 to 1.05)
Women (vs men)	0.68 (0.61 to 0.76)†	1.13 (1.03 to 1.23)†	1.19 (1.08 to 1.31)†
Community (vs urban)			
Mountainous	0.82 (0.65 to 1.04)	0.56 (0.45 to 0.69)†	0.87 (0.69 to 1.08)
Coastal	1.24 (0.93 to 1.66)	1.06 (0.84 to 1.34)	0.86 (0.66 to 1.11)

Radiographic spondylosis was determined at the severest level among L1/2–L5/S1.

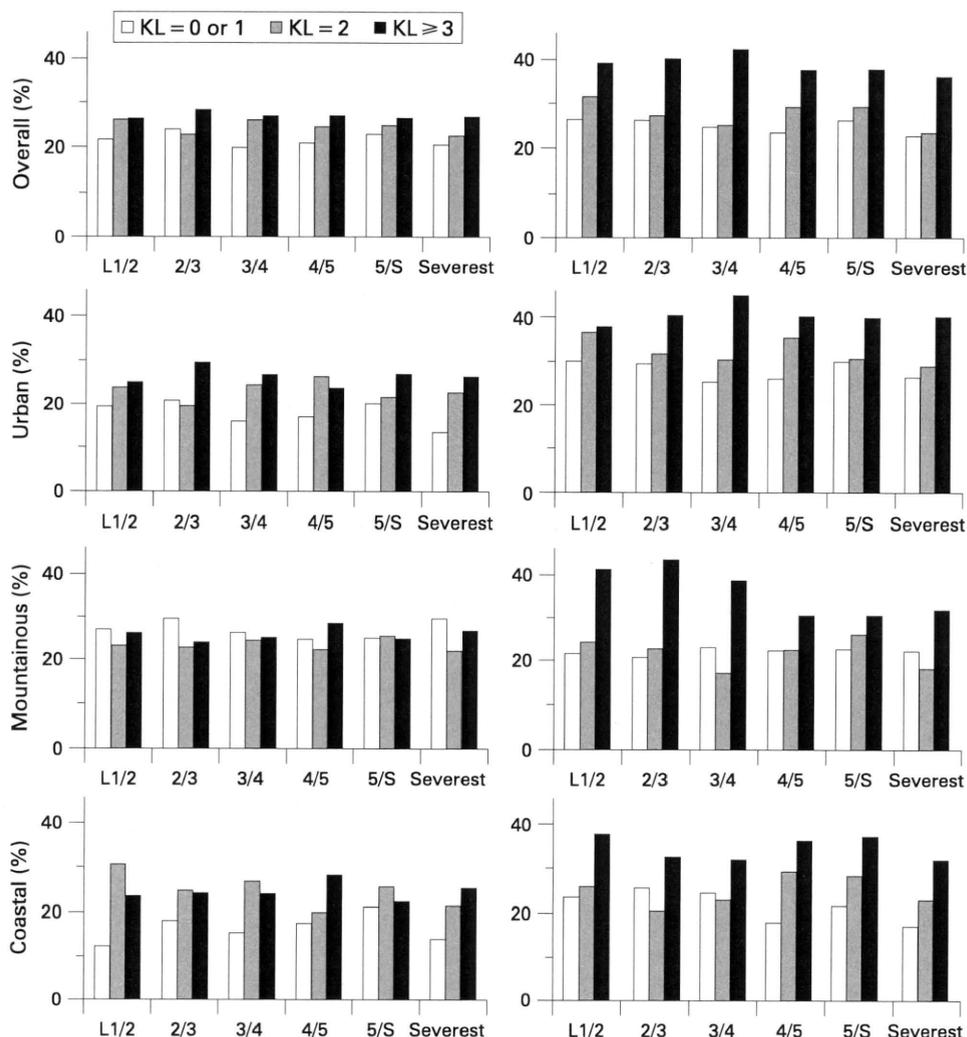
The odds ratios were calculated by logistic regression analysis after adjustment for all other variables.

\* $p < 0.05$ ; † $p < 0.01$ .

BMI, body mass index; KL, Kellgren/Lawrence grading; OR, odds ratio; CI, confidence interval.

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**Figure 1** Percentage of subjects with low back pain according to the Kellgren/Lawrence (KL) grade in the overall population and in urban, mountainous and coastal communities.



analysis does not, of course, lead to the conclusion that individual lumbar spondylosis hardly progresses after 80 years. Since the ROAD study is a prospective cohort study of >10 years, the follow-up data will clarify the progression with ageing. Furthermore, there was a difference in prevalence between urban and mountainous communities. Considering that lumbar spondylosis is a common disease whose progression is governed by environmental and genetic factors, the regional difference is inevitable, as previously reported.<sup>6</sup> Although age and obesity are known to be representative risk factors for lumbar spondylosis,<sup>2</sup> the difference between communities in the present study was significant even after adjustment for age and BMI, indicating the involvement of other factors. Here again, a further longitudinal survey of the ROAD database including

detailed environmental and genomic information will elucidate the underlying backgrounds.

Interestingly, KL $\geq$ 2 spondylosis was more prevalent in men than in women, while KL $\geq$ 3 spondylosis was more prevalent in women. We and others also have reported that osteophytosis of the lumbar spine is more common in men than in women,<sup>8,9</sup> while disc space narrowing is more prevalent in women.<sup>9</sup> Based on the definition of the KL grading,<sup>12</sup> the discrepancy may be due to distinct aetiological mechanisms between osteophyte formation and disc space narrowing. A cross-sectional study which investigated the extent, prevalence and distribution of spinal spondylosis in women also showed that osteophytosis and disc space narrowing were significantly correlated, but each predicted only 19% of the variation in the other.<sup>11</sup> A previous prospective study in knee joints in the Chingford Study cohort found no association between osteophyte formation and joint space narrowing.<sup>14</sup> A recent study using quantitative magnetic resonance imaging (MRI) in knee joints also reported that osteophyte formation was unrelated to cartilage loss.<sup>15</sup> Furthermore, in an experimental mouse knee osteoarthritis model, we have identified a cartilage-specific molecule, carminerin, that induces only osteophyte formation without affecting cartilage degeneration during the progression of osteoarthritis.<sup>16,17</sup> Further clinical and basic research will disclose the distinct backgrounds of these two representative features of osteoarthritis.

**Table 4** Number (%) of subjects with radiographic lumbar spondylosis at each intervertebral level in all cohorts

	KL $\geq$ 2		KL $\geq$ 3	
	Men	Women	Men	Women
L1/2	474 (57.9)	609 (41.4)	116 (14.2)	254 (17.3)
L2/3	541 (66.1)	749 (51.0)	164 (20.1)	355 (24.2)
L3/4	554 (67.7)	735 (50.0)	194 (23.7)	419 (28.5)
L4/5	523 (63.9)	736 (50.1)	306 (37.5)	605 (41.2)
L5/S	400 (48.9)	576 (39.2)	197 (24.2)	413 (28.1)

KL, Kellgren/Lawrence grading.

**Table 5** Association of Kellgren/Lawrence (KL) grade at each intervertebral level with low back pain

	L1/2	L2/3	L3/4	L4/5	L5/S	Severest
	OR (95% CI)					
<b>Men</b>						
KL = 2	1.30 (0.92 to 1.84)	0.94 (0.65 to 1.36)	1.43 (0.98 to 2.11)	1.24 (0.82 to 1.89)	1.12 (0.75 to 1.65)	1.15 (0.70 to 1.92)
KL $\geq$ 3	1.30 (0.79 to 2.11)	1.25 (0.80 to 1.94)	1.49 (0.96 to 2.32)	1.42 (0.97 to 2.08)	1.22 (0.82 to 1.81)	1.44 (0.89 to 2.38)
<b>Women</b>						
KL = 2	1.20 (0.91 to 1.57)	0.99 (0.75 to 1.31)	0.96 (0.71 to 1.30)	1.25 (0.82 to 1.88)	1.07 (0.73 to 1.54)	0.99 (0.69 to 1.42)
KL $\geq$ 3	1.66 (1.23 to 2.24)*	1.74 (1.32 to 2.30)*	2.10 (1.62 to 2.72)*	1.88 (1.48 to 2.38)*	1.60 (1.25 to 2.06)*	1.80 (1.38 to 2.37)*

The odds ratio was calculated by logistic regression analysis compared with subjects with KL grade 0 or 1 after adjustment for age and body mass index.

\*p<0.01.

OR, odds ratio; CI, confidence interval.

Symptomatic low back pain was associated with KL $\geq$ 3 spondylosis in women but not in men, but not with KL $\geq$ 2 spondylosis in either gender. Considering the definition of KL grading, this may suggest that disc space narrowing but not osteophytosis of the lumbar spine contributes to low back pain, which is consistent with previous reports.<sup>18</sup> Differences in the association between genders might be dependent on muscle strength to compensate for spinal instability due to disc space narrowing, since men are known to have greater muscle strength than women at all ages.<sup>19</sup> However, approximately 30% of participants without definite radiographic lumbar spondylosis (KL=0 or 1) had low back pain, and the odds ratio of KL $\geq$ 3 spondylosis for pain was 1.44 in men and 1.80 in women, which is much lower than the previously reported odds ratio of 8.5 for KL $\geq$ 3 osteoarthritis in the knee joint for knee pain.<sup>20</sup> This may be because low back pain arises from a number of disorders other than disc space narrowing such as nociceptive stimuli, inflammation, muscle weakness and abnormal load on muscle, ligament or capsular tissues.<sup>21</sup> Indeed, disc degeneration was detected by MRI in at least one lumbar level in all but one asymptomatic volunteers aged 60–80 years.<sup>22</sup> Furthermore, pain is also influenced by psychological factors such as depression, since a significant association between low back pain and depression has been confirmed in many longitudinal studies.<sup>23–25</sup> A recent psychophysical study has shown that anxiety was linked to self-reported and induced low back pain in men but not in women.<sup>26</sup> This might be an alternative reason for the lower association between radiographic spondylosis and low back pain in men.

This study has several limitations. First, prevalence figures using a large-scale population-based sample of elderly people may be generalisable to the Japanese population. However, this study investigated elderly participants who lived independently rather than those who lived in institutional settings, so the calculated prevalence may be underestimated. Second, the definition of low back pain in the present study did not determine the severity. The association of lumbar spondylosis with the severity of low back pain could not be examined in this study. Third, the analyses did not include facet joint osteoarthritis or vertebral fracture, which would probably be associated with low back pain. This is the next factor to be investigated in the ROAD study. Fourth, since the KL system emphasises osteophytosis, it is unclear how to handle lumbar spondylosis with disc space narrowing but no osteophytosis. Since quantitative MRI is still too laborious and expensive to perform in general clinical practice, we are now developing a computer-aided diagnostic program which enables the fully automatic measurement of major features of lumbar spondylosis including disc space narrowing and osteophytosis on plain radiographs.

In conclusion, this cross-sectional study using a large-scale population from the ROAD study revealed a high prevalence of radiographic lumbar spondylosis in elderly people. The prevalence differed to some extent by age, gender and community. Gender seems to be distinctly associated with KL $\geq$ 2 and KL $\geq$ 3 lumbar spondylosis, and disc space narrowing with or without osteophytosis in women may be a risk factor for low back pain. Further progress, along with continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of lumbar spondylosis and its relation with low back pain.

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## Prevalence of radiographic lumbar spondylosis and its association with low back pain in elderly subjects of population-based cohorts: the ROAD study

S Muraki, H Oka, T Akune, et al.

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## Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study

Noriko Yoshimura · Shigeyuki Muraki · Hiroyuki Oka · Akihiko Mabuchi · Yoshio En-Yo · Munehito Yoshida · Akihiko Saika · Hideyo Yoshida · Takao Suzuki · Seizo Yamamoto · Hideaki Ishibashi · Hiroshi Kawaguchi · Koza Nakamura · Toru Akune

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**Abstract** Musculoskeletal diseases, especially osteoarthritis (OA) and osteoporosis (OP), impair activities of daily life (ADL) and quality of life (QOL) in the elderly. Although preventive strategies for these diseases are urgently required in an aging society, epidemiological data on these diseases are scant. To clarify the prevalence of knee osteoarthritis (KOA), lumbar spondylosis (LS), and osteoporosis (OP) in Japan, and estimate the number of people with these diseases, we started a large-scale

population-based cohort study entitled research on osteoarthritis/osteoporosis against disability (ROAD) in 2005. This study involved the collection of clinical information from three cohorts composed of participants located in urban, mountainous, and coastal areas. KOA and LS were radiographically defined as a grade of  $\geq 2$  by the Kellgren–Lawrence scale; OP was defined by the criteria of the Japanese Society for Bone and Mineral Research. The 3,040 participants in total were divided into six groups based on their age:  $\leq 39$ , 40–49, 50–59, 60–69, 70–79, and  $\geq 80$  years. The prevalence of KOA in the age groups  $\leq 39$ , 40–49, 50–59, 60–69, 70–79, and  $\geq 80$  years 0, 9.1, 24.3, 35.2, 48.2, and 51.6%, respectively, in men, and the prevalence in women of the same age groups was 3.2, 11.4, 30.3, 57.1, 71.9, and 80.7%, respectively. With respect to the age groups, the prevalence of LS was 14.3, 45.5, 72.9, 74.6, 85.3, and 90.1% in men, and 9.7, 28.6, 41.7, 55.4, 75.1, and 78.2% in women, respectively. Data of the prevalence of OP at the lumbar spine and femoral neck were also obtained. The estimated number of patients with KOA, LS, and L2–L4 and femoral neck OP in Japan was approximately 25, 38, 6.4, and 11 million, respectively. In summary, we estimated the prevalence of OA and OP, and the number of people affected with these diseases in Japan. The ROAD study will elucidate epidemiological evidence concerning determinants of bone and joint disease.

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**Keywords** Epidemiology · Prevalence · Establishment of population-based cohort · Osteoarthritis · Osteoporosis

### Introduction

Osteoarthritis (OA) and osteoporosis (OP) are major public health problems in the elderly that affect their