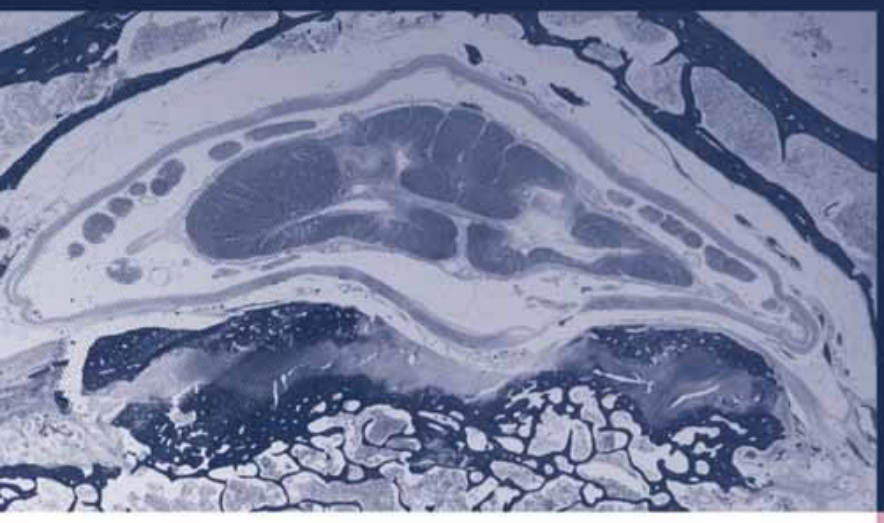
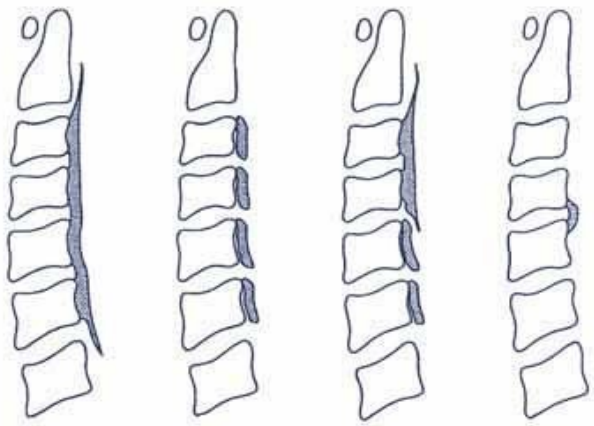
OPLL

Ossification of the Posterior Longitudinal Ligament

2nd Edition





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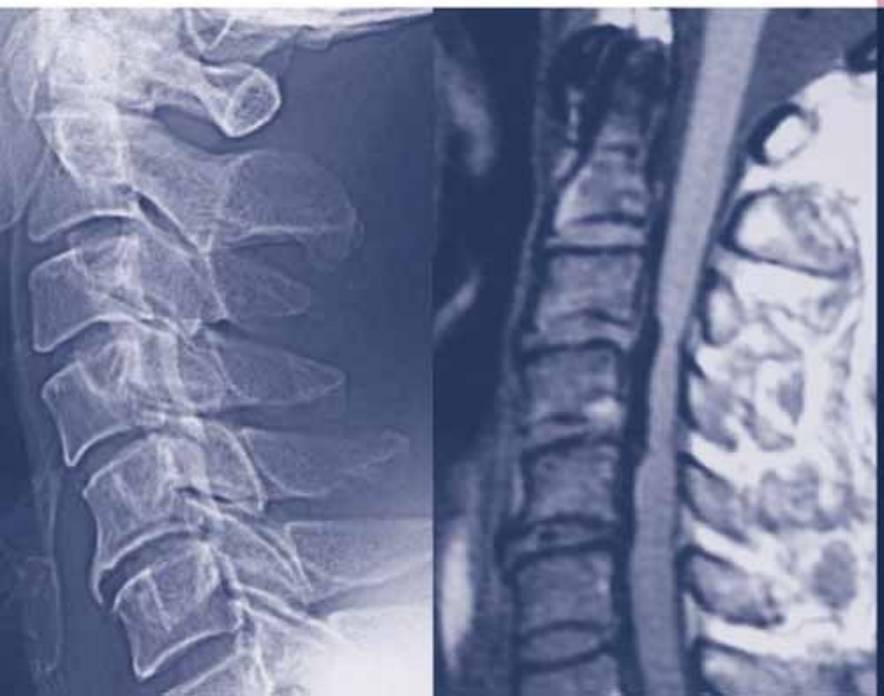

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K. Yonenobu · K. Nakamura · Y. Toyama (Eds.)

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With 280 Figures

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Preface to the Second Edition

Ossification of the posterior longitudinal ligament (OPLL) is no longer only a Japanese disease. In 2004, 18 papers on OPLL and related conditions were published, and 7 of those were from countries other than Japan. Major textbooks on spine surgery, such as *The Spine*, *The Cervical Spine*, and *Spine Surgery*, have devoted chapters to OPLL. Although OPLL has been recognized as a distinct spinal disease entity, several questions regarding etiology and treatment have remained unanswered.

In 2002, the Committee for Study of Ossification of Spinal Ligaments, subsidized by the Ministry of Health, Labour and Welfare and chaired by Professor K. Nakamura, decided to systematically review papers on OPLL and related conditions. The purposes were to direct the research activities of the committee more effectively and to provide more certain knowledge about OPLL, in the form of clinical practice guidelines, for general practitioners and for patients suffering from the condition. A committee for this task was formed in cooperation with the Japanese Orthopaedic Association, and clinical practice guidelines for OPLL, consisting of 4 chapters and 75 research questions, were developed after almost 3 years. Unfortunately, the guidelines have been published only in Japanese as of this writing. Therefore, 4 chapters of this book ("Overview of Epidemiology and Genetics," "Overview of Etiology and Pathogenesis," "Diagnosis of OPLL and OYL," and "Overview of Treatment for Ossification of the Longitudinal Ligament and the Ligamentum Flavum") were included as summaries of the 4 chapters of the guidelines.

One of the important issues that arose during the development of the guidelines was that of diagnostic criteria. OPLL was discovered before computerized tomography had been devised; therefore, OPLL was diagnosed on the basis of clinical and roentgenographic findings from conventional imaging techniques such as plain roentgenography or tomography. However, with an increase in the diversity of medical professionals who take care of patients with spinal disease and with advances in imaging technology such as computerized tomography, a small ossified lesion that usually would not grow to compress the spinal cord is sometimes diagnosed as OPLL, which confuses patients. Diagnosis of OPLL has been made based on tactical knowledge—that is, knowledge held by a closed society made up of experts in the field. This is not a rare example. Several common spinal diseases, such as cervical spondylotic myelopathy, lumbar disc herniation, and lumbar canal stenosis, are diagnosed in this manner. The committee has set tentative diagnostic criteria for OPLL until more definite criteria can be established scientifically, and those tentative diagnostic criteria for OPLL are included in this book.

Since 1997, when the first edition of *OPLL* was published, research on OPLL has progressed steadily in genetics and bone cell physiology. Genetic studies using a variety of approaches, supported by nationwide collaboration, seem to be narrowing in on a disease-related gene. The process of ossification in this condition has been elucidated by studies using techniques of bone cell physiology. Clinical studies using imaging and electrophysiological modalities have clarified the pathophysiology of the spinal cord in OPLL. Follow-up studies have revealed long-term (more than 10 years) results of surgical treatment of both posterior and anterior approaches. All the chapters have been updated with these findings.

As clearly shown in this new edition, many facts regarding hyperostotic conditions of the spine have been cleared up through research activities over the past 30 years, mainly by the successive committees on OPLL. However, many important questions in basic and clinical research have not yet been clarified. Among the basic ones: What are the causative genes? What mechanisms work in hypertrophy and ossification of spinal ligaments in the condition? And there are others. In the clinical area, surgical decompression of the spinal cord in thoracic OPLL and ossification of the yellow ligament (OYL) is still a challenging subject. Although arguments over choice of surgical procedure have been settling down, criteria for the surgical technique for individual patients have not yet been established.

Progress in basic research of OPLL may largely depend on advances in the basic sciences of genetics, bone cell physiology, and related fields. In surgery, assiduous efforts by surgeons to devise a technique for better and safer results are mandatory. Such improvement in treatment for any surgical condition is general. Additionally, for relatively rare conditions such as OPLL, establishment of a system of clinical trials is important to substantiate the significance of a new treatment, and this is the surgeon's task.

Through the challenge posed by this disease, we Japanese spine surgeons have learned many things about bone biology and about the spine and spinal cord as well, and we have developed various surgical techniques to conquer the condition. OPLL, however, still confronts us, and to surmount this refractory hyperostotic condition of the spine, we must expand our research into new fields. Development of drugs to control bone formation is one example—drugs that not only prevent progression of ossification of the spinal ligament but that also preserve spinal mobility, which we spine surgeons sometimes have neglected. Another example is repair or regeneration of the injured spinal cord. I hope that these goals will be achieved with further study of OPLL.

The editors express their sincere thanks to the members of the Committee on Clinical Practice Guidelines of OPLL: Drs. K. Yonenobu (Chairperson), M. Iwasaki, K. Satomi, T. Taguchi, M. Tanaka, Y. Toyama, and S. Matsunaga; and to the members of the working group for reviewing papers: Drs. H. Aono, Y. Itoh, S. Okuda, K. Kato, K. Kaneko, J. Kouno, K. Takeuchi, K. Toyoda, K. Hayashi, and A. Miyauchi. Without their perseverance, the guidelines as well as this book would not have been completed.

Kazuo Yonenobu

Preface to the First Edition

"Man can see only what he knows."
Goethe

Ossification of the Posterior Longitudinal Ligament (OPLL) has long been a challenge to orthopedic spinal surgeons in Japan, and their struggle to meet that challenge has marked a turning point in the history of spinal surgery. Investigation of the etiology and treatment of the condition has taught surgeons to see diseases of the spine and their surgical treatment in a new perspective.

It was truly a surprise to learn that the posterior longitudinal ligament could become a thick, bony plate in the cervical spine and impinge on the spinal cord, leading to paralysis. Even more amazing, however, is that innumerable roentgenological findings of such thick, bony lesions could be overlooked for decades before OPLL became well recognized by physicians in Japan. Progress in diagnostic imaging technology, first in computed tomography (CT) and then in magnetic resonance imaging (MRI), has helped in diagnosis and evaluation of the disease and in deciding therapeutic modalities. There is no better tool than CT and CT myelography for demonstrating the real threat of OPLL to the cervical spinal cord. MRI, however, provides more information on widespread ossified lesions from the cervical to lumbar regions, and on the intramedullary changes caused by chronic compression. It is not a great exaggeration to say that OPLL is one of the leading reasons for the enthusiastic expansion in the market for the newest diagnostic imaging tools in Japan.

Despite Tukiyama's autopsy report of OPLL in 1960, the etiology of OPLL remained unclear and its symptoms and characteristics were unfamiliar until 1975, when the Investigation Committee for OPLL moved toward better patient care and research of the etiology of the disease. Under the auspices of the Ministry of Health and Welfare, diagnostic criteria for OPLL scoring both of physical manifestations and of roentgenological findings were first established.

With dissatisfied patients who failed to recover after conventional laminectomy, a new technique of decompression had to be developed. Failure of surgical decompression was thought to be due to careless methods of laminectomy in which the thick rongeur blade or Kerrison punch was introduced into an extremely narrow spinal canal. Anterior diskectomy and interbody fusion by either the Smith-Robinson or Cloward method often caused paraplegia. In the 1960s, patients with OPLL thus remained unhappy even after surgery; it was a dreary time for spinal surgeons in this country. Then came the introduction of a high-speed surgical drill for laminectomy, along with technical developments such as expansive laminoplasty (Hirabayashi, 1981) and anterior decompression by the floating of OPLL (Yamaura, 1983), which ensured decompression of the spinal cord without excision.

Considered as a systemic disease, OPLL was recognized rather early to occur with high frequency in patients suffering from diabetes mellitus. There were also a few reports on metabolic and endocrine disorders in close relationship with OPLL: hypophosphatemic rickets or hypoparathyroidism. OPLL is not simple calcification, however, but ossification of the ligaments; the etiological relationship between these disorders of calcium metabolism and ectopic ossification was explored in vain. As

precise pathological study progressed, the real harm of the lesion proved to be hyperplasia or growth of the ligament leading to occupation of the spinal canal. Fibrocartilagenous cell proliferation and matrix hyperplasia and subsequent ossification were found to be the essential processes of OPLL.

What mechanism, then, stimulates the growth of the ligament in a middle-aged or older person? Various growth factors or cytokines were found to be present in the growing front of OPLL, but the mechanism that releases or regulates them has yet to be clarified. A metabolic or endocrine system abnormality may influence this renewed growth. Predisposition to OPLL has been examined in familial surveys including studies of twins, and in the future, HLA gene analysis may be able to identify those at high risk od OPLL.

Finally, we consider what impact surgery for OPLL has on traditional spinal surgery. Decompression with spinal stability unimpaired, expansion of developmental canal stenosis without laminectomy, or sufficient decompression without excision of a lesion mass—these have been developed to treat paralysis due to OPLL. They have been made possible through the enthusiastic research and practice of Japanese spinal surgeons, and are now widely applicable to all sorts of diseases of the spine, without being limited to the cervical spine.

This monograph should be dedicated to those patients who were destined to suffer pain and paralysis without benefit of the current achievements in spinal surgery.

Keiro Ono

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4. Diagnosis of OPLL and OYL

5. Treatment of OPLL and OLF

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1. Introduction

History of Research

Kozo Nakamura

The first report of ossification of the posterior longitudinal ligament (OPLL) is credited to Key [1], who described it during the mid-nineteenth century. Oppenheimer [2] later reported 18 cases with calcification or ossification of the anterior and posterior ligaments. In 1960, Tsukimoto [3] found OPLL during an autopsy. Following publication of this article, many Japanese surgeons reexamined their patients' radiographs, which resulted in the discovery of numerous missed OPLLs.

In 1975, the Japanese Ministry of Public Health and Welfare (the present Ministry of Health, Labor, and Welfare) added OPLL as one of the specified diseases for clarification of etiology, epidemiology, and pathogenesis as well as establishment of criteria for diagnosis and treatment regimens. The Investigation Committee on Ossification of the Posterior Longitudinal Ligament has taken the lead in the clinical and basic research of OPLL in Japan. The first chairman, Tsuyama, conducted epidemiological, radiographic, pathological, and clinical studies. He was followed by the second chairman, Terayama, in 1981. A nationwide family study [4] of 347 cases was performed. Kurokawa took the third chairmanship in 1988, and he organized the studies into four subgroups: (1) genetic research; (2) study of the hypertrophy and progression of OPLL; (3) the pathogenesis of myelopathy caused by OPLL; and (4) diagnostic criteria. Sakou took over in 1992, and biomolecular and genetic research [5] have been energetically conducted ever since. Harata, who became the fifth chairman in 1996, conducted an epidemiological study [6] in China and assessed the quality of life in patients with OPLL [7]. In 2002, Nakamura became the sixth chairman and developed guidelines regarding OPLL for physicians [8].

Morbidity associated with OPLL in Japan is estimated to be 1.9%–3.2%. In other Asian and Eastern countries, the morbidity is equivalent or lower: 3.0% in Taiwan, 1.6%–1.8% in China, and 0.95% in Korea. In the Western world, it is 0.12% in the United States and 0.1% in Germany [9]. Several members have investigated the relation between OPLL and calcium metabolism [10], diabetes, estrogen, and vitamin D. Diabetic patients were found to have a tendency to develop OPLL, and an abnormal secretion pattern of insulin by blood glucose was implicated [11]. Two animal models, the Zucker fatty rat [12] and the ttw (tip toe walking) mouse [13], were found to have ossification of spinal ligaments, and their study has contributed significantly to our understanding of OPLL. The ossification and compressed neural elements from surgical specimens or cadavers have been studied histologically [14]. Ossification of the spinal ligament is ectopic, with hypertrophy of the ligament and proliferation of cartilaginous cells in the ligament and cytokines related to bone formation (bone morphogenetic protein and transforming growth factor-β) appearing during the ossifying process. In recent years, genetic analysis has been intensively performed in humans and animal models. Various candidate genes were reported; three genes—*COL11A2* [5], *NPPS* [13], and *TGFβ1*—are most promising.

OPLL sometimes appears as long and multiple lesions and sometimes as ossification of the dura. Patients with severe myelopathy and thoracic OPLL are most vulnerable to neurological deterioration. The treatment of thoracic OPLL is still controversial. Surgical treatment of OPLL always demands perfect planning and masterful surgical skills.

Recording somatosensory evoked potentials (SEPs) was the first modern monitoring method to detect spinal nerve dysfunction during surgical maneuvers. Recently, multimodal spinal cord monitoring by SEPs and motor-evoked potentials (MEPs) [15] was proposed to find any subtle abnormality in the spinal cord.

As for OPLL in the cervical spine, several new surgical procedures have been developed after experiences with postlaminectomy kyphosis and subsequent neurological deterioration. Kirita and colleagues developed a new laminectomy procedure that was substantially a new fusion technique, from which laminoplasty by Hattori evolved. Most popular is the open-door (unilateral) laminoplasty by Hirabayashi [16] and French-door (bilateral) laminoplasty of Kurokawa [17]. For the anterior approach, wide adhesion of OPLL to the dura

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or ossification of the dura demands that the spinal surgeon do meticulous, skillful decompression. Yamaura proposed the anterior floating technique, in which the ossification is trimmed by a burr, promoting a shift ventrally [18].

The Investigation Committee on Ossification of the Posterior Longitudinal Ligament functions as the hub of the basic and clinical research, which has made significant contribution to our understanding of this disease and to the development of spinbal surgery.

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2. Epidemiology

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.

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.

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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

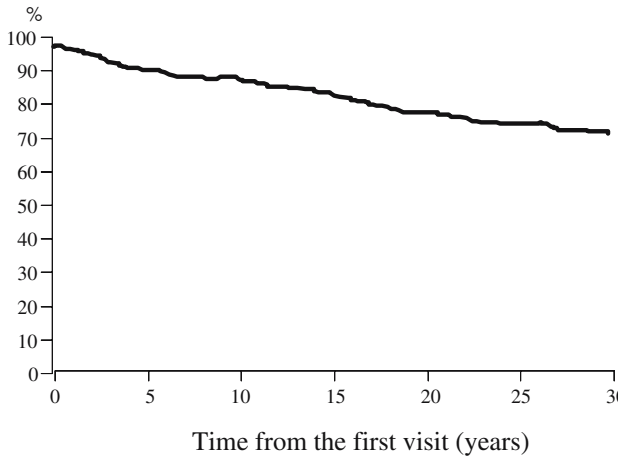

Fig. 1. Kaplan-Meier estimate of myelopathy-free rate among patients who did not exhibit myelopathy at the first examination

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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