these patients, when CSM was limited to the spinal cord tract (28 patients), CSM affected superior cervical intervertebral levels in 85 % of the patients, suggesting that the results were similar. As mentioned in previous reports, the pathophysiology of CSM in elderly patients involves a decreased range of intervertebral motility because of degeneration of the middle and inferior cervical vertebrae associated with a relative increase in instability of the superior cervical vertebrae. This may contribute to the onset of CSM affecting the superior intervertebral levels [10, 13], suggesting that it may be possible to manage CSM of the superior cervical intervertebral levels in elderly patients using selective decompression.

Reports regarding the selection of surgical procedures for CSM in the elderly are few. According to the results obtained by Tani et al. who determined the affected level using intraoperative SCEPs, favorable outcomes occur when selective anterior decompression and fusion are performed [10]. However, anterior decompression and fusion carries the risk of postoperative bone graft dislodgement and respiratory difficulties; thus, the indications in the elderly are limited. Kinko et al. [15] first reported selective laminoplasty with intraoperative electrophysiological diagnosis of the affected level, and Kato et al. reported favorable short-term outcomes of this technique [6]. Aftercare following selective laminoplasty using a posterior approach is easier than anterior fusion and is considered suitable for elderly patients. However, Kato et al. observed minimal improvement in severely affected patients (JOA score: 5 points); therefore, careful evaluation of risks and benefits is required in these patients. In our department, as a rule, selective laminoplasty is limited to elderly patients aged ≥75 years with complications (ASA Physical Status class 2 or greater) when a chest X-ray shows lordosis in the sagittal plane, intervertebral prolapse is not severe, the preoperative neurological findings and imaging findings indicate CSM at either one or two consecutive intervertebral levels, and the affected level determined during intraoperative electrophysiological assessment corresponds to that level. Duration of the procedure and a blood loss were both significantly smaller for selective laminoplasty compared to conventional C3–7 laminoplasty and to anterior decompression and fusion; no complications were observed in patients aged 75 years in our SL group. Furthermore, the rate of improvement was not inferior to the conventional surgery, and it is believed to be a less invasive and appropriate surgical procedure for elderly patients, particularly those with complications that are appropriately selected.

Limitations of this study are as follows: this is a retrospective study and may contain a bias of selection of a surgical method. Because we studied patients aged ≥75 years, the sample size was small, which increases the risk of patient bias within each group. In addition, the follow-up period was 6 months, and the timing of the final assessment varied.

Conclusions

We conducted a study in patients aged ≥75 years, who underwent surgery for CSM. Superior cervical intervertebral levels were affected in 85 % of the patients with spinal-tract CSM. The postoperative outcomes were generally favorable, and when the surgical methods were compared, duration of the procedure and the blood loss were significantly smaller with selective laminoplasty, compared with conventional C3–7 laminoplasty and anterior decompression and fusion, although the clinical outcomes were the same. When cases are properly selected, elective laminoplasty is less invasive and may be well suited for elderly patients with CSM.

References

1. Handa Y, Kubota T, Ishii H et al (2002) Evaluation of prognostic factors and clinical outcome in elderly patients in whom expansive laminoplasty is performed for cervical myelopathy due to multisegmental spondylotic canal stenosis: a retrospective comparison with younger patients. J Neurosurg 96:173–179
2. Hasegawa K, Homma T, Chiba Y et al (2002) Effects of surgical treatment for cervical spondylotic myelopathy in patients 70 years of age: a retrospective comparative study. J Spinal Disord Tech 15:458–460
3. Matsuda Y, Shibata T, Oki S et al (1999) Outcomes of surgical treatment for cervical myelopathy in patients more than 75 years of age. Spine 24:529–534
4. Nagashima H, Morio Y, Yamashita H et al (2006) Clinical features and surgical outcomes of cervical myelopathy in the elderly. Clin Orthop Relat Res 444:140–145
5. Nagata K, Ohashi T, Abe J et al (1996) Cervical myelopathy in elderly patients: clinical results and MRI findings before and after decompression surgery. Spinal Cord 34:220–226
6. Tanaka J, Seki N, Tokimura F et al (1999) Operative results of canal-expansive laminoplasty for cervical spondylotic myelopathy in elderly patients. Spine 24:2308–2312
7. Yamazaki T, Yanaka K, Sato H et al (2003) Cervical spondylotic myelopathy: surgical results and factors affecting outcome with special reference to age differences. Neurosurgery 52:122–126
8. Nagashima H, Dokai T, Hashiguchi H et al (2011) Cervical spondylotic myelopathy in patients aged 80 years or older: a multicenter retrospective study. Eur Spine J 20:240–246
9. Kato Y, Kojima T, Kataoka H et al (2009) Selective laminoplasty after the preoperative diagnosis of the responsible level using spinal cord evoked potentials in elderly patients with cervical spondylotic myelopathy. J Spinal Disord Tech 22(8):586–592
10. Tani T, Ishida T, Ushida T et al (2000) Intraoperative electroneurography in the assessment of the level of operation for cervical spondylotic myelopathy in the elderly. J Bone Joint Surg (Br) 82(B(2)):269–274
11. Hirabayashi K, Miyakawa J, Satomi K et al (1981) Operative results and postoperative progression of ossification among patients with ossification of cervical posterior longitudinal ligament. Spine 6:354–364

12. Kaneko K, Kawai S, Taguchi T et al (1998) Correlation between spinal cord compression and abnormal patterns of median nerve somatosensory evoked potentials in compressive cervical myelopathy: comparison of surface and epidurally recorded responses. J Neurol Sci 158:193–202
13. Tani T, Yamamoto H, Kimura J (1999) Cervical spondylotic myelopathy in elderly people: a high incidence of conduction block at C3–4 or C4–5. J Neurol Neurosurg Psychiatry 66:456–464
14. Kaneko K, Taguchi T, Morita H et al (2001) Mechanism of prolonged central motor conduction time in compressive cervical myelopathy. Clin Neurophysiol 112:1035–1040
15. Kaneko K, Kawai S, Taguchi T et al (2001) Pathophysiology in cervical spondylotic myelopathy in elderly patients. Nishinihon Sekitsui Kenkyukaishi 27:45–47 (in Japanese)
16. Yamaguchi H, Hirabayashi K (1994) Scoring system (17-2) for cervical myelopathy (Japanese Orthopaedic Association). J Jpn Orthop Assoc 68:490–503

J Neurosurg Spine 21:773–777, 2014
©AANS, 2014

Progression of ossification of the posterior longitudinal ligament of the thoracic spine following posterior decompression and stabilization

Clinical article

Shurei Sugita, M.D.,[1] Hirotaka Chikuda, M.D., Ph.D.,[1] Katsushi Takeshita, M.D., Ph.D.,[1] Atsushi Seichi, M.D., Ph.D.,[2] and Sakae Tanaka, M.D., Ph.D.[1]

[1]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Tokyo, Tokyo; and* [2]*Department of Orthopedics, Jichi Medical University, Tochigi, Japan*

Object. Despite its potential clinical impact, information regarding progression of thoracic ossification of the posterior longitudinal ligament (OPLL) is scarce. Posterior decompression with stabilization is currently the primary surgical treatment for symptomatic thoracic OPLL; however, it remains unclear whether thoracic OPLL increases in size following spinal stabilization. It is also unknown whether patients' clinical symptoms worsen as OPLL size increases. In this retrospective case series study, the authors examined the postoperative progression of thoracic OPLL.

Methods. Nine consecutive patients with thoracic OPLL who underwent posterior decompression and fixation with a minimum follow-up of 3 years were included in this study. Thin-slice CT scans of the thoracic spine obtained at the time of surgery and the most recent follow-up were analyzed. The level of the most obvious protrusion of ossification was determined using the sagittal reconstructions, and the ossified area was measured on the axial reconstructed scan at the level of the most obvious protrusion of ossification using the DICOM (digital imaging and communications in medicine) software program. Myelopathy severity was assessed according to the Japanese Orthopaedic Association (JOA) scale score for lower-limb motor function on admission, at postoperative discharge, and at the last follow-up visit.

Results. The OPLL area was increased in all patients. The mean area of ossification increased from 83.6 ± 25.3 mm^2 at the time of surgery to 114.8 ± 32.4 mm^2 at the last follow-up visit. No patients exhibited any neurological deterioration due to OPLL progression.

Conclusions. The present study demonstrated that the size of the thoracic OPLL increased after spinal stabilization. Despite diminished local spinal motion, OPLL progression did not decrease or stop. Physicians should pay attention to ossification progression in patients with thoracic OPLL.

(http://thejns.org/doi/abs/10.3171/2014.7.SPINE131191)

Key Words • **posterior decompression and fixation** • **thoracic spine** • **ossification of the posterior longitudinal ligament** • **progression**

Ossification of the posterior longitudinal ligament (OPLL) is a condition of the spine characterized by the ectopic ossification of the spinal ligaments, potentially resulting in myelopathy due to spinal cord compression.[11] Although cervical OPLL progression is well documented in the literature,[1,7,14,17,18] information regarding thoracic OPLL progression is lacking. Currently, posterior decompression and stabilization using instrumentation is a widely used first-choice treatment for symptomatic thoracic OPLL and achieves good short-term outcomes.[8,9,12,20] Anterior decompression is technically demanding, and the technique is associated with a high rate of complications.[13,16] Spinal fixation with instrumentation is believed to diminish spinal cord damage and suppress further ossification by eliminating dynamic effects and reducing mechanical stress.[19] Although the long-term progression of OPLL may compromise the surgical benefits, it remains unclear whether thoracic OPLL continues to grow after spinal stabilization. We hypothesized that spinal stabilization decreases the rate of OPLL progression by immobilizing the spine. To address this

Abbreviations used in this paper: JOA = Japanese Orthopaedic Association; OPLL = ossification of the posterior longitudinal ligament.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

issue, we examined thin-slice CT scans of patients with thoracic OPLL who underwent posterior decompression and fixation to examine the postoperative progression of thoracic OPLL.

Methods

Patients

There were 16 patients who underwent surgery for thoracic OPLL in the study period (from 2004 to 2007). Nine consecutive patients with thoracic OPLL who underwent posterior decompression and instrumentation-assisted fixation and had a minimum follow-up period of 3 years were included in this study. Three patients were excluded because they underwent OPLL extirpation via an anterior approach. Another 4 patients were excluded because the follow-up period was shorter than 3 years. All patients presented with progressive gait disturbance. We performed posterior decompression and fixation with a pedicle screw and rod system. The surgical plans were individualized according to OPLL extension and concomitant ossification of the ligamentum flavum. We fixed the spine 2–3 levels above and below the decompression levels and harvested local bone for grafting. In this group, plain radiography did not provide sufficient information regarding the instrumentation failure or ossification progression. Therefore, as part of the standard follow-up protocol, we obtained CT scans of OPLL patients every 2–3 years after surgery. We examined the thin-slice CT images of the thoracic spine obtained at the time of surgery and at the most recent follow-up visit. The CT scans were obtained with a slice thickness of 0.75 mm and a pixel size of 0.352 × 0.352 mm. The data were transferred via a DICOM (digital imaging and communications in medicine) network to a computer workstation using the OsiriX software program (OsiriX Imaging Software).[5] Our institution's ethics board approved the study protocol.

Clinical Data

The patients' medical charts were reviewed for age, sex, type and extension of OPLL, and surgical procedure. Myelopathy severity was assessed according to the Japanese Orthopaedic Association (JOA) scale for lower-limb motor function,[8] which was administered on admission, at discharge, and the latest follow-up visit.

Measurement of Ossification

We reconstructed all preoperative CT scans for 3D multiplanar reconstruction and, using the sagittal reconstruction, determined the thoracic spine level with the most obvious level of ossification protrusion. We then measured the area of ossification on the axial reconstruction, which was set parallel to the endplate of the corresponding vertebra, using the OsiriX software program (Fig. 1). We also measured ossification area on the latest follow-up CT scan at the same level. All measurements were obtained twice for each CT data set by a board-certified spine surgeon (author S.S.), and the average value of the 2 measurements was used.

Statistical Analysis

We performed statistical analyses of the data using the Wilcoxon signed-rank test. Differences were considered statistically significant if p values were < 0.05. Mean values are presented ± SD.

Results

Demographic Data

The population included 3 males and 6 females, whose mean age was 56 ± 12.2 years (range 38–75 years). The mean follow-up period was 4.6 ± 2.0 years (range 3–9 years). The type of OPLL was continuous in 3 patients, mixed in 4 patients, and circumscribed in 2 patients. The level of OPLL, the level of the most obvious protrusion, and the surgical areas of decompression and fixation are shown in Table 1.

OPLL Progression

The area of OPLL was found to have increased in all patients (Table 2 and Fig. 2). The average area of ossification was 83.6 ± 25.3 mm^2 preoperatively and 114.8 ±

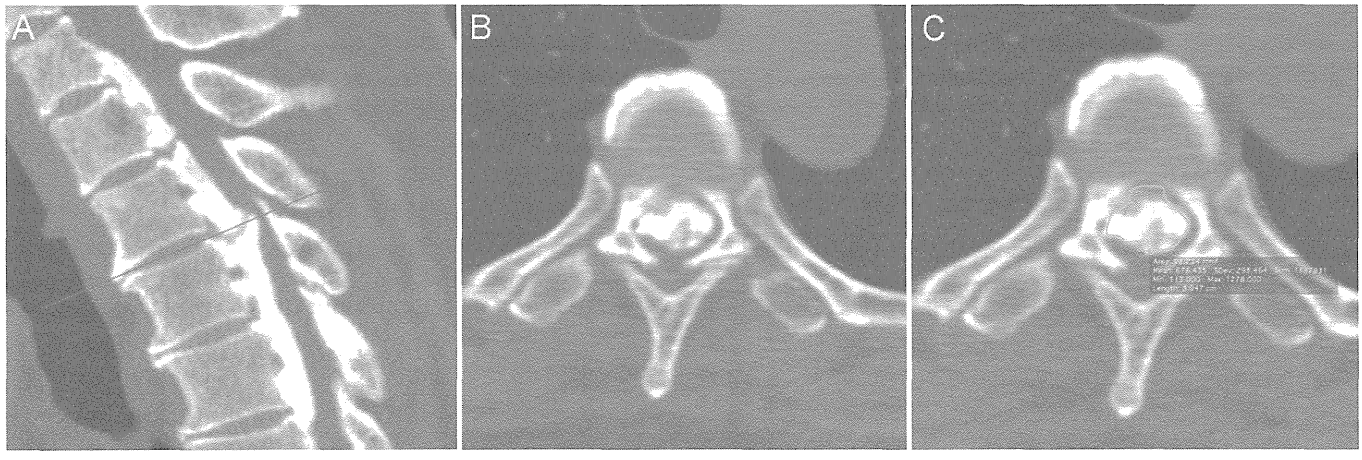

Fig. 1. A: The level of the most obvious protrusion of ossification was determined in the sagittal reconstruction *(line)*. **B:** Cross-section at the determined level. **C:** The area of ossification, shown in *green*, was measured using a software function.

TABLE 1: Patient demographics

Patient No.	Age (yrs), Sex	Type of OPLL	Extension of OPLL		Most Protruded OPLL Level	Surgical Level		Implant Density*	Rod Diameter (mm)	Follow-Up (yrs)
			Preop	Last Follow-Up		Decompression	Fixation			
1	48, M	mixed	C7–T10	C7–T10	T7–8	T1–10	T1–12	0.5	5.5	9
2	58, F	continuous	T3–6	T3–6	T5–6	T1–10	T1–10	0.55	5.5	3
3	38, M	circumscribed	T7–11	T7–11	T8–9	T7–L1	T5–L2	0.75	5.5	4
4	55, F	mixed	T4–10	T4–10	T5–6	T2–12	T2–12	0.55	6.5	3
5	64, F	continuous	T5–10	T3–L1	T7–8	T5–10	T5–10	0.92	5.5	7
6	39, M	circumscribed	T7–8	T7–8	T7–8	T5–10	T5–10	0.67	5.5	5
7	75, F	continuous	T3–9	T1–T11	T8–9	T5–10	T5–10	0.75	5.5	3
8	63, F	mixed	C4–T7	C4–T8	T3–4	C3–T8	C7–T8	0.56	6.5	4
9	70, F	mixed	C7–T5	C6–T5	T–2	C3–T6	C7–T8	0.67	5.5	3

* Implant density = no. implants per fixation segment × 2.

32.4 mm^2 at the last follow-up visit. All areas of ossification increased in both width and thickness. Longitudinal OPLL progression was also noted in 4 of 9 patients. The rate of OPLL progression (the most recent size before surgery) was not correlated with the rod diameter or implant density. Neither screw loosening nor rod breakage was observed on any of the follow-up postoperative CT scans.

Clinical Course

The mean JOA score for lower-limb motor function was 1.8 ± 0.6 before surgery, 1.7 ± 0.6 at discharge, and 1.4 ± 0.7 at the most recent follow-up visit (Table 3). No patients exhibited neurological deterioration due to OPLL progression. One patient developed a severe gait disturbance due to an unrelated cause (worsening of lumbar canal stenosis), but the other 8 experienced gait disturbance improvements.

Illustrative Case

A 55-year-old woman presented with a walking disturbance and lower-extremity muscle weakness. She had mixed-type OPLL, extending from T-4 to T-10. The level of the most obvious protrusion was T5–6, with an OPLL area of 97.3 mm^2. We performed T2–10 laminectomy and posterior fixation from T-2 to T-12. Three years after surgery, the area of OPLL at T5–6 had increased to 113.9 mm^2 (Fig. 3).

TABLE 2: Area of thoracic OPLL at the level of the most obvious protrusion

Patient No.	Area of the OPLL (mm^2)		Progression Rate (%)*
	Preop	At Last Follow-Up	
1	65.77	141.80	216
2	101.00	114.20	113
3	54.00	77.75	144
4	97.30	113.90	117
5	66.54	105.30	158
6	134.70	173.30	129
7	83.14	133.70	161
8	98.17	132.50	135
9	52.47	62.76	120

* The OPLL progression rate was determined by dividing the last follow-up area by the preoperative area.

Discussion

This is the first study to investigate the progression of thoracic OPLL after spinal stabilization. The use of thin-slice CT scans allowed us to conduct a detailed analysis of thoracic OPLL, which is difficult to do with plain radiographs. We found that the postoperative area of ossification increased both axially and longitudinally.

It is well recognized that cervical OPLL is progressive during the natural course of the disease and after decompressive surgery.[4–6,10,15] Several investigators have reported that ossification progression aggravates myelopathy, whereas others have found no relationship between neurological function deterioration and ossification progression.[2,5,7] This study is the first to show that ossification also progresses in the thoracic spine; however, this progression did not aggravate patients' myelopathy in the present series.

The pathomechanisms underlying the progression of OPLL remain unclear, but mechanical stress has been implicated as an exacerbating factor.[19] Our initial hypothesis was that spinal stabilization suppresses OPLL progression by eliminating local motion of the spine. Contrary to our hypothesis, we found that OPLL continued to progress after spinal stabilization. A study with a longer follow-up period may provide additional information regarding the time course of OPLL progression.

There are several limitations associated with this study that deserve mention. First, the number of patients examined in this study was small. However, our findings were consistent among the cohort. Similarly, the length of follow-up was relatively short. Although OPLL progression did not result in functional deterioration in the present study, such progression could manifest in neurological dysfunction over a longer time span. Finally, we did not measure local spinal motion. A previous study showed that dynamic factors, such as the segmental range of mo-

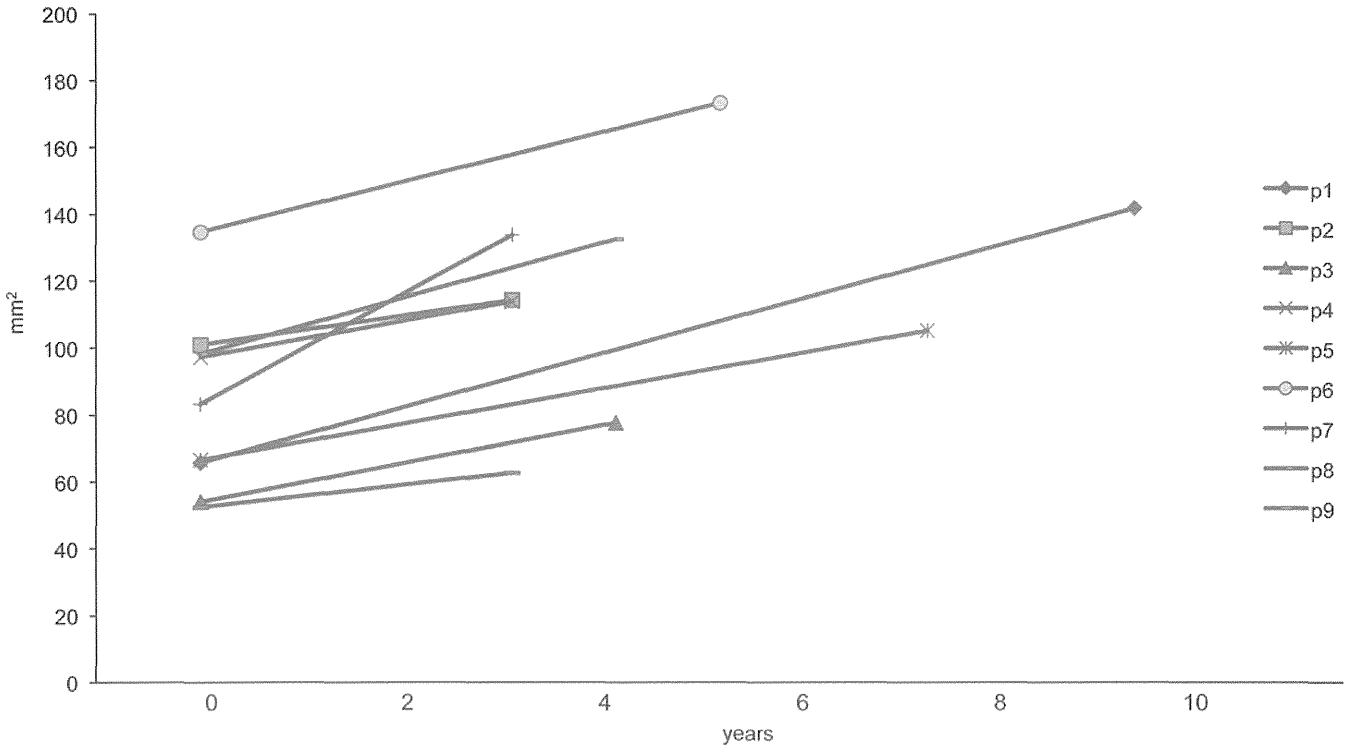

FIG. 2. Progression of OPLL during the follow-up period. The area of ossification increased in all patients. p = patient.

tion, contribute to the development of myelopathy in the cervical spine among patients with OPLL.[3] However, it is difficult to precisely measure local thoracic spine motion with plain radiographs. Notably, we observed neither screw loosening nor rod breakage on any of the follow-up CT scans, indicating that we successfully stabilized the patients' spines. A detailed analysis of spinal motion is needed in future studies.

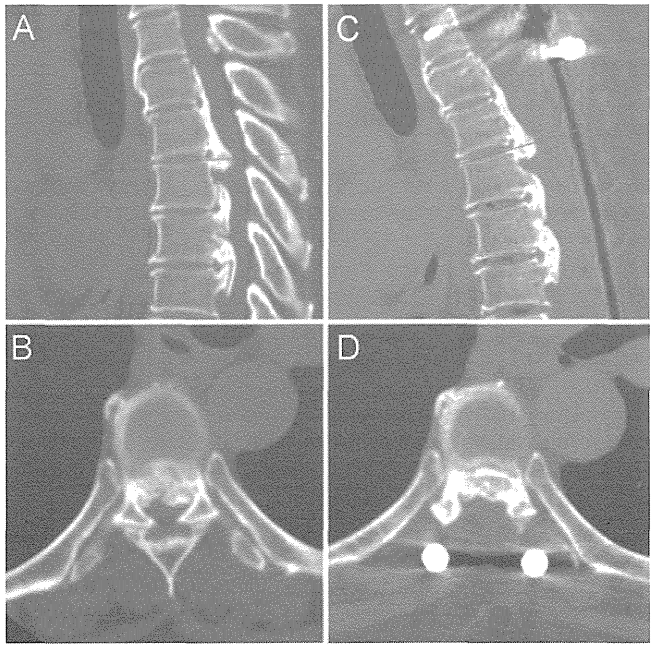

FIG. 3. **A:** The level of the most obvious protrusion of ossification was determined as previously described *(line)*. **B:** Preoperative axial view of ossification at the determined level. **C:** The same level was selected on postoperative CT scans. **D:** Axial postoperative CT scan showing enlargement of the area of ossification.

Conclusions

The present study demonstrated that thoracic OPLL does not decrease or stop and affects a larger area over time, even after spinal stabilization. Although OPLL progression did not result in functional deterioration in this study, physicians should pay attention to continued ossification in patients with thoracic OPLL.

Disclosure

The authors report no conflict of interest concerning the mate-

TABLE 3: JOA scores for lower-limb motor function in each patient

Patient No.	JOA Score		
	Preop	Postop	Last Follow-Up
1	3	3	2
2	2	2	1
3	2	2	2
4	2	2	2
5	1	1	1
6	2	2	2
7	1	1	0
8	1	1	1
9	2	2	2

rials or methods used in this study or the findings specified in this paper. This study was funded by a grant from the Ministry of Health, Labour, and Welfare of Japan (Research on Intractable Diseases grant no. H23-Nanchi-032). The funders played no role in the design of the study, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sugita, Chikuda. Acquisition of data: Sugita. Analysis and interpretation of data: Sugita. Drafting the article: Sugita. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sugita.

References

1. Fargen KM, Cox JB, Hoh DJ: Does ossification of the posterior longitudinal ligament progress after laminoplasty? Radiographic and clinical evidence of ossification of the posterior longitudinal ligament lesion growth and the risk factors for late neurologic deterioration. A review. **J Neurosurg Spine 17:**512–524, 2012
2. Fujimura Y, Nishi Y, Chiba K, Nakamura M, Hirabayashi K: Multiple regression analysis of the factors influencing the results of expansive open-door laminoplasty for cervical myelopathy due to ossification of the posterior longitudinal ligament. **Arch Orthop Trauma Surg 117:**471–474, 1998
3. Fujiyoshi T, Yamazaki M, Okawa A, Kawabe J, Hayashi K, Endo T, et al: Static versus dynamic factors for the development of myelopathy in patients with cervical ossification of the posterior longitudinal ligament. **J Clin Neurosci 17:**320–324, 2010
4. Inoue H, Ohmori K, Ishida Y, Suzuki K, Takatsu T: Long-term follow-up review of suspension laminotomy for cervical compression myelopathy. **J Neurosurg 85:**817–823, 1996
5. Iwasaki M, Kawaguchi Y, Kimura T, Yonenobu K: Long-term results of expansive laminoplasty for ossification of the posterior longitudinal ligament of the cervical spine: more than 10 years follow up. **J Neurosurg 96 (2 Suppl):**180–189, 2002
6. Kato Y, Iwasaki M, Fuji T, Yonenobu K, Ochi T: Long-term follow-up results of laminectomy for cervical myelopathy caused by ossification of the posterior longitudinal ligament. **J Neurosurg 89:**217–223, 1998
7. Kawaguchi Y, Kanamori M, Ishihara H, Nakamura H, Sugimori K, Tsuji H, et al: Progression of ossification of the posterior longitudinal ligament following en bloc cervical laminoplasty. **J Bone Joint Surg Am 83-A:**1798–1802, 2001
8. Kawahara N, Tomita K, Murakami H, Hato T, Demura S, Sekino Y, et al: Circumspinal decompression with dekyphosis stabilization for thoracic myelopathy due to ossification of the posterior longitudinal ligament. **Spine (Phila Pa 1976) 33:** 39–46, 2008
9. Matsumoto M, Toyama Y, Chikuda H, Takeshita K, Kato T, Shindo S, et al: Outcomes of fusion surgery for ossification of the posterior longitudinal ligament of the thoracic spine: a multicenter retrospective survey. Clinical article. **J Neurosurg Spine 15:**380–385, 2011
10. Matsunaga S, Kukita M, Hayashi K, Shinkura R, Koriyama C, Sakou T, et al: Pathogenesis of myelopathy in patients with ossification of the posterior longitudinal ligament. **J Neurosurg 96 (2 Suppl):**168–172, 2002
11. Matsunaga S, Sakou T: Ossification of the posterior longitudinal ligament of the cervical spine: etiology and natural history. **Spine (Phila Pa 1976) 37:**E309–E314, 2012
12. Matsuyama Y, Sakai Y, Katayama Y, Imagama S, Ito Z, Wakao N, et al: Indirect posterior decompression with corrective fusion for ossification of the posterior longitudinal ligament of the thoracic spine: is it possible to predict the surgical results? **Eur Spine J 18:**943–948, 2009
13. Min JH, Jang JS, Lee SH: Clinical results of ossification of the posterior longitudinal ligament (OPLL) of the thoracic spine treated by anterior decompression. **J Spinal Disord Tech 21:** 116–119, 2008
14. Murakami M, Seichi A, Chikuda H, Takeshita K, Nakamura K, Kimura A: Long-term follow-up of the progression of ossification of the posterior longitudinal ligament. Case report. **J Neurosurg Spine 12:**577–579, 2010
15. Ogawa Y, Toyama Y, Chiba K, Matsumoto M, Nakamura M, Takaishi H, et al: Long-term results of expansive open-door laminoplasty for ossification of the posterior longitudinal ligament of the cervical spine. **J Neurosurg Spine 1:**168–174, 2004
16. Ohtsuka K, Terayama K, Tsuchiya T, Wada K, Furukawa K, Ohkubu M: [A surgical procedure of the anterior decompression of the thoracic spinal cord through the posterior approach.] **Orthop Surg Traumatol 26:**1083–1090, 1983 (Jpn)
17. Seichi A, Hoshino Y, Ohnishi I, Kurokawa T: The role of calcium metabolism abnormalities in the development of ossification of the posterior longitudinal ligament of the cervical spine. **Spine (Phila Pa 1976) 17 (3 Suppl):**S30–S32, 1992
18. Suzuki K, Ishida Y, Ohmori K: Long term follow-up of diffuse idiopathic skeletal hyperostosis in the cervical spine. Analysis of progression of ossification. **Neuroradiology 33:**427–431, 1991
19. Tsukamoto N, Maeda T, Miura H, Jingushi S, Hosokawa A, Harimaya K, et al: Repetitive tensile stress to rat caudal vertebrae inducing cartilage formation in the spinal ligaments: a possible role of mechanical stress in the development of ossification of the spinal ligaments. **J Neurosurg Spine 5:**234–242, 2006
20. Yamazaki M, Mochizuki M, Ikeda Y, Sodeyama T, Okawa A, Koda M, et al: Clinical results of surgery for thoracic myelopathy caused by ossification of the posterior longitudinal ligament: operative indication of posterior decompression with instrumented fusion. **Spine (Phila Pa 1976) 31:**1452–1460, 2006

Manuscript submitted December 26, 2013.
Accepted July 7, 2014.
Please include this information when citing this paper: published online August 15, 2014; DOI: 10.3171/2014.7.SPINE131191.
Address correspondence to: Shurei Sugita, M.D., 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. email: ssugita-tky@umin.ac.jp.

J Bone Miner Metab
DOI 10.1007/s00774-014-0583-9

ORIGINAL ARTICLE

Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) of the whole spine and its association with lumbar spondylosis and knee osteoarthritis: the ROAD study

Ryohei Kagotani · Munehito Yoshida · Shigeyuki Muraki · Hiroyuki Oka · Hiroshi Hashizume · Hiroshi Yamada · Yoshio Enyo · Keiji Nagata · Yuyu Ishimoto · Masatoshi Teraguchi · Sakae Tanaka · Kozo Nakamura · Hiroshi Kawaguchi · Toru Akune · Noriko Yoshimura

Received: 23 August 2013 / Accepted: 23 February 2014
© The Japanese Society for Bone and Mineral Research and Springer Japan 2014

Abstract We aimed to assess the prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and its association with lumbar spondylosis (LS) and knee osteoarthritis (KOA) using a population-based cohort study entitled Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In the baseline ROAD study, which was performed between 2005 and 2007, 1,690 participants in mountainous and coastal areas underwent anthropometric measurements and radiographic examinations of the whole spine (cervical, thoracic, and lumbar) and both knees. They also completed an interviewer-administered questionnaire. Presence of DISH was diagnosed according to Resnick criteria, and LS and KOA were defined as Kellgren-Lawrence (KL) grade ≥3. Among the 1,690 participants, whole-spine radiographs of 1,647 individuals (97.5 %; 573 men, 1,074 women; mean age, 65.3 years) were evaluated. Prevalence of DISH was 10.8 % (men 22.0 %, women 4.8 %), and was significantly higher in older participants (presence of DISH 72.3 years, absence of DISH 64.4 years) and mainly distributed at the thoracic spine (88.7 %). Logistic regression analysis revealed that presence of DISH was significantly associated with older age [+1 year, odds ratio (OR): 1.06, 95 % confidence interval (CI): 1.03–1.14], male sex (OR: 5.55, 95 % CI: 3.57–8.63), higher body mass index (+1 kg/m^2, OR: 1.08, 95 % CI: 1.02–1.14), presence of LS (KL2 vs KL0: 1, OR: 5.50, 95 % CI: 2.81–10.8) (KL ≥3 vs KL0: 1, OR: 4.09, 95 % CI: 2.08–8.03), and presence of KOA (KL ≥3 vs KL0: 1, OR: 1.89, 95 % CI: 1.14–3.10) after adjusting for smoking, alcohol consumption, and residential area (mountainous vs coastal). This cross-sectional population-based study clarified the prevalence of DISH in general inhabitants and its significant association with LS and severe KOA.

Keywords Prevalence · Diffuse idiopathic skeletal hyperostosis · Knee osteoarthritis · Lumbar spondylosis · ROAD study

R. Kagotani · M. Yoshida (✉) · H. Hashizume · H. Yamada · Y. Enyo · K. Nagata · Y. Ishimoto · M. Teraguchi
Department of Orthopaedic Surgery, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8509, Japan
e-mail: yoshimunenoriko@yahoo.co.jp

S. Muraki · T. Akune
Department of Clinical Motor System Medicine, 22nd Century Medical and Research Centre, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

H. Oka · N. Yoshimura
Department of Joint Disease Research, 22nd Century Medical and Research Centre, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

S. Tanaka · H. Kawaguchi
Department of Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

K. Nakamura
Rehabilitation Services Bureau, National Rehabilitation Centre for Persons with Disabilities, Tokorozawa, Japan

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is characterised by calcification and ossification of soft tissue such as entheses and joint capsules [1]. Resnick and Niwayama specifically defined DISH as the radiographic finding of calcification or ossification along the anterolateral aspects of at least 4 contiguous vertebral levels (across 3 disc spaces), with relative preservation of disc height in the involved vertebral segments and without degenerative disc disease [2]. In 1998, Mata and co-workers [3] developed a

Published online: 13 March 2014

scoring system such that the presence of DISH could be assessed reproducibly. This system scores individuals who fulfill the Resnick criteria by numerically classifying each vertebral level based on the amount of ossification and whether partial or complete bridging of the disc space is present [3].

Although some reports have indicated a significant association between DISH and ossification of the posterior longitudinal ligament (OPLL) [4–7], DISH is thought to be an asymptomatic condition in many affected individuals; however, several clinical symptoms have been described including pain, limited range of spinal motion, and increased susceptibility to unstable spinal fractures after trivial trauma [8]. In addition, dysphagia and airway obstruction at the cervical levels [8, 9], as well as radiculopathy and spinal injury after spinal fracture [10–12], have been reported as clinical manifestations of DISH.

Although the condition is recognised in many parts of the world [13–20], there are relatively few population-based studies concerning its prevalence. Such data are important in order to characterise the burden of the disease. In addition, regarding its characteristics, several epidemiologic studies have reported that DISH is observed mainly in the elderly, and that prevalence increases with age [18, 19]. Men are affected by DISH much more frequently than women [20]. Although metabolic disturbance is hypothesised to be a factor [21, 22], the aetiology of the condition remains unknown.

Based on the definition of DISH as the radiographic finding of calcification or ossification, it appears that the condition might be associated with osteoarthritis (OA) of the spine. The severity of OA, as observed on radiography, was determined according to Kellgren-Lawrence (KL) grading as follows [23]: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes; and KL4, bone sclerosis, joint or intervertebral space narrowing, and large osteophytes. KL2 is commonly used as the diagnostic criterion for lumbar spondylosis (LS) or OA at other sites. Thus, LS—defined as KL2 (defined as the definite presence of osteophytes)—could easily be associated with DISH. However, there are few reports to confirm the association between DISH and severe LS with the criterion of KL3 (defined as the presence of intervertebral space narrowing) or KL4 (defined as the presence of bone sclerosis). In addition, there are few reports to clarify the association between DISH and OA at other sites, such as the knees.

We conducted a survey, known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study, using a population-based cohortto determine the prevalence of DISH using lateral whole-spine radiography in recently examined subjects, which included men and women in Japan. Another aim of our study was to clarify the association of DISH with LS and knee osteoarthritis (KOA) based on KL grade.

Materials and methods

Outline of the ROAD study

We conducted the present study using the cohorts established in 2005 for the ROAD study—a nationwide, prospective study of OA comprising population-based cohorts in several communities in Japan. Details of the cohort profile have been reported elsewhere [24, 25]. Briefly, from 2005 to 2007, we developed a baseline database that included clinical and genetic information of 3,040 residents of Japan (1,061 men, 1,979 women) with a mean age of 70.3 (SD, 11) years [men: 71 (SD, 10.7) years, women: 69.9 (SD, 11.2) years]. Subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects (465 men, 885 women) from an urban region in Itabashi, Tokyo; 864 (319 men, 545 women) from a mountainous region in Hidakagawa, Wakayama; and 826 (277 men, 549 women) from a coastal region in Taiji, Wakayama.

Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information, such as occupation, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. The questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS) [26]; some new items also were added to the modified questionnaire. Participants were asked whether they took prescription medication daily or nearly every day (no = 0, yes = 1). If the participants did not know the reason for the prescribed medication, they were asked to bring their medication to the medical doctor (NY).

Anthropometric measurements, including height (cm), body weight (kg), arm span (cm), bilateral grip strength (kg), and body mass index (BMI, kg/m^2) were recorded for each patient. Medical information was recorded by experienced orthopaedic surgeons on systematic, local, and mental status, including information on back, knee, and hip pain; swelling and range of motion of the joints; and patellar and Achilles tendon reflexes.

Eligible subjects of the present study

In the ROAD study, radiographic examination of the thoracic spine was performed only in subjects in mountainous and coastal regions. These subjects also underwent blood and urinary examinations. In the present study, among 1,690 subjects (596 men, 1,094 women) in mountainous and

coastal regions in the ROAD study, we excluded 43 whose radiograph quality was so poor that it was difficult to observe the sites of thoracic–lumbar junction and lumbosacral junction; thus, we analysed 1,647 participants (573 men, 1,074 women) ranging in age from 23 to 94 years (mean: 65.3 years, men: 66.3 years, women: 64.7 years).

Study participants provided written informed consent, and the study was approved by the ethics committees of the University of Wakayama Medical University (No. 373) and the University of Tokyo (No. 1264 and No. 1326).

Radiographic assessment

Plain radiographs of the cervical, thoracic, and lumbar spine in the anteroposterior and lateral views, and bilateral knees in the anteroposterior view with weight-bearing and foot-map positioning were obtained. DISH was diagnosed according to the following criteria, defined by Resnick and Niwayama [2]: (1) flowing ossification along the lateral aspect of at least 4 contiguous vertebral bodies, (2) relative preservation of intervertebral disc height in the involved segments, and (3) absence of epiphyseal joint bony enclosing and sacroiliac joint erosion. In the assessment of lateral radiographs, since it was difficult to read the C7/Th1 to T3/4 vertebral levels, 'whole spine' in the present study implies radiographs assessed from the C0/1 to C6/7, Th4/5 to Th12/L1, and L1/L2 to L5/S1 levels.

The radiographic severity of OA was determined according to the above-mentioned KL grade [20]. Radiographs of each site (i.e., vertebrae and knees) were examined by a single experienced orthopaedic surgeon (SM) who was blinded to the participants' clinical status. In the present study, the maximum grade, diagnosed in at least 1 intervertebral level of the lumbar spine or at least 1 knee joint, was regarded as the subject's KL grade.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the Chi-square test. Differences in continuous variables were tested for significance using analysis of variance for comparisons among multiple groups or Scheffe's least significant difference test for pairs of groups.

To test the association between the presence of DISH and LS and/or KOA, we used logistic regression analysis. In the analysis, we used presence of DISH as the objective variable (absence = 0, presence = 1), and severity of prevalent LS (KL0, 1 = 0 vs. KL2 = 1; KL0, 1 = 0 vs. KL3 or 4 = 2) and KOA (KL0, 1 = 0 vs. KL2 = 1; KL0, 1 = 0 vs. KL3 or 4 = 2) as explanatory variables, in addition to basic characteristics such as age (+1 year), sex (men = 1, women = 0), BMI (+1 kg/m^2), and regional differences (mountainous area = 0, coastal area = 1). Other potential associated factors were selected with significant or marginal ($p < 0.1$) association with DISH status in a simple linear analysis. The selected explanatory variables for logistic regression analysis are described in the Results section.

Results

Prevalence of DISH was 10.8 % (men: 22.0 %, women: 4.8 %), and was significantly higher in men than in women. Figure 1 shows the prevalence of DISH according to age and sex. Prevalence increased with age in both men and women. Prevalence in subjects classified by age-strata—<50, 50–59, 60–69, 70–79, and ≥80 years—was 1.8, 11.7, 15.4, 32.6, and 39.6 % in men, and 0.7, 1.5, 3.5, 7.6, and 11.8 % in women, respectively.

Table 1 shows the baseline characteristics of the 1,647 participants with and without DISH. In total, subjects with DISH tended to be older, taller, heavier, and have higher BMI than those without DISH ($p < 0.0001$). In the comparison classified by sex, age was significantly higher in those with DISH in both men and women ($p < 0.0001$). In women, mean weight and BMI were significantly higher in those with DISH than in those without DISH (weight: $p < 0.05$, BMI: $p < 0.0001$).

Prevalence of DISH was lower in individuals residing in a coastal area. Individuals with DISH had a higher frequency of smoking and alcohol consumption ($p < 0.05$). The difference in the residing area was significantly observed in men. However, in the comparison classified by sex, differences in smoking and drinking were diluted (Table 1).

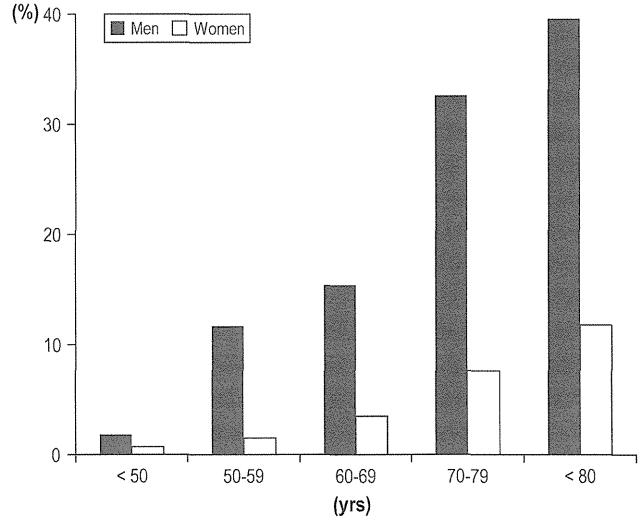

Fig. 1 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) according to sex and age

Table 1 Mean values (standard deviations) of the anthropometric measurements and the prevalence of lifestyle factors for the participants classified by presence or absence of DISH

	Total (n = 1647)			Men (n = 573)			Women (n = 1074)		
	DISH (−) n = 1470	DISH (+) n = 177	p	DISH (−) n = 447	DISH (+) n = 126	p	DISH (−) n = 1023	DISH (+) n = 51	p
Age (years)	64.4 (12.1)	72.3 (8.4)	<0.0001***	64.6 (12.1)	72.4 (8.2)	<0.0001***	64.3 (12.2)	71.9 (8.8)	<0.0001***
Height (cm)	154.7 (9.2)	158.6 (8.8)	<0.0001***	163.7 (7.3)	162.5 (6.7)	0.0918	150.8 (7.0)	148.9 (5.5)	0.0589
Weight (kg)	55.9 (10.6)	60.1 (10.5)	<0.0001***	62.3 (11.0)	62.1 (10.0)	0.8806	51.9 (8.8)	55.0 (10.3)	0.0126*
BMI (kg/m^2)	22.9 (3.4)	23.8 (3.3)	0.0005***	23.2 (3.2)	23.5 (2.9)	0.3378	22.8 (3.4)	24.7 (3.9)	0.0001***
Residing in the coastal area (%)	50.48	40.11	0.009**	50.3	35.7	0.004**	50.5	51.0	0.951
Current smoking habit (regularly, ≥1 month) (%)	11.9	21.3	<0.001***	29.9	29.0	0.858	3.8	2.0	0.506
Current alcohol consumption (regularly, ≥1 month) (%)	38.7	48.0	0.017*	68.5	61.1	0.122	25.7	15.7	0.108
Presence of LS (KL grade ≥2) (%)	59.1	93.8	<0.001***	72.0	94.4	<0.001***	53.4	92.2	<0.001***
Presence of LS (KL grade ≥3) (%)	35.6	48.0	0.001**	35.4	45.2	0.043*	35.7	54.9	0.005**
Presence of KOA (KL grade ≥2) (%)	48.2	65.5	<0.001***	35.5	58.7	<0.001***	53.8	83.3	<0.001***
Presence of KOA (KL grade ≥3) (%)	18.4	34.5	<0.001***	11.0	27.0	<0.001***	21.7	54.2	<0.001***

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

DISH (−) absence of DISH, *DISH (+)* presence of DISH

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1 also shows the prevalence of LS and KOA defined by KL grade ≥2 and grade ≥3, according to DISH status. In total, the prevalence of LS was higher in those with DISH than in those without DISH ($p = 0.001$). A similar tendency was observed in the prevalence of KOA ($p < 0.001$). This tendency also was noted in the comparison classified by sex.

We classified subjects with DISH into 4 types: (1) cervical, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the cervical region (C0/1–C6/7); (2) thoracic, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the thoracic region (Th4/5–Th12/L1); (3) lumbar, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the lumbar region (L1/2–L5/S1); and (4) diffuse, ossification along the lateral aspect of at least 4 contiguous vertebral bodies in more than 2 regions or through more than 2 regions. Table 2 shows the prevalence of DISH classified by location in the spine. A total of 89 % was shown to be thoracic, whereas the remaining was diffuse; there were no subjects with cervical-type or lumbar-type DISH.

Figure 2 shows the distribution of DISH classified by vertebral level (Th4/5–LS/S1). Among diffuse-type DISH, although 2 subjects had ossification in the cervical region, the cervical site is excluded from the figure. Figure 2 shows that ossification was observed mainly in the middle-lower thoracic sites (Th7/8–Th9/10).

Logistic regression analysis was performed with DISH as the objective variable, LS and KOA as explanatory variables, and patient characteristics including age, sex, BMI, regional differences, smoking, and alcohol consumption as potential risk factors. Presence of DISH was significantly associated with presence of LS (KL2 vs KL0: 1, KL ≥3 vs KL0: 1) and KOA (KL ≥3 vs KL0: 1). Among other potential associated factors, older age, male sex, and higher BMI remained as significantly associated with the presence of DISH (Table 3).

Table 2 Number (proportion, %) of DISH (+) patients classified by spinal ossification site

Type of DISH	Total	Men	Women
Cervical type	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Thoracic type	157 (88.7 %)	111 (88.1 %)	46 (90.2 %)
Lumbar type	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Diffuse type	20 (11.3 %)	15 (11.9 %)	5 (9.8 %)
Total	177 (100.0 %)	126 (100.0 %)	51 (100.0 %)

Cervical type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the cervical region (C0/1–C6/7)

Thoracic type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the thoracic region (Th4/5–Th12/L1)

Lumbar type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the lumbar region (L1/2–L5/S1)

Diffuse type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing in more than 2 regions or through more than 2 regions

Finally, to clarify the association of DISH with LS and KOA, we performed logistic regression analysis using DISH as an objective variable, LS and KOA as explanatory variables, and patient characteristics including age, sex, BMI, regional differences, smoking, and alcohol consumption as potential risk factors. Presence of DISH was significantly associated with presence of LS (KL2 vs KL0: 1, KL ≥3 vs KL0: 1) and KOA (KL ≥3 vs KL0: 1) independently (Table 4).

Discussion

In the present study, using lateral whole-spine radiographs of recently examined population-based samples, we estimated that the prevalence of DISH was one-tenth of the population, which consisted of participants from the ROAD study. The subjects with DISH tended to be older and had bigger body build than those without DISH. In addition, DISH was observed more frequently in men than

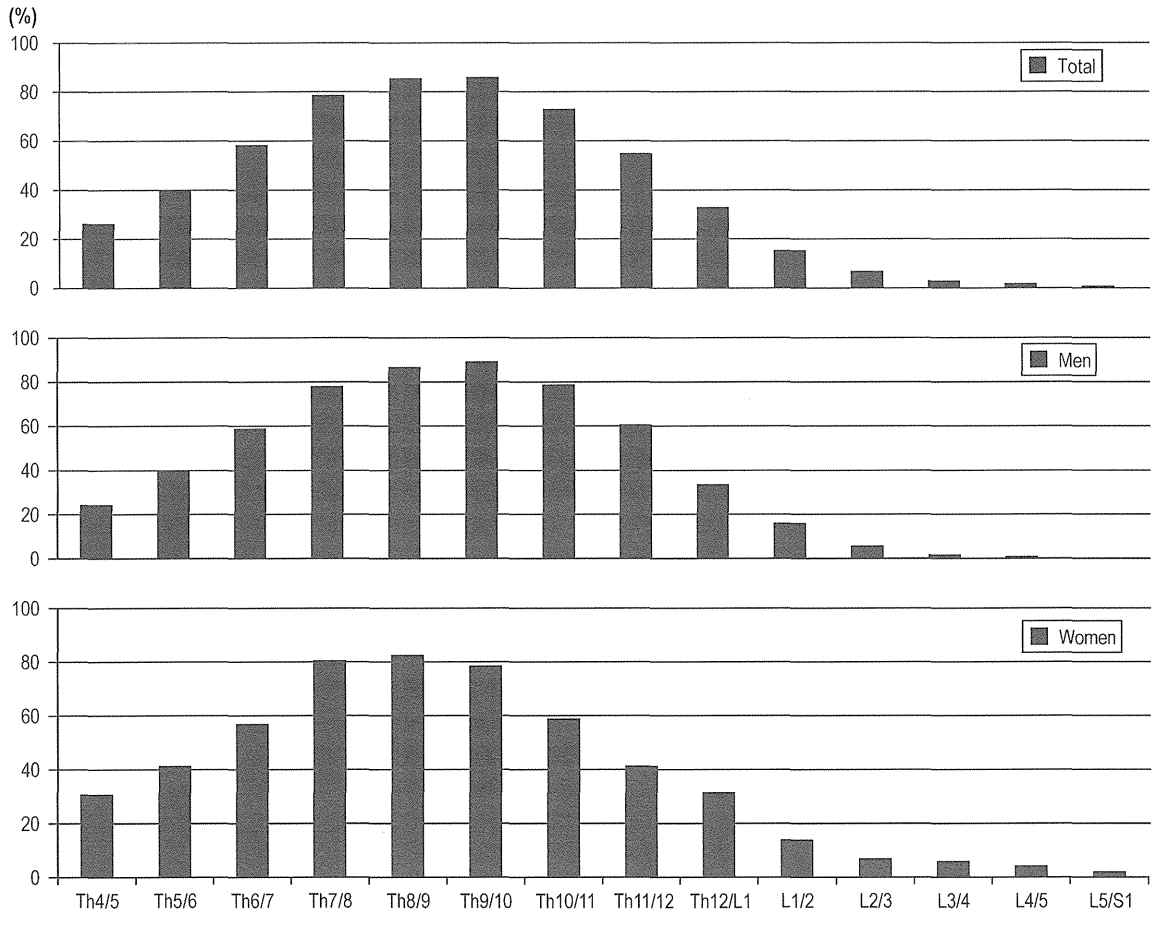

Fig. 2 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in each vertebral level, classified by sex

Table 3 Odds ratios of lumbar spondylosis or knee osteoarthritis, and potentially associated factors for the presence of DISH vs. absence of DISH

Explanatory variables	Category	OR	95 % CI	*p*
Lumbar spondylosis				
Presence of LS	0: KL grade = 0, 1, 1: KL grade = 2	5.80	2.97–11.3	<0.001***
	0: KL grade = 0, 1, 2: KL grade ≥3	4.54	2.34–8.84	<0.001***
Age (years)	+1 year	1.07	1.05–1.09	<0.001***
Gender	1: men, 0: women	4.61	3.05–6.99	<0.001***
Region	0: mountainous area, 1: coastal area	0.88	0.61–1.26	0.475
BMI (kg/m^2)	+1 kg/m^2	1.11	1.05–1.17	<0.001***
Smoking	0: ex or never smoker, 1: current smoker	1.65	1.04–2.63	0.034*
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.82	0.56–1.22	0.329
Knee osteoarthritis				
Presence of KOA	0: KL grade = 0, 1, 1: KL grade = 2	1.34	0.85–2.10	0.211
	0: KL grade = 0, 1, 2: KL grade ≥3	2.15	1.32–3.52	0.002**
Age (years)	+1 year	1.07	1.04–1.09	<0.001***
Gender	1: men, 0: women	6.90	4.48–10.6	<0.001***
Region	0: mountainous area, 1: coastal area	0.95	0.65–1.37	0.771
BMI (kg/m^2)	+1 kg/m^2	1.09	1.03–1.15	0.002**
Smoking	0: ex or never smoker, 1: current smoker	1.52	0.95–2.42	0.079
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.85	0.58–1.26	0.431

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

OR odds ratios, *95 % CI* 95 % confidence interval

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4 Odds ratios of lumbar spondylosis and knee osteoarthritis, and potentially associated factors for the presence of DISH vs. absence of DISH

Explanatory variables	Category	OR	95 % CI	*p*
Presence of LS (KL grade = 2)	vs. KL grade = 0, 1	5.50	2.81–10.8	<0.001***
Presence of LS (KL grade ≥3)	vs. KL grade = 0, 1	4.09	2.08–8.03	<0.001***
Presence of KOA (KL grade = 2)	vs. KL grade = 0, 1	1.22	0.77–1.92	0.404
Presence of KOA (KL grade≥ 3)	vs. KL grade = 0, 1	1.89	1.14–3.10	0.013**
Age (years)	+1 year	1.06	1.03–1.14	<0.001***
Gender	1: men, 0: women	5.55	3.57–8.63	<0.001***
Region	0: mountainous area, 1: coastal area	0.88	0.60–1.29	0.522
BMI (kg/m^2)	+1 kg/m^2	1.08	1.02–1.14	0.008**
Smoking	0: ex or never smoker, 1: current smoker	1.59	1.00–2.55	0.052
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.81	0.54–1.21	0.298

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

OR odds ratios, *95 % CI* 95 % confidence interval

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

in women, and the most common site was the thoracic vertebrae. Presence of DISH was significantly associated with the presence of KOA and LS, after adjusting for potential associated factors.

There have been several epidemiologic studies on DISH in many parts of the world [12–19]. The results indicate that DISH is observed mainly in men and the elderly; prevalence increases with age, and it is distributed mostly in the thoracic spine. These results are supported by the results of the present study. However, there are considerable differences in the prevalence. Weinfeld et al. [20] reported that genetic or hereditary differences are

important predisposing factors for DISH. Their previous study involved patients from ethnic populations, including 667 white, 144 black, 72 Native American, 11 Hispanic, and 30 Asian patients. They showed that the Asian, black, and Native American populations had a remarkably lower prevalence of DISH; however, their study population was small. In a recent study, Kim et al. [18] reported that race influences the prevalence of DISH. Their prevalence of DISH was 5.4 % in men and 0.8 % in women aged over 80 years in a Korean population, which is remarkably lower than the prevalence in our study, despite the similar race. Our prevalence was similarly high as the white population in Weinfield's report. Therefore, it is believed that genetic factors influence the prevalence of DISH more than race.

The present study clarified that most cases of DISH were observed in the thoracic vertebrae. There were no cases of DISH located in only the cervical or lumbar region. All cases of DISH in the cervical region were categorised as diffuse-type. Even if subjects were categorised into diffuse-type DISH, thoracic vertebrae were found to be the most affected. In addition, among the thoracic vertebrae, we found the predilection site to be the middle thoracic vertebrae (Th7–Th9). Holton et al. [27] reported that the distribution of the lowest level of DISH in 298 male subjects aged $\geq$65 years was 38 % in the thoracic region, 49 % in the thoracolumbar region, and 13 % in the lumbar region. It is interesting that DISH has predilection sites, which might be due to anatomic alignment of the vertebrae. For example, the middle thoracic vertebrae are likely to be affected by compressive mechanical stress because the Th8 is located nearly at the top in physiologic kyphosis. DISH originates mainly from the thoracic spine and extends to the cervical and/or lumbar spine by mechanical stress. In the present cross-sectional study, we could not evaluate whether DISH tends to occur in the thoracic vertebrae and then forms in the lumbar spine secondarily; however, we were able to follow-up on the ROAD study and clarify the disease course of thoracic DISH.

Regarding the definition of DISH, it might be easy to imagine that LS, defined by KL2 (defined as radiographically definite osteophytes), is associated with DISH. However, there are few reports to confirm the association between DISH and severe LS with the criterion of KL3 or 4. In the present study, we confirmed the significant association between DISH and LS, not only with the criterion of KL2, but also with KL $\geq$3. In addition, there are few reports to clarify the association between DISH and OA of other sites. In the present study, we also confirmed the significant association between DISH and KOA. In fact, the OR of the presence of DISH for KOA significantly increased according to the severity of KOA. The effects of LS and KOA coexisted independently. This result suggests that DISH and OA might be in a similar vein of disease, for example, the so-called 'bone proliferative group'. There have been several reports regarding the association between DISH and OPLL [4–7]. Resnick et al. [4] described 4 patients with coexisting DISH and cervical OPLL, and found OPLL in 50 % of 74 additional patients with DISH after reviewing their cervical spine radiographs. However, there has been no report on the association of DISH and OA; thus the etiology of ossification might not be similar to that of OA. Therefore, with only the results of the present study, we cannot definitely claim that DISH and OA are in a similar disease group, even though DISH tends to have similar associated factors, such as age, overweight (bigger BMI), and mechanical stress, as OA.

Another hypothesis is that there might be hidden associated factors that might affect both DISH and OA. We considered risk factors for metabolic syndrome as potential confounders. Several constitutional and metabolic abnormalities have been reported to be associated with DISH including obesity, large waist circumference, hypertension, diabetes mellitus, hyperinsulinemia, dyslipidemia, and hyperuricemia [21, 28–30]. In addition, both LS and KOA are well known to be associated with obesity [31]. We have already reported on the presence of hypertension and impaired glucose tolerance, and shown that the accumulation of metabolic risk factors is associated with the presence and occurrence of KOA [32, 33]. In addition, we found that current smoking, a known risk factor for cardiovascular disease as well as metabolic risk factors, was significantly associated with DISH. These findings may indicate that DISH is a candidate surrogate index for metabolic risk factors as a predictor of OA, or vice versa. We could not evaluate this hypothesis at present, but we would clarify the association including the causal relationships between DISH, OA, and metabolic risk factors in a further study.

Alternatively, we considered associated factors for inflammation or cartilage metabolic turnover as potential confounders between DISH and OA. These factors might coexist as risk factors for DISH and OA. Thus, there might be a direct or indirect pathway between DISH and OA via hidden associated factors, which should be investigated in a further study.

This study has several limitations. First, although the ROAD study includes a large number of participants, these subjects may not truly represent the general population. To address this, we compared the anthropometric measurements and frequencies of smoking and alcohol consumption between study participants and the general Japanese population; no significant differences were found, with the exception that male ROAD study participants aged 70–74 years were significantly smaller in terms of body structure than the overall Japanese population ($p < 0.05$)

[25]. This difference should be considered when evaluating potential risk factors in men aged 70–74 years; factors such as body build, particularly greater weight, are known to be associated with LS and KOA. Therefore, our results may be an underestimation of the prevalence of these conditions. Second, in the present study, we used only the data of the baseline study. Thus, we were not able to confirm a causal relationship between DISH status and other associated factors, as mentioned above. Nevertheless, we have performed a follow-up study, so we will be able to clarify the causal relationship between DISH status and OA in the near future. Third, this study could not evaluate the cervicothoracic junction (C7–Th4) because we assessed only radiographs. Although most cases of DISH existed in the inferior thoracic spine, as Fig. 2 shows, the lack of findings in the C7/C1–Th3/Th4 levels might have underestimated the prevalence of DISH. To evaluate the cervicothoracic junction, it would be necessary to use computed tomography or magnetic resonance imaging of the whole spine, which appeared impossible to perform on more than 1,600 subjects. Fourth, LS defined by KL2 may have been included in cases of DISH, but there is no method to confirm the overlap of the presence of DISH and LS of KL2 using the radiographic diagnostic criteria. DISH is observed mainly in the thoracic region, and only the diffuse type expands partly into the lumbar region. Therefore, there is a small possibility that LS of KL2 might be contaminated into DISH. Finally, in the present study, we could not evaluate other sites of OA besides the knee and lumbar spine, such as the hands or hip. To evaluate DISH and other sites of OA, we should evaluate the presence or occurrence of OA at other sites in a further study.

In conclusion, in the present population-based study, we found that the prevalence of DISH was 10.8 % in the overall population. Prevalence was significantly higher in older subjects, and mainly distributed at the thoracic spine. Logistic regression analysis revealed that the presence of DISH was significantly associated with older age, male sex, higher BMI, and presence of severe KOA.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research B23390172 and B20390182 to NY, C20591737 to TA, and C20591774 to SM, for Young Scientists A18689031 to HO, and Collaborating Research with NSF 08033011-00262 (Director, NY) from the Ministry of Education, Culture, Sports, Science and Technology; and H17-Men-eki-009 (Director, KN), H18-Choujyu-037 (Director, TN), H20-Choujyu-009 (Director, NY), H23-Chojyu-002 (Director, TA), and H25-Chojyu-007 (Director, NY) from the Ministry of Health, Labour and Welfare in Japan. This study also was supported by grants from the Japan Osteoporosis Society (NY, SM, HO, and TA) and research aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1 and 2010-2 [Director, HK]). The authors wish to thank Dr. Takako Nojiri and Mr. Kazuhiro Hatanaka of the Gobo Public Health Centre; Dr. Naoki Hirabayashi of the Kawakami Clinic, Hidakagawa Town; Mrs. Tomoko Takijiri, Mrs. Kumiko Shinou, Mrs. Rie Takiguchi, Mrs. Kyoko Maeda, Ms. Ikuyo Ueyama, Mrs. Michiko Mori, Mrs. Hisayo Sugimoto, and other members of the public office in Hidakagawa Town; Dr. Shinji Matsuda of the Shingu Public Health Centre; and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, Mr. Shoichi Shimoichi, Mrs. Megumi Takino, Mrs. Shuko Okada, Mrs. Kazuyo Setoh, Mrs. Chise Ryouno, Mrs. Miki Shimosaki, Mrs. Chika Yamaguchi, Mrs. Yuki Shimoji, and other members of the public office in Taiji Town for their assistance in locating and scheduling participants for examinations. We also thank Ms. Kyoko Yoshimura, Mrs. Toki Sakurai, and Mrs. Saeko Sahara for their assistance with data reduction and administration.

Conflict of interest All authors declare that (1) no author has received corporate support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) the authors' spouses, partners, or children do not have financial relationships that may be relevant to the submitted work; and (4) the authors have no nonfinancial interests that may be relevant to the submitted work.

References

1. Mader R, Sarzi-Puttini P, Atzeni F, Olivieri I, Pappone N, Verlaan JJ, Buskila D (2009) Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis. Rheumatology (Oxford) 48: 1478–1481
2. Resnick D, Niwayama G (1976) Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 119:559–568
3. Mata S, Chhem RK, Fortin PR, Joseph L, Esdaile JM (1998) Comprehensive radiographic evaluation of diffuse idiopathic skeletal hyperostosis: development and interrater reliability of a scoring system. Semin Arthr Rheum 28:88–96
4. Resnick D, Guerra J Jr, Robinson CA, Vint VC (1978) Association of diffuse idiopathic skeletal hyperostosis (DISH) and calcification and ossification of the posterior longitudinal ligament. AJR 131:1049–1053
5. Ono M, Russell WJ, Kudo S, Kuroiwa Y, Takamori M, Motomura S, Murakami J (1982) Ossification of the thoracic posterior longitudinal ligament in a fixed population. Radiological and neurological manifestations. Radiology 143:469–474
6. Ehara S, Shimamura T, Nakamura R, Yamazaki K (1998) Paravertebral ligamentous ossification: DISH, OPLL and OLF. Eur J Radiol 27:196–205
7. Yoshimura N, Nagata K, Muraki S, Oka H, Yoshida M, Enyo Y, Kagotani R, Hashizume H, Yamada H, Ishimoto Y, Teraguchi M, Tanaka S, Kawaguchi H, Toyama Y, Nakamura K, Akune T (2013) Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and its associated factors in the Japanese population: a 3-year follow-up of the ROAD study. Osteoporos Int [E-pub ahead of print]
8. Hannallah D, White AP, Goldberg G (2007) Diffuse idiopathic skeletal hyperostosis. Oper Tech Orthop 17:174–177
9. Albert TJ, Mader R (2002) Clinical manifestations of diffuse idiopathic skeletal hyperostosis of the cervical spine. Semin Arthr Rheum 32:130–135
10. Meyer PR Jr (1999) Diffuse idiopathic skeletal hyperostosis in the cervical spine. Clin Orthop Relat Res 359:49–57
11. Westerveld LA, Verlaan JJ, Oner FC (2009) Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J 18:145–156
12. Hendrix RW, Melany M, Miller F, Rogers LF (1994) Fracture of the spine in patients with ankylosis due to diffuse skeletal hyperostosis: clinical and imaging findings. AJR 162:899–904

13. Julkunen H, Heinonen OP, Knekt P, Maatela J (1975) The epidemiology of hyperostosis of the spine together with its symptoms and related mortality in a general population. Scand J Rheumatol 4:23–27
14. Tsukamoto Y, Onitsuka H, Lee K (1977) Radiological aspects of DISH in the spine. AJR 129:913–918
15. Bloom RA (1984) The prevalence of ankylosing hyperostosis in a Jerusalem population–with description of a method of grading the extent of the disease. Scand J Rheumatol 13:181–189
16. Cassim B, Mody G, Rubin D (1990) The prevalence of diffuse idiopathic skeletal hyperostosis in African blacks. Br J Rheumatol 29:131–132
17. Kiss C, O'Neill TW, Mituszova M, Szilagyi M, Donath J, Poor GY (2002) Prevalence of diffuse idiopathic skeletal hyperostosis in Budapest, Hungary. Rheumatology 41:1335–1336
18. Kim SK, Choi BR, Kim CG, Chung SH, Choe JY, Joo KB, Bae SC, Yoo DH, Jun JB (2004) The prevalence of diffuse idiopathic skeletal hyperostosis in Korea. J Rheumatol 31:2032–2035
19. Kiss C, O'Neill TW, Mituszova M, Szilagyi M, Poor G (2002) The prevalence of diffuse idiopathic skeletal hyperostosis in a population-based study in Hungary. Scand J Rheumatol 31:226–229
20. Weinfeld RM, Olson PN, Maki DD, Griffiths HJ (1997) The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large American Midwest metropolitan hospital populations. Skeletal Radiol 26:222–225
21. Kiss C, Szilagyi M, Paksy A, Poor G (2002) Risk factors for diffuse idiopathic skeletal hyperostosis: a case control study. Rheumatology (Oxford) 41:27–30
22. Mader R, Novofestovski I, Adawi M, Lavi I (2009) Metabolic syndrome and cardiovascular risk in patients with diffuse idiopathic skeletal hyperostosis. Semin Arthr Rheum 38:361–365
23. Kellgren JH, Lawrence LS (1957) Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494–502
24. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T (2010) Cohort profile: research on osteoarthritis/osteoporosis against disability (ROAD) study. Int J Epidemiol 39:988–995
25. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Yoshida H, Suzuki T, Yamamoto S, Ishibashi H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628
26. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K (2005) Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study–a large observational study of the determinants of fracture in older men. Contemp Clin Trials 26:569–585
27. Holton KF, Denard PJ, Yoo JU, Kado DM, Barrett-Connor E, Marshall LM, Osteoporotic Fractures in Men (MrOS) Study Group (2011) Diffuse idiopathic skeletal hyperostosis and its relation to back pain among older men: the MrOS Study. Semin Arthr Rheum 41:131–138
28. Littlejohn GO (1985) Insulin and new bone formation in diffuse idiopathic skeletal hyperostosis. Clin Rheumatol 4:294–300
29. Denko CW, Boja B, Moskowitz RW (1994) Growth promoting peptides in osteoarthritis and diffuse idiopathic skeletal hyperostosis–insulin, insulin-like growth factor-I, growth hormone. J Rheumatol 21:1725–1730
30. Vezyroglou G, Mitropoulos A, Kyriazis N, Antoniadis C (1996) A metabolic syndrome in diffuse idiopathic skeletal hyperostosis: a controlled study. J Rheumatol 23:672–676
31. Muraki S, Akune T, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Nakamura K, Kawaguchi H, Yoshimura N (2009) Association of occupational activity with radiographic knee osteoarthritis and lumbar spondylosis in elderly patients of population-based cohorts: a large-scale population-based study. Arthr Care Res 61:779–786
32. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T (2011) Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance in Japanese men and women: the ROAD study. J Rheumtol 38:921–930
33. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, Akune T (2012) Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthr Cartil 20:1217–1226

J Orthop Sci
DOI 10.1007/s00776-014-0631-2

CASE REPORT

Cervical myelopathy due to calcification of the posterior atlantoaxial membrane associated with generalized articular deposition of calcium pyrophosphate dihydrate: a case report and review of the literature

Kanji Mori · Shinji Imai · Kazuya Nishizawa · Yoshitaka Matsusue

Received: 17 March 2014 / Accepted: 30 July 2014
© The Japanese Orthopaedic Association 2014

Introduction

The ligamentum flavum can undergo either calcification or ossification that can lead to radiculomyelopathy [1, 2]. Calcification of the ligamentum flavum (CLF) characteristically occurs in the cervical spine in elderly women [1]. Theoretically speaking, calcification of the spinal ligament can affect any level of the cervical spine; however, we seldom encounter calcification of the posterior atlantoaxial membrane.

In the present report, we illustrate a unique case of cervical myelopathy due to calcification of the posterior atlantoaxial membrane that occurred concomitantly with generalized deposition of calcium pyrophosphate dihydrate (CPPD) as well as cervical ossification of the longitudinal ligament of the spine (OPLL).

Report of case

An 83-year-old woman visited our institution due to spastic gait, clumsiness, and numbness of bilateral hands progressing over the course of 2 months without preceding craniocervical trauma. Neurological examination revealed hyperreflexia of all four extremities, disturbance of discrete movement of bilateral hands, and bilateral positive Babinski signs. There was no bowel or bladder dysfunction. She had a history of surgical treatment of bilateral carpal tunnel release and right total knee arthroplasty. Routine blood tests were unremarkable except for a mildly increased blood sugar level (mild diabetes mellitus).

K. Mori (✉) · S. Imai · K. Nishizawa · Y. Matsusue
Department of Orthopaedic Surgery, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga 520-2192, Japan
e-mail: kanchi@belle.shiga-med.ac.jp

On X-ray examination, mixed-type OPLL extending from C2 to C5, retro-odontoid calcification, as well as a round calcified mass between the posterior arch of C1 and the lamina of C2 were noted (Fig. 1a). Calcified lesions were also found in the left knee, shoulders, and fingers (Fig. 1b–d). Joint fluid analyses of the left knee joint by polarization microscopy revealed CPPD crystals. Computed tomography (CT) clearly demonstrated oval calcification of the posterior atlantoaxial membrane, retro-odontoid calcification, as well as OPLL extending from C2 to C5. A calcified lesion was visualized as vague spotty images on CT (Fig. 2a, b). Subsequent magnetic resonance (MR) imaging demonstrated overt compression of the spinal cord due to calcification of the posterior atlantoaxial membrane, which was low intensity on both T1- and T2-weighted images (Fig. 3a–c). In turn, subaxial spinal cord compression due to OPLL was not evident (Fig. 3a–c). A change in the intensity of the spinal cord on T2-weighted images was also identified at the level of C1/2 (Fig. 3b).

Taking all of these findings into account, we attributed cervical myelopathy to the calcification of the posterior atlantoaxial membrane and posterior decompression surgery was performed. After bilateral exposure of C1/2, en-block extirpation of the posterior atlantoaxial membrane including the left calcified lesion was performed with partial laminectomy of C2, whereas we were able to preserve the posterior arch of C1. At the surgery, the lesion was carefully dissected from the dura matter. Chalky white deposits within the degenerated posterior atlantoaxial membrane were confirmed (Fig. 4a). Extensor muscles dissected from C2 were reconstructed after the decompression as much as possible. Histopathological examination revealed that calcified granules within degenerated fibrous tissue were surrounded by macrophages (Fig. 4b). The calcified granules were Alizarin red S positive (Fig. 4c). Furthermore, Raman

Published online: 08 September 2014

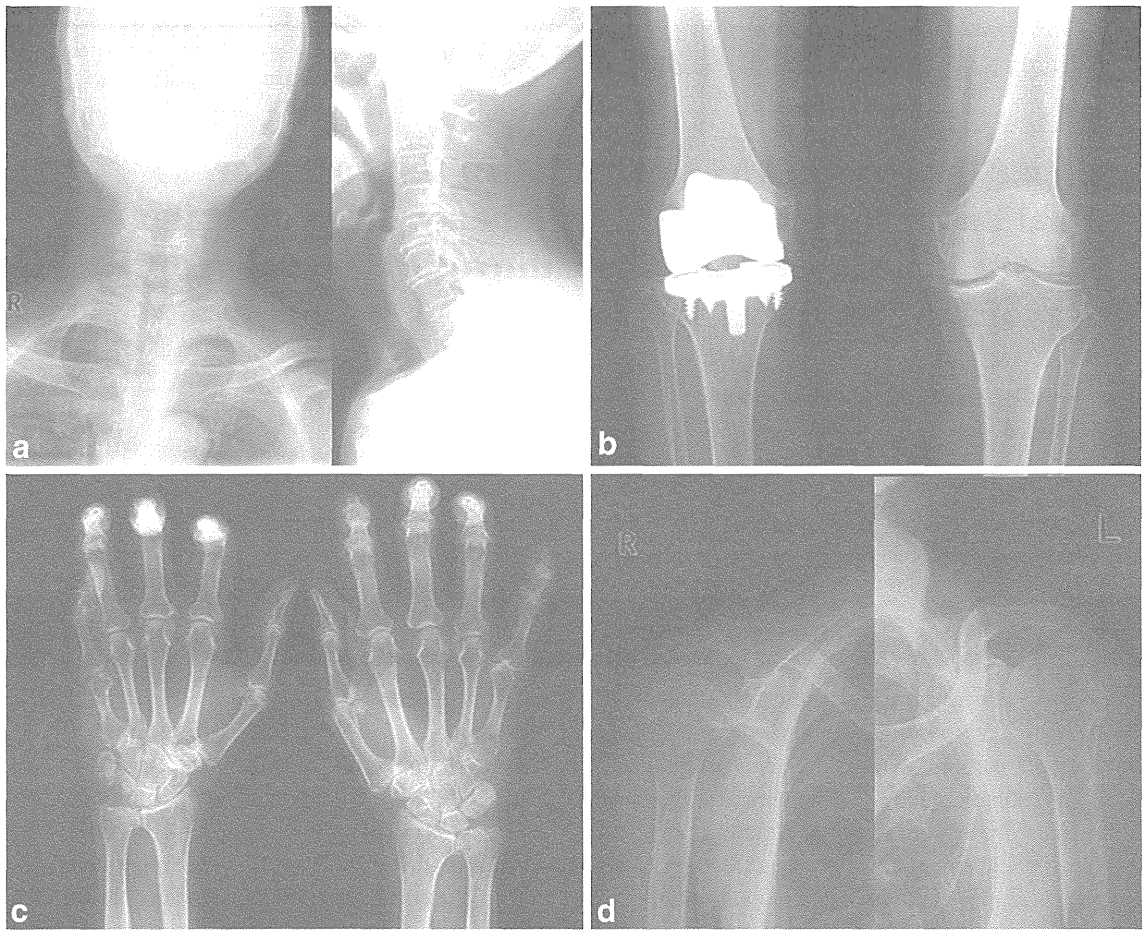

Fig. 1 Standard X-rays. **a** Ossification of the posterior longitudinal ligament of the cervical spine and an oval mass between the posterior arch of C1 and the lamina of C2 were confirmed. **b–d** Generalized articular calcifications were also seen

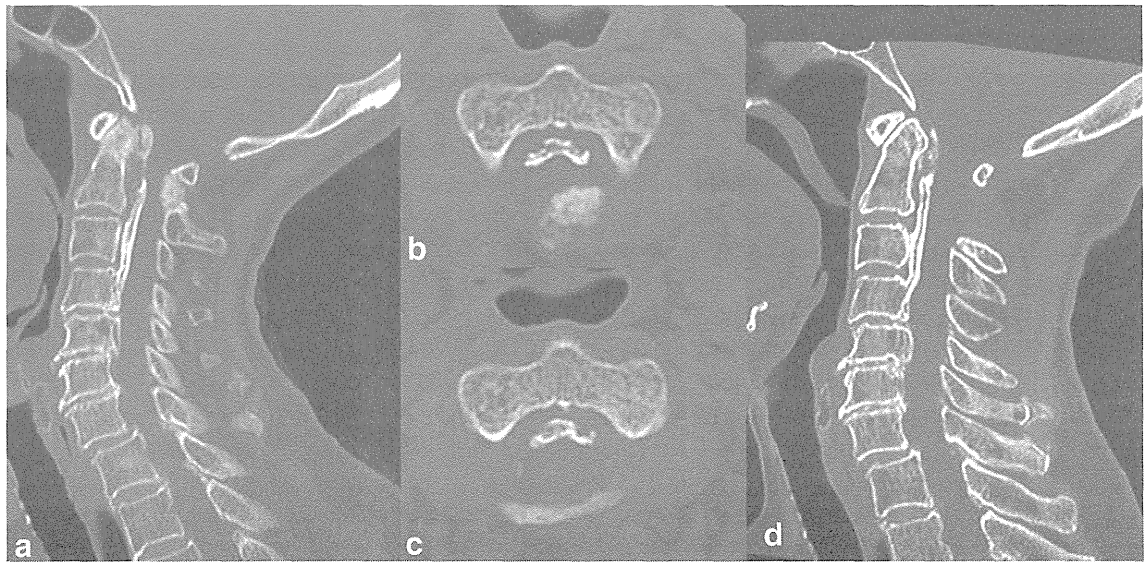

Fig. 2 **a, b** Pre-operative computed tomography (CT) revealed ossification of the longitudinal ligament of the spine extending from C2 to C5 and calcification at the posterior atlantoaxial membrane and retro-odontoid space. **c, d** Post-operative CT revealed extirpation of the calcification of the posterior atlantoaxial membrane

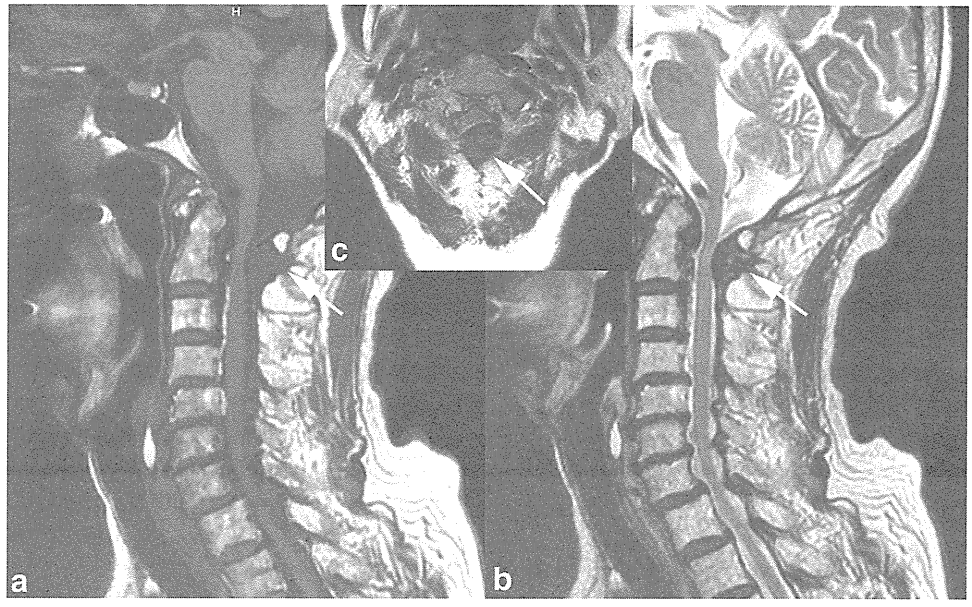

Fig. 3 Pre-operative magnetic resonance imaging demonstrated overt compression of the spinal cord due to calcification of the posterior atlantoaxial membrane (**c**), which was low intensity on both T1- (**a**) and T2-weighted (**b**) images (*arrows*), as well as a change in the intensity of the spinal cord on the T2-weighted image

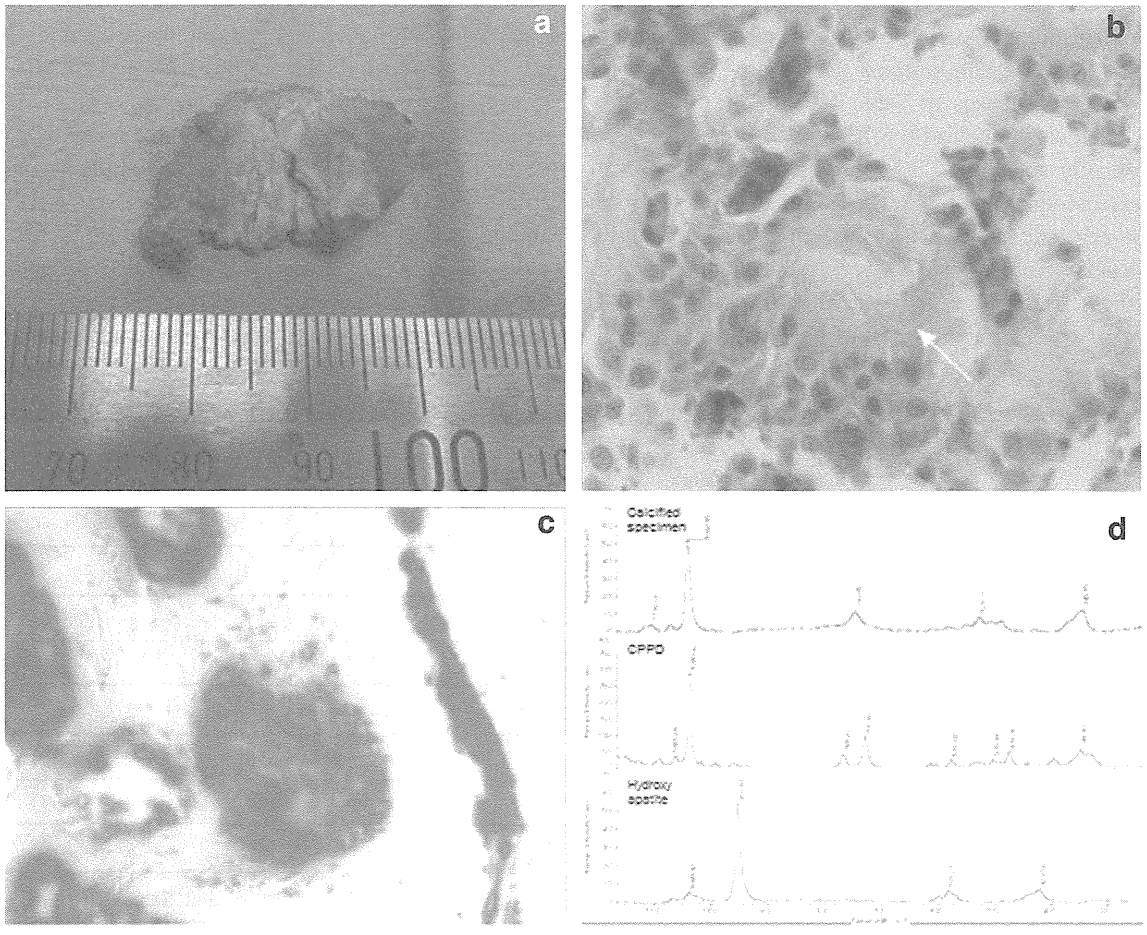

Fig. 4 **a** The presence of marked chalky white matter in the posterior atlantoaxial membrane was confirmed. **b** Histopathological examination revealed calcium pyrophosphate dihydrate (CPPD) crystals surrounded by macrophages (*arrow*, Original maginification ×400, H&E). **c** The calcified granules were positive for Alizarin red S staining (Original maginification×400). **d** Raman spectroscopy analysis revealed that the calcified lesion consisted only of CPPD, not hydroxy apatite

spectroscopy analysis revealed that the calcified lesion consisted only of CPPD, not hydroxyapatite (Fig. 4d).

After the surgical treatment, the patient quickly recovered from neurological deterioration. At the latest follow-up, 2 years after the surgery, the patient was doing well and had no neurological deterioration. Postoperative CT revealed complete resection of the calcification of the posterior atlantoaxial membrane (Fig. 2c, d). No obvious instability and progression of OPLL were observed in dynamic X-rays of the cervical spine.

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

Discussion

The first case of myelopathy due to CLF at the cervical spine was described in the late 1970s [3, 4]. Since those reports, to the best of our knowledge, more than 100 cases of symptomatic cervical CLF have been reported. The overwhelming majority of these cases have been reported from Japan. We have summarized the data available from previously reported cases in Table 1. This entity is more prevalent in elderly females [1, 5].

Theoretically speaking, CLFs can arise from any level of the cervical spine; but they predominantly arise from the lower cervical spine, with the two most commonly affected levels being C4/5 and C5/6 (Table 1). To the best of the authors' knowledge, Inoue et al. [6] briefly reported the first case of calcification of the posterior atlantoaxial membrane. The case was a 42-year-old man without any systemic background for ectopic ossification, yet he displayed multiple-level cervical ossification of the ligamentum flavum (OLF), thoracic OPLL, cervical CLF, and calcification of the posterior atlantoaxial membrane. However, the authors did not perform a detailed crystallographic analysis of the calcification of the posterior atlantoaxial membrane. Although the present case is the second report of calcification of the posterior atlantoaxial membrane, this is the first to include a crystallographic analysis.

The precise pathophysiology of CLF remains unknown; however, elastic fibers undergoing breakdown (i.e., degenerative changes in the ligamentum flavum) have been reported to exhibit increased affinity for calcium [7, 8]. It is commonly recognized that degenerative changes in the ligamentum flavum are induced by a combination of various factors, including the aging process, the decrease in estrogen in elderly women, mechanical stress of the lower cervical spine [7, 8], and chondrocytic metaplasia [9].

There have been no previous reports on calcification of the posterior atlantoaxial membrane. Functionally speaking, the ligamentum flavum provides a static, elastic force to support the spinal column in its return to a neutral position after flexion and extension movements. In turn, the posterior atlantoaxial membrane predominantly consists of a collagenous tissue, while elastic fibers comprise a minor counterpart [10]. Macroscopically, Ramsey [10] reported a definite lack of yellow color in these two upper cervical ligaments attached to the laminae of C1 and C2. On microscopic examination of the posterior atlantoaxial membrane

Table 1 Age distribution and topographic and crystallographic characterization of the 33 previously reported papers on the calcification of ligamentum flavum, along with a list of those papers

	Cervical segment						
	C1/2	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1
Distribution of calcium deposits	1	5	37	62	71	36	8
	Crystal type						
	CAP		CPPD	CPPD + HAP		HAP	Others
Number of identified calcium deposits	2		63	15		22	2
	Patient's age group						
	40s		50s	60s			Over 70
Female/total number	2/2		4/9	29/35			43/57

(1) Nanko et al. [14][a], (2) Kamakura et al. [4], (3) Jyotoku and Harada [16][a], (4) Kawano et al. [17], (5) Kida and Tabata [18][a], (6) Nagashima et al. [19][a], (7) Fujiwara et al. [20][a], (8) Akino et al. [15][a], (9) Iwasaki et al. [11], (10) Nakajima et al. [7], (11) Nagashima et al. [37], (12) Ogata et al. [12], (13) Hirano et al. [21][a], (14) Berghausen et al. [22], (15) Kubota et al. [23], (16) Kawano et al. [24], (17) Koyama et al. [38][a], (18) Hankey et al. [25], (19) Gomez and Chou [26], (20) Sato et al. [27], (21) Ohnishi et al. [28][a], (22) Okada et al. [8], (23) Takayama et al. [29][a], (24) Baba et al. [5], (25) Haraguchi et al. [30][a], (26) Higashi et al. [31][a], (27) Yamagami et al. [32], (28) Cabre et al. [13], (29) Ugarriza et al. [33], (30) Guesmi et al. [34], (31) Muthukumar and Karuppaswamy [35], (32) Yabuki and Kikuchi [36], (33) Mwaka et al. [9]

CAP carbonate apatite, *CPPD* calcium pyrophosphate dihydrate, *HAP* hydroxy apatite

[a] Articles in Japanese