松永俊二、小宮節郎、林協司、山元拓哉、長友淑美、今村勝行、武富栄二、砂原伸彦、米延策雄	関節リウマチ患者における頚椎手術の新しい成績評価基準に関する研究	九州リウマチ	25巻2号	136-139	2006
今村勝行、長友淑美、松永俊二、山元拓哉、宮口文宏、鶴　亜里抄、中村和史、横内雅博、林協司、米　和徳、小宮節郎	頚椎頚椎後縦靭帯骨化症における術後のしびれの経過について	整形外科と災害外科	55巻1号	22-24	2006
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Overview of Epidemiology and Genetics

Shunji Matsunaga[1] and Takashi Sakou[2]

In 1838, Key [1] reported that ossification of the spinal ligaments could be responsible for spinal cord paralysis. After Tsukimoto [2] reported a postmortem examination of a Japanese patient in whom severe spinal cord symptoms had been caused by ossification of the posterior longitudinal ligament in 1960, this condition attracted attention as a disease causing neurological symptoms as well as restriction of spinal movement. Onji et al. [3], Minagi and Gronner [4], and Nagashima [5] reported in non-Japanese journals that this condition could induce spinal cord symptoms. The condition was previously called "calcification of the posterior longitudinal ligament." After a pathology study showed that this condition involves ossified tissue, it began to be called "ossification of the posterior longitudinal ligament," as proposed by Terayama et al. [6]. Resnick and Niwayama [7] suggested that this condition was a subtype of diffuse idiopathic skeletal hyperostosis (DISH) on the grounds that ossification is seen in some other ligaments as well as the spinal ligaments. According to epidemiological reports on ossification of spinal ligaments published to date, some patients had symptoms attributable to ossification, whereas others were symptom-free but showed ossification on radiographs or computed tomography (CT) scans. In this chapter, the term "ossification of the posterior longitudinal ligament of the cervical spine" (OPLL) is used to indicate cases presenting with clinical symptoms attributable to ossification of this ligament; the term "ossified posterior longitudinal ligament of the cervical spine" (asymptomatic OPLL) is used for cases where no clinical symptoms are noted.

In Japan, epidemiological studies of OPLL have been performed primarily within the framework of the Ministry of Health and Welfare (MHW) study group on specific diseases, which was formed in 1975. A number of Japanese epidemiological studies of this disease have been published in Japan, but few such studies have been reported in other countries. Epidemiological studies have shown that OPLL is seen relatively frequently among Japanese people, that it occurs about twice as often in men as in women, and that it develops predominantly during middle age. Although the exact etiology of OPLL is unknown, involvement of genetic factors has been suggested, as some patients have a positive familial history. Attempts to identify a gene responsible for OPLL have been unsuccessful. This chapter outlines the evidence related to epidemiology and genetics derived from guidelines concerning the diagnosis and treatment of OPLL.

When the incidence of OPLL is compared among different countries, the incidence is higher for the Japanese population than for Western populations. Most reports on OPLL published to date have originated from Japan, with only a few such reports from Western countries—OPLL has been considered a disease specific to the Japanese [8,9]. The incidence of OPLL among Japanese people is reported to be about 3% (1.8%–4.1%) [10], which is higher than the incidence reported for Chinese (0.2%–1.8%) [11,12], Koreans (0.95%) [13], Americans (0.12%) [13], or Germans (0.10%) [13]. However, some investigators have reported an incidence of OPLL among Italians (1.8%) [14] and Taiwanese (3.0%) [15] comparable to that of the Japanese population. The diagnostic criteria for OPLL differ among countries, and no published report has definitively demonstrated that the incidence of OPLL is significantly higher for Japanese people than for other countries' people. No evidence of regional difference in the incidence of OPLL within Japan has been observed [10]. According to nationwide MHW statistics reported in 1975, the male/female ratio for patients diagnosed as having OPLL was 1.96 [16] (the ratio has been 1.1–3.0 in many reports). Although the MHW data were not derived from cross-sectional epidemiological surveys, the sex ratio for OPLL is estimated to be about 2:1. A Japanese survey in Yachiho, a village in Nagano Prefecture, revealed a male/female ratio of 1.79 in regard to the incidence of OPLL (4.3% in men and 2.4% in women) [17]. According to surveys of 2529 employees in three cities of China (Beijing, Changchun, and Chifeng), the incidence is 1.67% for men and 1.04% for

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women, with a male/female ratio of 1.6:1:0 [18]. In a survey of Italians [14], no marked sex-related difference was noted in the incidence of OPLL between men (1.9%) and women (1.75%), with a male/female ratio of 1.08:1.00.

OPLL often develops during middle age. Its incidence is particularly high near the age of 50 years. Reports from the MHW study group for 1976 [16] and 1986 [19] showed that the disease had a high incidence at about age 50. No conclusions have yet been drawn as to whether the incidence of OPLL has been changing over time. According to a nationwide survey conducted in 1975 by the MHW study group on intractable diseases [16] 2142 OPLL patients had been registered, and the number of OPLL patients per one million population was estimated at 19.8. In the MHW study group survey conducted in 1985, the number of registered OPLL patients had increased to 5818, and the number of OPLL patients per one million population was estimated at 63.3 [19]. Although these reports by the MHW study group suggest an increase in the number of registered OPLL patients, the figures shown in their reports do not seem to reflect the actual number of patients. We cannot be sure that the OPLL incidence has been increasing.

The results of pedigree surveys, twin surveys, HLA haplotype analyses, and genetic analyses supported the involvement of genetic factors in the onset of OPLL. In a nationwide pedigree survey of OPLL in Japan [20], radiographic evidence of OPLL was seen in 23% of all blood relatives and in 29% of brothers of OPLL patients. In a twin-pair survey [21], OPLL was seen in both twins in 85% of all monozygotic twins investigated. However, the inheritance of OPLL was not identified by pedigree or twin surveys. In a survey of the HLA haplotype, conducted primarily in Kagoshima [22], the HLA haplotype coincidence rate was significantly high between OPLL patients and their brothers, endorsing the view that OPLL has some genetic background. The coincidence of the HLA haplotype was also demonstrated in an analysis conducted in Sapporo [23]. A mutation of type 11 collagen A2 gene on the short arm of chromosome 6 [24] and polymorphism of the nucleotide pyrophosphatase (NPPS) gene [25] have been reported to be possibly responsible for OPLL. More recently, a mutation of type 6 collagen A1 gene on chromosome 21 was suggested by genome-wide chain analysis to be a gene possibly involved in OPLL [26]. However, none of these genes has been established as a factor responsible for the onset of OPLL.

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OPLL: Disease Entity, Incidence, Literature Search, and Prognosis

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Disease Entity

Ossification of the posterior longitudinal ligament (OPLL) is a hyperostotic condition of the spine associated with severe neurological deficit [1–5]. The disease was first reported more than a century and a half ago [6]. OPLL was previously considered specific to Asian peoples [7] and did not attract attention in Europe or the United States. However, because of reports that this disease occurs in Caucasians [8–14] and that about half of the patients with diffuse idiopathic skeletal hyperostosis (DISH), which is well known in Europe and the United States, had OPLL, this disease has come to be recognized as a subtype of DISH [15,16].

Resnick et al. [15] reported DISH to be a common disorder characterized by bone proliferation in axial and extraaxial sites. The most characteristic abnormalities in this condition are ligamentous calcification and ossification along the vertebral body [16]. Changes in extraspinal locations are also frequent, including ligament and tendon calcification and ossification, paraarticular osteophytes, and bony excrescence at sites of ligament and tendon attachment to bone. In their study of a group of 74 patients with DISH, 37 (50%) patients had concomitant OPLL on cervical radiographs [17]. Whereas DISH is a fairly common disease among the general population of Caucasians more than 50 years of age, its frequent association with OPLL suggests that OPLL itself cannot be a rare disease in Caucasians.

In 1992, Epstein proposed a new concept for OPLL. Epstein examined computed tomography (CT) scans of the cervical spine in Caucasians and noted hypertrophy of the posterior longitudinal ligament with punctuate calcification. This finding was described as ossification of the posterior longitudinal ligament in evolution (OEV) [18]. Epstein emphasized that the prevalence of OPLL among Caucasians with cervical myelopathy has recently increased from 2% to 25% [19]. All epidemiological surveys of OPLL by Japanese researchers were conducted using plain radiography of the cervical spine for OPLL diagnosis. Most Japanese researchers did not include OEV in the OPLL survey. There is controversy between Japanese and North American researchers regarding the definition of OPLL.

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Incidence

OPLL was found to occur in 1.5%–2.4% [20–27] of adult outpatients with cervical disorders at several university hospitals in Japan (Table 1). In the same survey of foreign countries, the prevalence of OPLL was 0.4%–3.0% in Asian countries [28–32]. In a review of plain cervical spine films by Yamauchi and colleagues [28,33] and Izawa [27], the incidence of OPLL among Japanese patients was 2.1% (143/6994), 1.0% in Koreans, 0.1% in North Americans, and 0.1% in Germans. A survey in Italy in 1984 by Terayama and Ohtsuka [34], however, revealed a high incidence of OPLL in Italy (Table 2). Our overseas survey of OPLL at the Utah University Hospital in the United States [35] revealed 8 (1.3%) cases of OPLL in the cervical spine among 599 subjects.

To determine the incidence of OPLL in various countries around the world, epidemiological studies among the general population were sought. The incidence of OPLL in the general Japanese population was reported to be 1.9%–4.3% [36–41] among people more than 30 years of age (Table 3). However, few studies have been conducted on the general population in other countries. We performed a study in Taiwan on 1004 Chinese and 529 Takasago Tribe people who were more than 30 years of age [42,43]. The incidence of OPLL was 0.2% for the Chinese and 0.4% for the Takasago Tribe population, figures that are lower than those for the Japanese population. Recently, Tomita et al. [44] carried out an epidemiological study of OPLL in China that involved 2029 Chinese and 500 Mongolian subjects. According to that study, the prevalence of OPLL was 1.6% among the Chinese and 1.8% among the Mongolians.

Table 1. OPLL in outpatient clinic for cervical disorders in Japan

Study	Year	Location of survey	Subjects (no.)	Age of subject (years)	OPLL (no.)	Incidence of OPLL (%)
Okamoto [20]	1967	Okayama	1000	ND	21	2.1
Yanagi [21]	1967	Nagoya	1300	>20	37	2.8
Onji [22]	1967	Osaka	1800	ND	31	1.7
Shinoda [23]	1971	Sapporo	3747	>10	55	1.5
Harata [24]	1976	Hirosaki	2275	ND	33	1.5
Sakou [25]	1978	Okinawa	1969	>30	30	1.5
Kurihara [26]	1978	Kobe	9349	>15	183	2.0
Izawa [27]	1980	Tokyo	6944	>20	143	2.1

ND, not detailed

Table 2. OPLL in outpatient clinics worldwide

Study	Year	Country	Subjects (no.)	Age of subject (years)	OPLL (no.)	Incidence of OPLL (%)
Asia						
Yamauchi [28]	1978	Korea	529	>20	5	1.0
Kurokawa [29]	1978	Taiwan	395	>40	12	3.0
		Hong Kong	498	>40	2	0.8
Yamaura [30]	1978	Philippines	332	ND	5	1.5
Tezuka [31]	1980	Taiwan	661	>20	14	2.1
Lee [32]	1991	Singapore	5167	>30	43	0.8
Europe and USA						
Yamauchi [33]	1979	West Germany	1060	>27	1	0.1
Terayama [34]	1984	Italy	1258	>35	22	1.7
Izawa [27]	1980	USA (Minnesota)	840	>30	1	0.1
		USA (Hawaii)	490	>20	3	0.6
Firoozmia [12]	1982	USA (New York)	1000	>20	7	0.7
Ijiri [35]	1996	USA (Utah)	599	>30	8	1.3

Table 3. Incidence of OPLL among general population in Japan

Study	Year	Location of survey	Subjects (M/F)	Age of subjects (years)	OPLL (no.)	Incidence of OPLL (%)
Ikata [36]	1979	Tokushima	705 (330/366)	>20	21	2.0
Ohtani [37]	1980	Yaeyama	1046 (578/468)	>20	21	2.0
Yamauchi [38]	1982	Kamogawa	788 (408/379)	>40	20	2.5
		Kofu	383 (169/214)	>40	13	3.4
Sakou [39]	1982	Kagoshima	585 (195/390)	>30	11	1.9
Ohtsuka [40]	1984	Yachiho	1058 (440/618)	>50	34	3.2
Ikata [41]	1985	Tokushima	415 (122/293)	>30	18	4.3

Literature Search

Several studies [4,5,45–47] on the clinical characteristics of OPLL have been published. The clinical characteristics of patients with OPLL in articles from Japanese researchers and those from other countries have been similar. Terayama, a member of the Investigation Committee on Ossification of the Spinal Ligaments of the Japanese Ministry of Public Health and Welfare, performed the first national survey of OPLL in 1975 [46]. A total of 880 hospitals, including university hospitals, were asked to participate in this survey, and 2142 OPLL patients were registered.

The results of the survey indicated that OPLL typically develops in patients older than 40 years of age and has a male predominance of 2:1 to 3:1. The average age of onset was 51.2 years in male patients and 48.9 years in female patients. Altogether, 67% of patients were 45–65 years old. A total of 95% of the patients had some clinical symptoms, with the other 5% symptom-free. The initial complaints typically consisted of cervical discomfort in conjunction with numbness of the upper extremity.

The typically recognized symptoms of OPLL are as follows: sensory and motor dysfunction of the upper and lower extremities, hyperreflexia of the tendon reflex, pathological reflex, and bladder dysfunction. In all, 16.8% of the patients in the survey needed help with activities of daily living; 5.4% of patients exhibited rapid aggravation of symptoms, and 11.4% had chronic aggravation. Symptoms appeared spontaneously and continued to progress. Initial complaints typically consisted of cervical discomfort in conjunction with numbness or myeloradiculopathy usually characterized by symmetrical upper and lower extremity findings. Commonly, if quadriparesis evolves rapidly, sphincteric dysfunction may also be noted [47]. Altogether, 9.7% of the survey patients had diabetes mellitus. As for the glucose tolerance test, 29% of the patients exhibited a diabetes mellitus pattern, an incidence significantly higher than that (5%) of an age-equivalent group without OPLL. About one-fourth (23%) of the patients had a history of trauma to the cervical region. Trauma to the cervical spine may have precipitated the onset of symptoms, including quadriparesis [48–50]. However, the incidence of trauma that caused symptoms was only 15% [46].

A genetic survey of OPLL patients has revealed a high rate of occurrence among families [51,52]. The nationwide survey of 347 families of OPLL evaluated by Terayama revealed that OPLL was detected radiographically in 24% of the second-degree or closer blood relatives and 30% of OPLL patients' siblings. The authors looked at another 220 of the second-degree or closer blood relatives of 72 patients with OPLL and determined that 32 families (44%) were indeed predisposed to this condition [53]. A nationwide study was conducted by the Committee; it included 10 sets of twins (eight monozygotic twin-pairs and two dizygotic twin-pairs) who exhibited OPLL[54]. Six of the eight monozygotic twin-pairs had OPLL, suggesting or indicating that a genetic factor contributes to the frequency of this disease among twins.

A human leukocyte antigen (HLA) haplotype analysis provides a useful means for studying the genetic background of diseases, and it has been performed in patients with OPLL [55]. A specific HLA haplotype for OPLL was not found in this study, although an interesting finding was that if a sibling had the same two haplotypes as the proband, the incidence of OPLL was much higher than if the sibling had only one haplotype that was the same as that of the proband [56]. If neither haplotype was seen in the proband, the occurrence was almost nil (Table 4). The HLA gene is located on the short arm of chromosome 6. DNA analysis was therefore performed in the region of HLA genes on chromosome 6. Genetic linkage evidence of the genetic susceptibility of OPLL mapped to the HLA complex of chromosome 6 by a nonparametric genetic linkage study with 91 affected sib-pairs with OPLL revealed that collagen α2(XI) is a candidate gene for OPLL [57,58].

Table 4. Relation between the share of identical HLA haplotypes and existence of OPLL in 61 siblings

No. of identical strands	No. of siblings with OPLL
Two ($n = 19$)	10 (53%)
One ($n = 21$)	5 (24%)
None ($n = 21$)	1 (5%)

HLA, human leukocyte antigen
The percentages represent the proportion of siblings with OPLL, a seen on roetgenograms and CT scans in each group. The percentage of OPLL in the two-strands identical group is significantly higher than in the other two groups ($P < 0.05$)

Prognosis

Few studies have evaluated the progression of OPLL in a prospective fashion. Altogether, 112 patients with OPLL who had been treated conservatively were studied (75 men, 37 women) [59]. They ranged in age from 27 to 78 years (mean 54.5 years), and they were followed 1.0–16.9 years. Progression of ossification (length and thickness) was demonstrated in these patients (24% increased length, 13% increased thickness) over a 5-year follow-up. However, the amount of progression was small. At 10 years the maximum progression in length was 43 mm (equivalent to the height of two vertebral bodies) and 3.4 mm in thickness in one case of continuous OPLL.

During ossification progression, the type of ossification changed in some instances. The continuous type changed to the mixed type in three cases. The segmental type changed to the mixed type in three cases and to the continuous type in three cases, and the mixed type changed to the continuous type in one instance. In our biomechanical study, progression of OPLL was recognized at the site of increased strain in the intervertebral disc [60]. Progression of ossification did not always lead to exacerbation of symptoms, although there were some instances of worsening.

The course of the ossification in 94 patients who underwent surgery was carefully followed. There were 75 men and 19 women in this cohort, whose ages ranged from 23 to 79 years (mean 54.8 years). Follow-up periods varied from 8.9 years for anterior decompressions and fusions, to 2.5 years for laminoplasties, and to 6.6 years for laminectomy. Ossification progressed markedly and at a higher rate in laminectomy (40%) and laminoplasty (35%) patients and appeared at relatively shorter intervals following these surgical procedures (i.e., earliest within 2 months after surgery and most often within 6 months). The frequency of the ossification progression

was shown to be higher in laminectomy and laminoplasty patients when compared with conservatively treated individuals [61,62]. Possible explanations include (1) mechanical stress increasing in the cervical spine because of destruction of the posterior supportive elements and (2) biological stimulation produced by the laminoplasty or laminectomy.

The prognosis of patients with OPLL has generally been thought to be disappointing. We examined the natural course of this disease [63]. In our recent study [64], a total of 450 patients, average age 74.6 years at last evaluation, were prospectively followed neurologically for an average of 17.6 years (10–30 years) to discern the "natural history" of the disease progression. Myelopathy was originally recognized in 127 patients, 91 of whom were managed surgically. The remaining 36 myelopathic patients were treated conservatively, with increased myelopathy being observed in 23 (65%) of these individuals. For the 323 patients without original myelopathy, 64 (20%) became myelopathic during the follow-up interval. The Kaplan-Meier estimates [65] of myelopathy-free survival among patients without myelopathy at the first visit was 71% at 30 years of follow-up (Fig. 1). The 45 patients with more than 60% of the spinal canal compromised by OPLL were all myelopathic.

As a dynamic factor, range of motion (ROM) of the cervical spine was calculated by dynamic X-ray radiography. The relation between the presence or absence of myelopathy and ROM was determined in 204 patients with a minimum space available—spinal canal (SAC) diameters of 6 mm to less than 14 mm. The total ROM in the group with myelopathy was significantly greater than in the group without myelopathy (Table 5). Although myelopathy was recognized in all patients with more than 60% of the spinal canal compromised by OPLL, minimal OPLL at first examination rarely developed to OPLL with more than 60% stenosis during the follow-up. Therefore, one cannot simply say that myelopathy develops with OPLL. Rather, dynamic factors (e.g., ROM) appear to be more important for the evolution of myelopathy in patients with less than 60% of the canal compromised by OPLL [66]. Findings in this long-term prospective analysis of OPLL patients revealed that the cumulative myelopathy-free survival rate among patients without myelopathy at the first visit was 71% after 30 years.

A longitudinal cohort study of 216 elderly patients with OPLL for an average of 12.6 years was performed to determine the quality of life (QOL) of the patients after treatment [67]. The cumulative survival rate of patients with (Nurick) grade 5 severe myelopathy before treatment was 20% at 70 years of age, whereas that of patients without myelopathy or with grade 1, 2 , 3, or 4 myelopathy before treatment was 80%. Patients were statistically more likely to live independent of assistance for activities of daily living when they underwent surgical therapy for grade 3 or 4 myelopathy than those with similar degrees of myelopathy who underwent conservative therapy. For patients with grade 5 myelopathy at the first examination, the final QOL was poor regardless of the therapeutic method. The prevalence of fractures in patients with OPLL was 1.4% for men and 8.6% for women. The bone mineral density in these patients without myelopathy was significantly higher than that in healthy subjects of the same age. These data

Table 5. Range of motion of the cervical spine in patients with a minimum spinal canal diameter of ≥6 mm but <14 mm

Presence of myelopathy	ROM of cervical spine
Yes	51.0° ± 17.5°
No	39.0° ± 9.5°

Rom, range of motion
Results are expressed as the mean ± SD
$P < 0.01$ between groups

Fig. 1. Kaplan-Meier estimate of myelopathy-free rate among patients who did not exhibit myelopathy at the first examination

suggest that surgical treatment should be chosen for patients exhibiting moderate myelopathy to obtain satisfactory QOL for a long period of time.

Severe myelopathy can be induced by minor cervical trauma in patients with OPLL. Results of surgical treatment for this condition are far from satisfactory. Some advocate preventive surgery prior to the onset of myelopathy for patients with OPLL and potential spinal stenosis due to ossified ligaments. However, a rationale for preventive surgery for patients with OPLL who do not exhibit myelopathy has not been established. In our prospective investigation of 368 patients who did not have myelopathy at the time of the initial consultation, only 6 (2%) patients subsequently developed myelopathy induced by trauma [68]. Ossification types in patients who developed myelopathy induced by trauma were mainly the mixed type. Preventive surgery prior to the onset of myelopathy is unnecessary for most patients with OPLL.

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Diagnostic Imaging of Cervical Ossification of the Posterior Longitudinal Ligament

Kensei Nagata and Kimiaki Sato

Introduction

The range of ossification in the ligaments of the cervical spine that can be examined using imaging include ossification of the posterior longitudinal ligament (OPLL), ossification of the yellow ligament (ligamentum flavum) (OYL), ossification of the anterior longitudinal ligament, and ankylosing spondylitis. OPLL is one of a group of diffuse idiopathic skeletal hyperostoses that can affect the various spinal ligaments. Cervical OPLL is the most common among this group and often leads to compression myelopathy. Clinical guidelines for diagnosing and treating OPLL were published in 2005 by a committee within the Japanese Orthopedic Association and funded by the Japanese Ministry of Public Health and Welfare [1]. This section describes the diagnostic imaging for cervical OPLL based on those clinical guidelines and on the research referred to by the guidelines.

The presence of cervical OPLL is generally confirmed on a lateral plain radiograph. Tomography and computed tomography (CT) are, however, much more sensitive for visualizing the detailed outlines of any ossified mass. The guidelines committee proposed that the diagnostic criteria for OPLL include clear radiographic findings as well as documentation of the clinical symptoms; thus, early small ossification not visible on lateral plane radiography and that can be detected only by CT does not fulfill the diagnostic definition for OPLL [1].

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Cervical OPLL

Radiography

Cervical OPLL is visualized on a lateral plain radiograph as an abnormal mass of ossification along the posterior margin of the vertebral bodies. The incidence is 1.9%–3.2% in Japan [2,3]. Plain radiography is also useful for long-term follow-up of OPLL, but the radiographic findings of OPLL do not always correlate with the clinical symptoms. OPLL is classified into four types according to a classification established by the Investigation Committee on Ossification in the Spinal Ligaments of the Japanese Ministry of Public Health and Welfare (now the Japanese Ministry of Health, Labour, and Welfare) (Fig. 1): (1) continuous OPLL: a long lesion extending over several vertebral bodies (Fig. 2a); (2) segmental OPLL: one or several separate lesions behind the vertebral bodies (Fig. 3a); (3) mixed OPLL: a combination of the continuous and segmental types (Fig. 4A,a); and (4) circumscribed OPLL: mainly located posterior to a disc space [2,4].

Among the 2142 patients with cervical OPLL reviewed, the segmental type was most common, occurring in 39% of patients with cervical OPLL. The continuous, mixed, and circumscribed types occurred in 27%, 29%, and 7%, respectively [2,3]. Cervical OPLL is most frequently found (in order of frequency) at levels C4, C5, and C6. The greatest thickness of OPLL is often seen at these levels. Ossification covering two to five vertebral bodies is most frequent; the average number of vertebral bodies involved is 3.1. The continuous type most frequently extends over the levels C2 to C4. The spinal canal is most severely compromised by the continuous and mixed types [2,3].

Radiographic Findings and Onset of Myelopathy

The relation between static factors and an onset of myelopathy has been discussed in literatures. It is thought that the static factors are (1) a developmentally

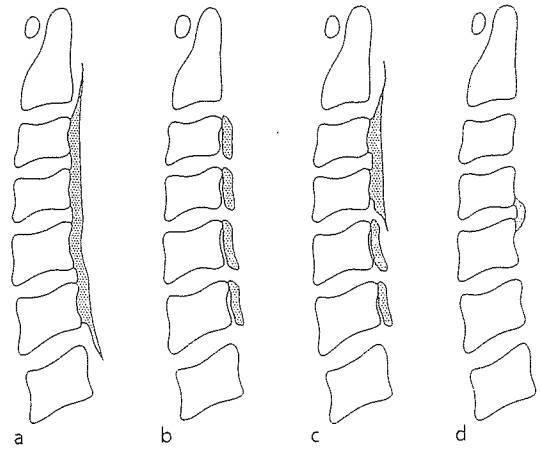

Fig. 1. Classification of ossification of the posterior longitudinal ligament (OPLL). The ossified PLL was classified into one of four types according to the classification established by the Investigative Committee on the Ossification of the Spinal Ligaments, of the Japanese Ministry of Public Health and Welfare (now the Japanese Ministry of Health, Labour, and Welfare). **a** Continuous: presents as a long lesion extending over several vertebral bodies. **b** Segmental: appears as one or several separate lesions behind the vertebral bodies. **c** Mixed: appears as a combination of the continuous and segmental types. **d** Circumscribed: mainly located posterior to a disc space

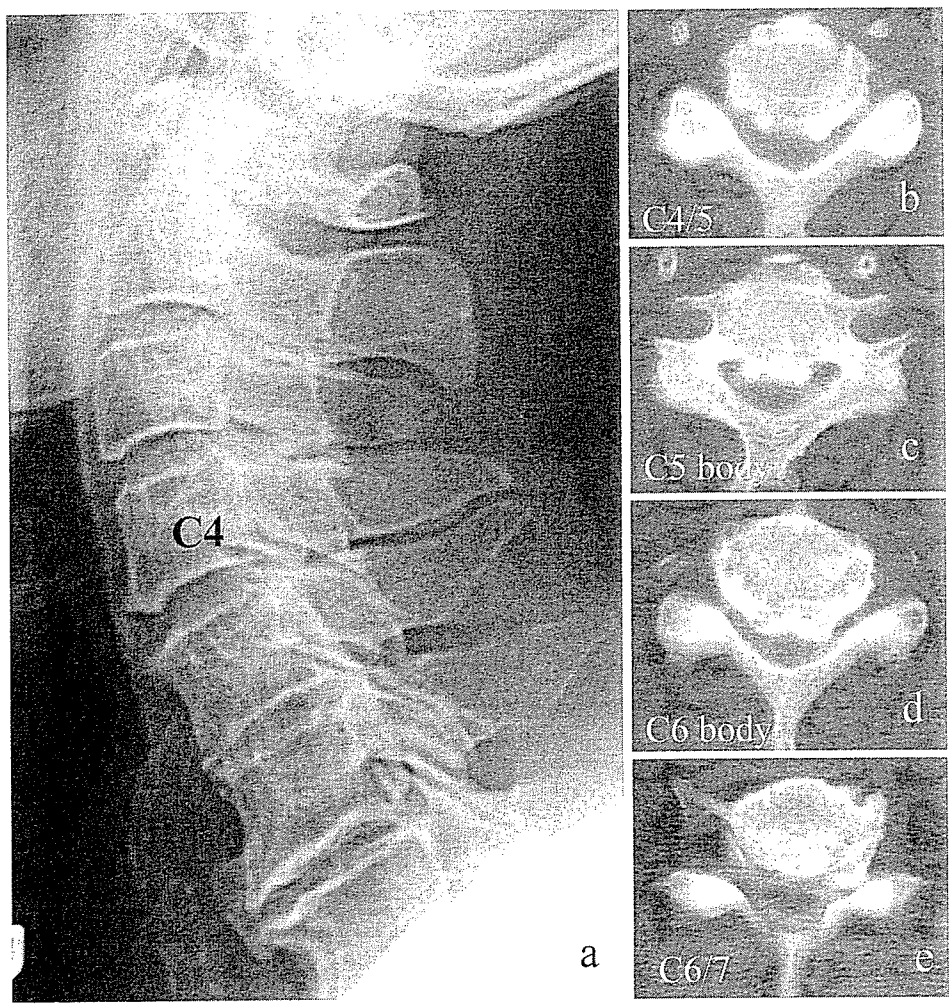

Fig. 2. Continuous-type OPLL in a 66-year-old man. **a** Radiograph shows OPLL from C4 to C6-C7. The OPLL can be detected more easily using computed tomography (CT). CT shows various types of OPLL, such as the hill type at C4-C5 (**b**), the square type at C5 (**c**) and C6 (**d**). **e** A small ossified mass is seen in the left intervertebral foramen at the C6-C7 level

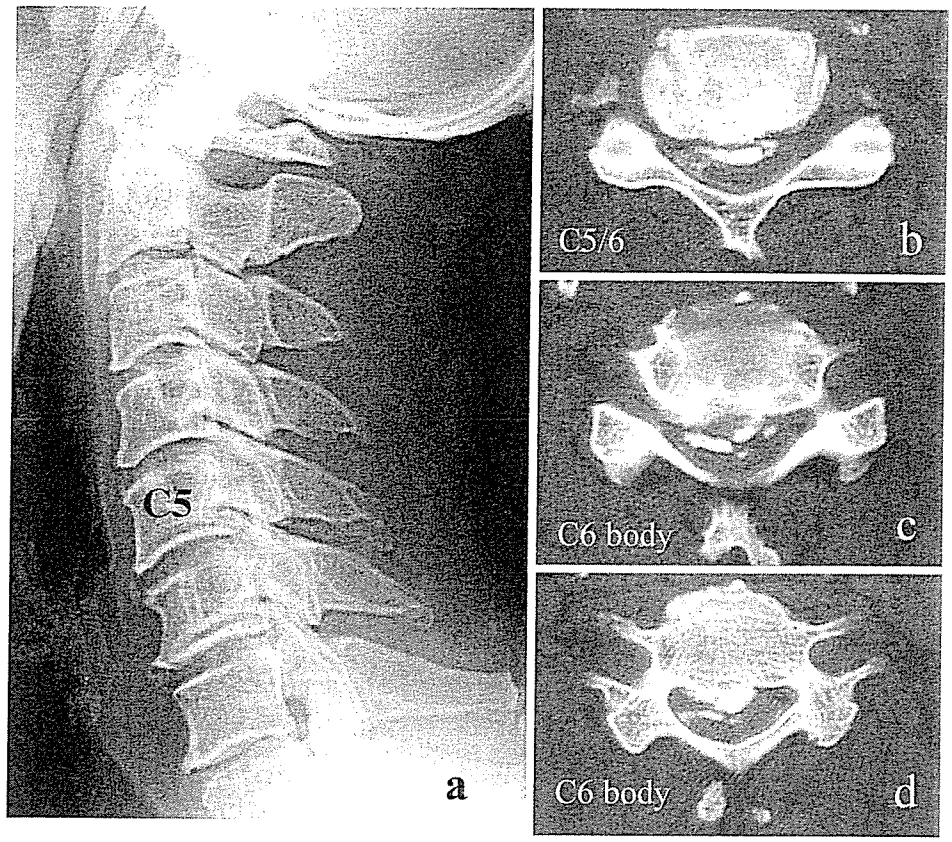

Fig. 3. Segmental-type OPLL in a 62-year-old man. a Radiograph shows segmental OPLL at the C4, C5, and C6 levels. b CT-myelogram shows thin laminated ossification behind the C5-C6 disc. It is also seen at the upper part (c) and lower part (d) of the C6 vertebral body. The dural sac is severely compressed by the OPLL. d Hill-type OPLL is seen at the lower part of the C6 vertebral body

narrow spinal canal and (2) the space available for the cord measured on lateral plain radiographs.

Many authors have noted that a developmentally narrow canal through the cervical spine was the most important factor for the onset of myelopathy [5–9]. Ono et al. reported that a cervical canal whose anteroposterior (AP) diameter has decreased more than 40% on cervical spine films is susceptible to spinal cord symptoms [10]. Seki et al. reported that a decrease in AP diameter due to OPLL of more than 50% was a high-risk factor for the onset of myelopathy [11], and Nishiura et al. reported that the incidence of myelopathy was 57% in patients with an AP diameter reduced by OPLL by more than 50% [6]. Matsunaga et al. reported that all 45 patients whose AP diameter of the cervical canal had decreased more than 60% developed spinal cord symptoms without dynamic factors during long-term follow-up [12]. A narrow cervical spinal canal caused by OPLL can be evaluated by the rate of its narrowing as calculated in Fig. 5.

Some authors have reported that the shape of OPLL in the transverse plane and the cross-sectional area of the spinal canal narrowed by OPLL are the most important factors for the onset of myelopathy [13]. The mobility of the cervical spine (dynamic factor) or associated soft tissue elements (i.e., disc herniation and hypertrophy of ligaments) may be another prerequisite for the onset of myelopathy [14]. Based on these reports, the guidelines committee announced that patients with a spinal canal narrowed more than 50% by OPLL are at high risk for myelopathy, whereas a wide spinal canal is a barrier against the onset of myelopathy [1].

The space available for the cord (SAC) on a cervical spine lateral plain radiograph is measured at a constant 1.5-m distance from the patient. The measurement is useful for estimating the risk of developing cervical myelopathy. SAC is measured on this radiograph as the AP diameter of the spinal canal minus the width of the OPLL. Toh et al. reported that the average SAC in

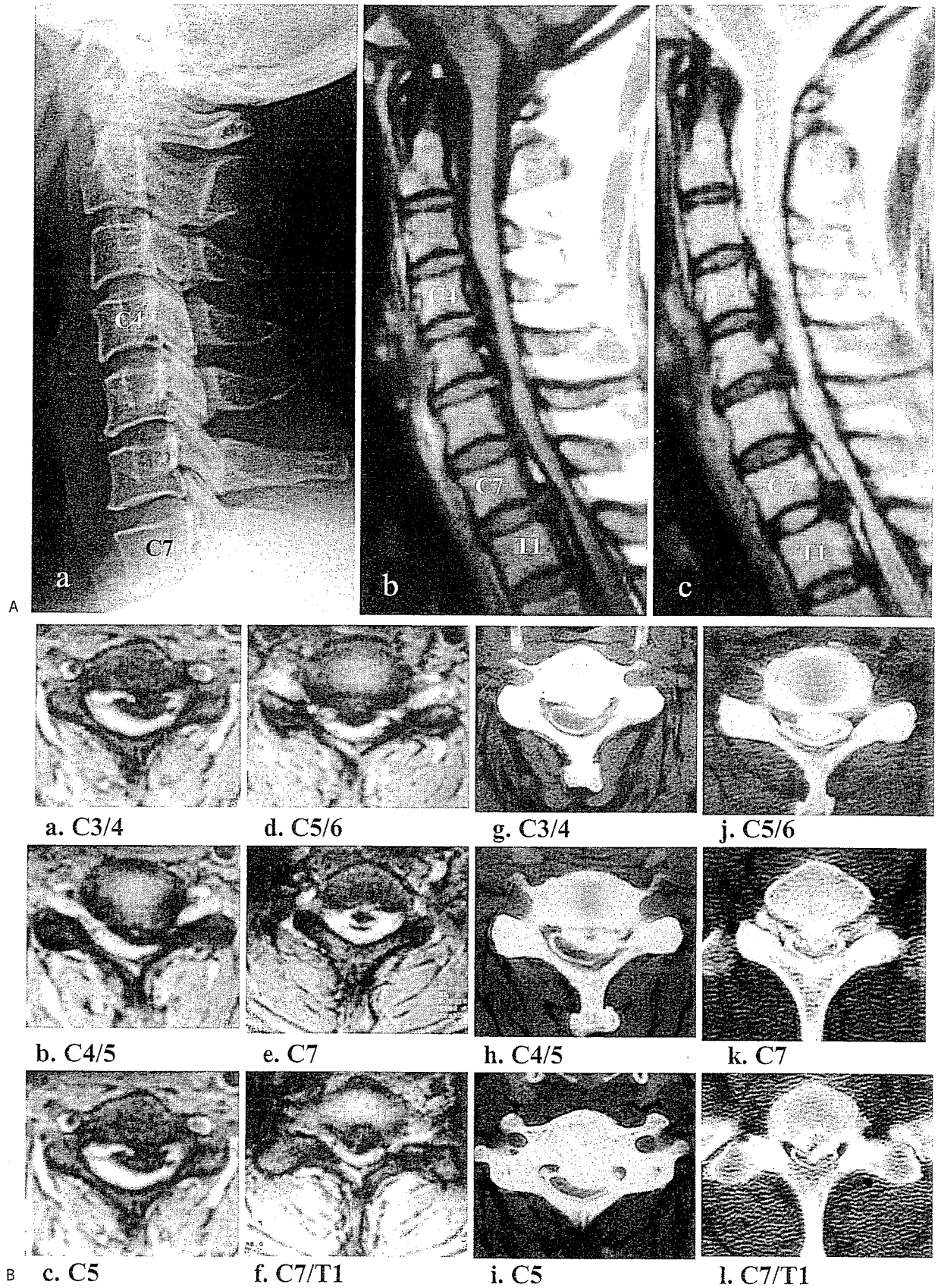

Fig. 4. Mixed-type OPLL in a 46-year-old woman. A, a Radiograph shows continuous-type OPLL extending over the C4, C5, and C6 levels. T1-weighted (b) and T2-weighted (c) sagittal magnetic resonance imaging (MRI) shows a low signal intensity mass from C3-C4 to C6 and the C7-T1 level. The spinal cord was severely compressed by the low intensity mass, as seen on the T1-weighted sagittal image. A high signal intensity area was seen in the spinal cord on T2-weighted sagittal image. B, a–f T2-weighted axial MRI. g–l CT-myelograms show severe compression in the spinal cord. Axial T2-weighted images show various sizes of low intensity mass from C3-C4 to C7-T1 (a–f), and the CT-myelograms show various types of OPLL at each cervical level (g–l)

patients at the onset of myelopathy was 8.2 mm [15], and Harsh reported that the critical SAC at the onset of myelopathy in the United States was 9.0 mm [16].

The Guidelines reported the overall findings concerning the relation between SAC and the onset of myelopathy as follows: Myelopathy can easily occur when the SAC is narrow; however, even a SAC of <8 mm is not an absolute condition because of the dynamic factor [1]. The risk of cervical myelopathy is high in patients with a SAC of <6 mm, and the risk is low in patients with a SAC of >14 mm (Figs. 6a, 7a). In patients with an SAC of >6 mm but <14 mm, it is thought that the dynamic factor, rather than the static factor, becomes the dominant factor for the onset of cervical myelopathy [1].

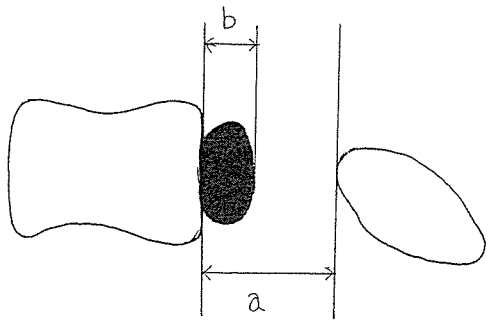

Fig. 5. Rate of narrowing in the spinal canal. The rate of narrowing in the spinal canal is calculated as (*a*) the width of OPLL divided by (*b*) the anteroposterior (AP) diameter on a lateral cervical radiograph, multiplied by 100; the result is given as a percentage narrowing: Rate of narrowing in the spinal canal = $a/b \times 100$ (%)

Coexistence with Other Ossification

Cervical OPLL may be complicated by other ossification. Ohtsuka et al. reported the results of an investigation of cervical and thoracic lateral radiography findings in 10 508 people. They reported that the incidence of cervical OPLL was 3.2%, thoracic OPLL 0.8%, and combined cervical and thoracic OPLL 0.3%. Thoracic OPLL was seen in 9.2% of the patients with cervical OPLL [17]. Wada et al. reported that the incidence of combined cervical and thoracic OPLL was 17.5% in 254 patients with cervical OPLL. They reported also that the incidence of combination with OYL was 48.7% in the same series [18].

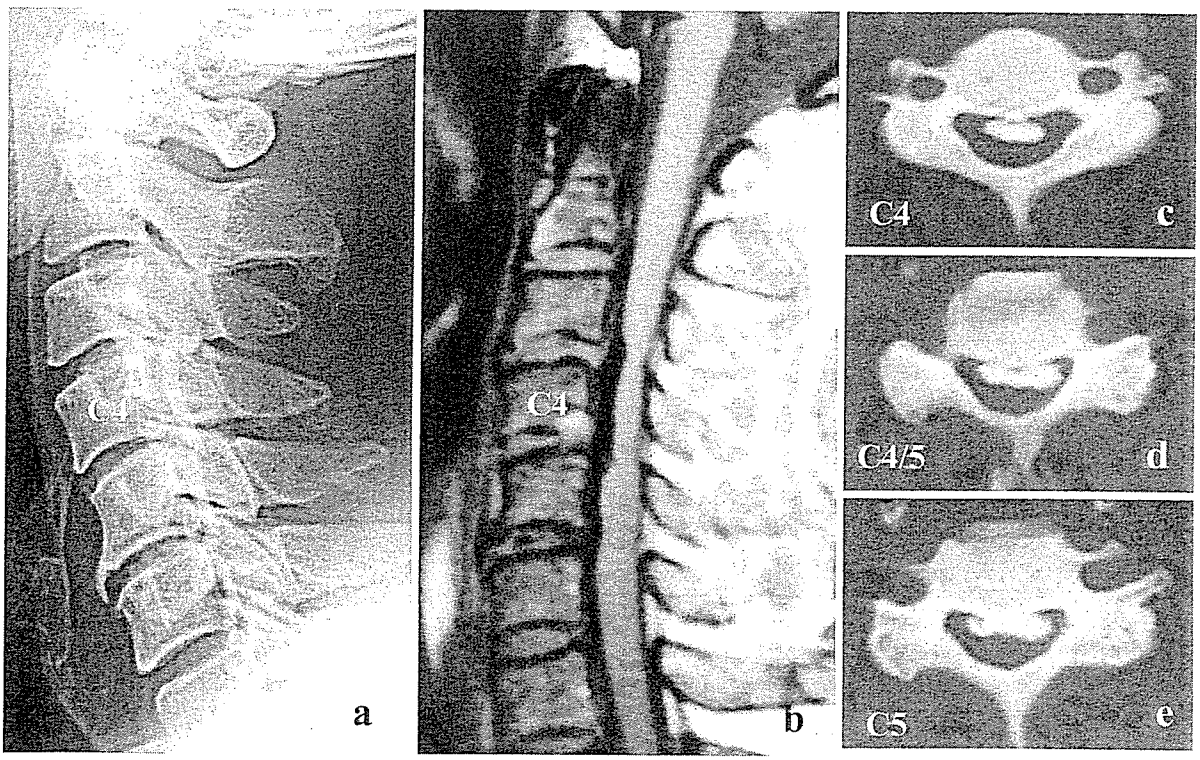

Fig. 6. Segmental-type OPLL in a 65-year-old man **a** Radiograph shows segmental-type OPLL at C4, C5, and C6 levels. **b** T1-weighted MRI shows moderate spinal cord compression due to a narrow space available for the spinal cord (SAC) compared with the case shown in **a**. **c–e** CT shows mushroom-type OPLL at the C4 vertebral body level (**c**) and square-type OPLL at the C4-C5 (**d**) and C5 (**e**) vertebral body levels. The patient underwent expansive laminoplasty because of progressive myelopathy

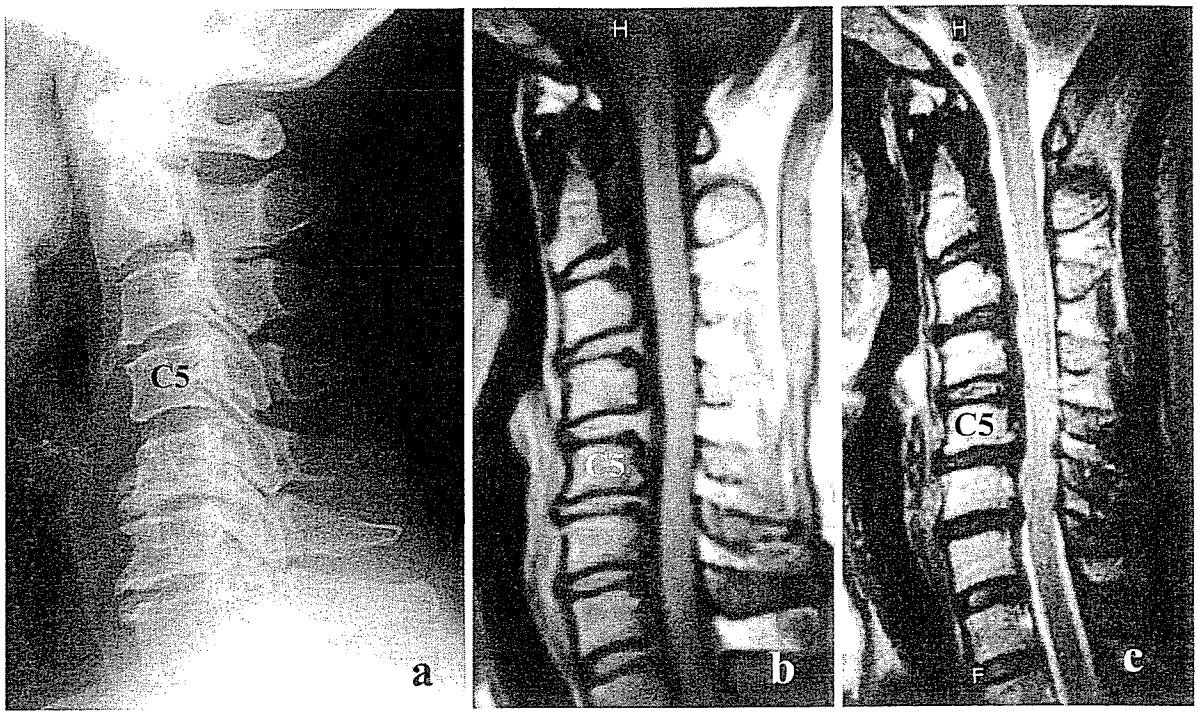

Fig. 7. Mixed type-OPLL in a 50-year-old woman. a Radiograph shows mixed-type OPLL from the C2 to C6 levels. T1-weighted (b) and T2-weighted (c) MRI scans show mild spinal cord compression. She had no neurological symptoms because of the wide SAC

Computed Tomography

Computed tomography is exquisitely sensitive to ligamentous ossification and calcification, and it represents a "gold standard" in the diagnosis of OPLL [4]. OPLL is observed on CT as an ossified mass in the posterior margin of the vertebral bodies or discs. When OPLL occurs at the lower cervical levels, it may be masked by shadows from the shoulder girdles on lateral plain radiography. In such cases, OPLL is detected more easily by CT (Fig. 4B, k,l).

Occasionally, the ligament is patchily or less densely calcified. Diagnosis is difficult in some cases of segmental-type OPLL because differentiating it from osteophytes of cervical spondylosis on a lateral radiograph is problematic. In such cases, CT and tomography are useful for the differential diagnosis.

Computed tomography is particularly helpful for determining the thickness, lateral extension, and shape of OPLL and for observing the SAC. It is also valuable when planning surgical intervention [13,14,16], especially when deciding on the surgical method to be employed. When OPLL extends to the lateral spinal canal including the pedicle, anterior decompression is not indicated. CT is valuable for evaluating objectively the effect of the decompression surgery [14].

The shape of OPLL in the transverse plane varies considerably [13,14]; it may be mushroom-like, cubic, round, or tandem. OPLL is either attached (Fig. 3c) or unattached (Fig. 3b) to the vertebral bodies, and sometimes it is fused to vertebral bodies (Figs. 2b–d, 3d). The ossified foci are usually located in the middle of the posterior margin of the vertebral bodies and can be classified into three types (Fig. 8): (1) square (Fig. 2c); (2) mushroom-shaped (Fig. 6c); and (3) hill-shaped (Fig. 2b) [19]. However, OPLL can also occur extending away from the midline and can be quite asymmetrical in shape (Fig. 4B, g–l). Occasionally, the ossification extends laterally toward the intervertebral foramen along the intervertebral disc or along the dural sac (Fig. 2e). These extensions follow the anatomy of the posterior longitudinal ligament (PLL), which is relatively narrow over the vertebral bodies and wide over the discs [20]. The superficial layer of the PLL extends laterally to cover the intervertebral discs, and at the same time some of the other fibers of the layer merge into the dura mater [20]. Excessive OPLL overgrowth, however, sometimes expands in thickness and width beyond the anatomical limits of the PLL [10]. The ossified ligament may adhere densely to the dural sac (Figs. 3b,c; 4B, g). In cases of dural extension, the risk of needing dural excision and the consequent

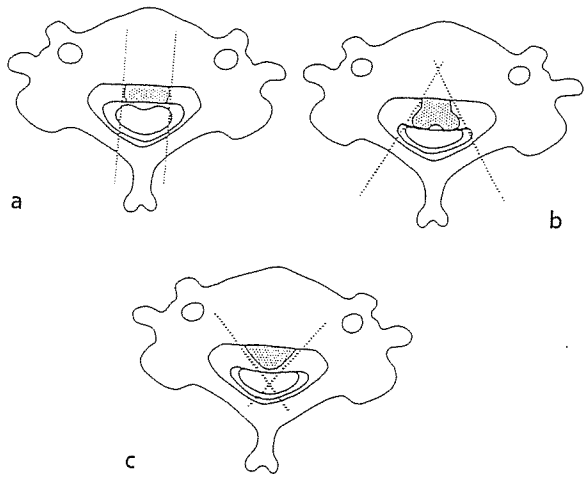

Fig. 8. Classification of OPLL based on CT findings. a Square type: the lines tangential to the bilateral margin of the ossified mass are parallel. b Mushroom type: the two lines cross ventrally. c Hill type: the lines cross dorsally. (From Terayama S, Miyasaka K [1997] Image diagnosis of cervical ossification of the posterior longitudinal ligament. In: Yonenobu K, Sakou T, Ono K (eds) OPLL. Springer, Tokyo)

dural defect can increase during anterior decompression surgery.

According to Yamamoto et al. [13], not only the AP diameter but also the transverse diameter is correlated with the types of neurological symptoms present. The laterality of the ossification is another important factor influencing the patient's symptoms. Associated spondylosis or degenerated discs can be responsible for neurological symptoms, especially when the OPLL is small [13]. When a small ossified mass is discovered unexpectedly by CT, investigating the possibilities of an increase in size and any consequent occurrence of spinal cord compression are important for choosing the level for surgery. However, there has been no clear evidence regarding these important factors of spinal cord compression caused by increasing size of a small ossified mass [1].

Magnetic Resonance Imaging

Diagnostic imaging for cervical disorders in Japan involves first radiography and then magnetic resonance imaging (MRI). Even when OPLL is not seen on a plain radiograph (Fig. 9A, a), MRI findings may nonetheless suggest a diagnosis of OPLL (Fig. 9B, center). CT helps clarify the presence of OPLL in such patients (Figs. 9B, right; 10B, e). Because MRI is less sensitive and less specific for diagnosing an ossified or calcified mass, its principal use is to assess the associated cord compression and intramedullary cord lesions, such as local cord edema and myelomalacia.

MR Images of OPLL

MR images of calcification and compact bone show low signal intensity. In a correlative study of T1-weighted images and the histopathological findings of OPLL, low signal intensity in the ligament corresponded to a hyperplastic ligament around the ossification and the transitional area between ligament and ossification (Fig. 4A, b); an isointensity signal corresponded to the proliferation in small vessels in the hyperplastic ligament [21]. In other studies, T1-weighted images demonstrated intermediate to high signal intensity in areas of ossification in 34.7%–41.5% of patients with OPLL, which was thought to represent bone marrow [22,23]. This intermediate to high signal intensity has been seen more frequently with the continuous and mixed types than with the segmental type of OPLL [22].

Otake et al. have published the largest study concerning MR imaging and cervical OPLL in 147 patients using a 1.5-Tesla (T) unit [22]. Their study showed that the T1- and T2-weighted sagittal images allowed a diagnosis of OPLL in only 32.7%–44.7% of cases—and usually only in patients with a thick OPLL lesion. Axial imaging was more sensitive, with a diagnosis in 74.1% and 91.1% on T1- and T2-weighted images, respectively [22].

In the second largest study, by Yamashita et al. [23], the sensitivity of detecting cervical OPLL in 98 patients was slightly higher for T1- and T2-weighted sagittal images (43.9% and 57.1%, respectively) but rather low for PD (proton-density)-weighted sagittal and T2-weighted axial images (55.1% and 51.1%, respectively); however, ossification of more than 3.2 mm was detected in 91% on T2-weighted axial images by 0.5-T and 0.22-T units. The thickness of the ossification was greater in continuous and mixed types than in the segmental type [22,23], and the continuous type was more easily recognized on MRI. Because small ossified lesions cannot be detected by MRI, it is prudent to correlate the MRI findings with the CT findings when OPLL is suspected [4].

MR Images of Morphological Changes in the Spinal Cord

MRI is useful for assessing associated cord compression and intramedullary abnormalities. It can demonstrate the level and degree of spinal cord compression directly and noninvasively. Degeneration in discs is frequently associated with cervical OPLL (Fig. 7b,c) and can be evaluated well by MRI (Fig. 9A, b,c; see also axial T2-weighted MRI of Fig. 9B) [22]. Intervertebral disc degeneration at the level of the OPLL on MRI is not related to the clinical symptoms caused by the spinal cord lesions. When disc herniation with compression of the spinal cord is detected at a level not affected by OPLL in patients who have OPLL elsewhere, the finding is important for identifying the cause of the myelopathy and indicating some other treatment. The MRI findings

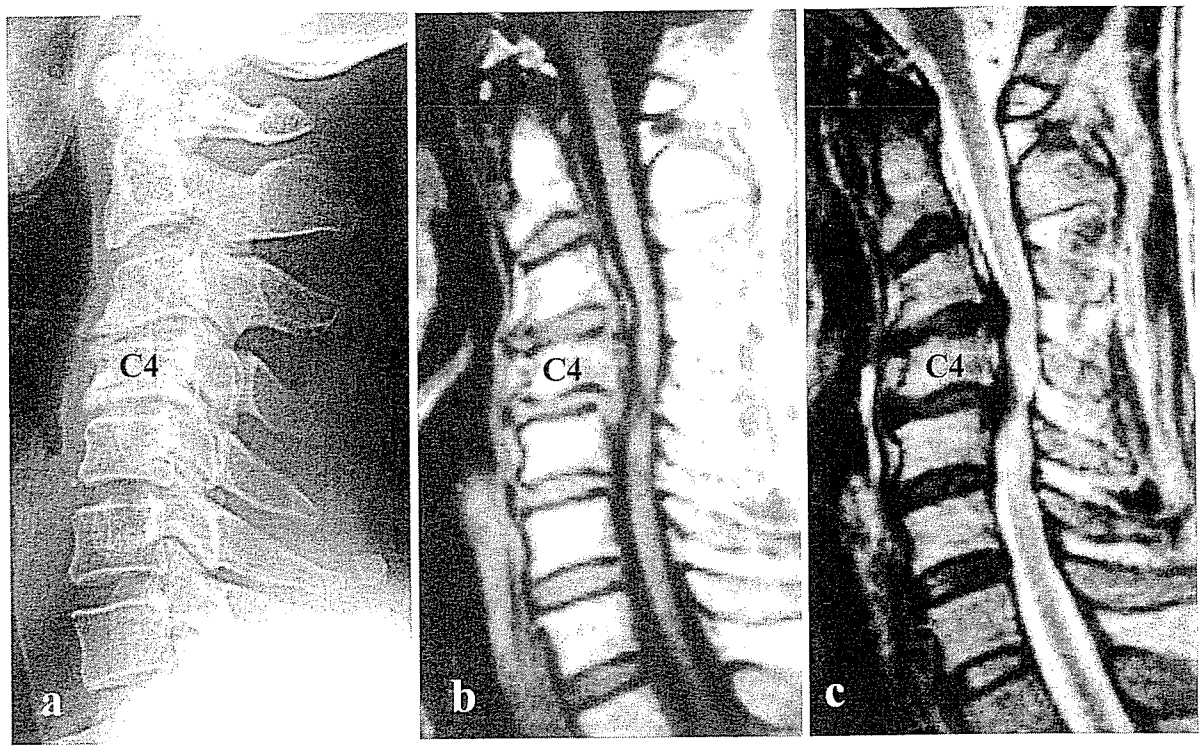

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Fig. 9. Circumscribed-type OPLL in a 68-year-old man. A, a Radiograph shows cervical spondylosis from C3 to C5. OPLL is not seen on a plain radiograph. b T1-weighted sagittal MRI shows an isointensity mass of intervertebral disc hernation at C3-C4 and C4-C5. (c) T2-weighted sagittal MRI shows a high intensity area in the spinal cord and a low signal intensity mass at C3-C4 and at C4-C5. B T2-weighted axial MRI (*center four figures*) shows a low intensity mass within an isointensity mass at C3-C4 and high signal intensity mass at C4-C5. CT (*right three figures*) shows an immature ossified mass behind the intervertebral disc at C3-C4 and C4-C5 and behind the upper part of the C5 vertebral body

of compression and signal changes in the spinal cord are more important than the findings of the ossified mass for guiding nonsurgical management and decisions regarding whether to perform surgery.

The relation of the MRI findings and the severity of the myelopathy in OPLL patients has drawn the attention of many authors. Takahashi et al. and Okada et al. reported that a good correlation was found between the severity of the myelopathy and the degree of cord compression or the transverse area of the spinal cord seen on MRI [24,25]. However, Koyanagi et al. found no correlation between the degree of myelopathy and the transverse area of the spinal cord seen on CT myelography [26]. They found that the transverse area of the spinal cord is correlated with the recovery rate only after surgery [25,26]. Matsuyama et al. reported that preservation of the transverse area of the spinal cord was an important factor for a good surgical outcome [27]. In other words, a poor surgical outcome was expected in patients with spinal cord atrophy.

The conclusion of the clinical guidelines committee about the correlation between spinal cord morphology seen on MRI and the results of treatment was controversial. Many authors have reported that the transverse area of the spinal cord on MRI before operation correlated with the operative results, but the evidence level was not of high quality. The morphology of the spinal cord, such as its flatness or narrowness, on MRI before operation did not correlate with the operative results in some reports, but the evidence in these reports was also not of high quality [1].

MR Images of Signal Change in the Spinal Cord

High signal intensity in the spinal cord on T2-weighted images has been reported in 25.3%–47.6% of patients with cervical OPLL [21,23]. The incidence of high signal intensity was greater in continuous OPLL (34%) than in segmental OPLL (15.6%) in the series of Yamashita et al. [23], probably because cord compression was significantly more severe with the continuous type. High signal intensity is thought to represent edema, demyelination, myelomalacia, cavitation, or necrosis (Fig. 9A, c) [10,24]. The high signal intensity in the spinal cord on T2-weighted images has also been reported to correlate with the severity of the myelopathy [24].