Multilevel ossification of the posterior longitudinal ligament causing cervical myelopathy: An observational series of North American patients

ABSTRACT

Background: Few studies regarding ossification of the posterior longitudinal ligament (OPLL) outside of Asia currently exist in the literature. A set of patients with multilevel cervical OPLL causing symptomatic myelopathy or radiculopathy from a North American sample is analyzed.

Objective: The objective of this study was to describe the demographics, radiographic findings, and surgical outcomes of a cohort of North American patients with degenerative spondylosis presenting for operative management of multilevel (>3 segments) cervical OPLL.

Materials and Methods: Forty-three patients diagnosed with multilevel cervical OPLL and degenerative spondylosis presenting with symptomatic cervical myelopathy or radiculopathy were surgically treated over a 9-year period at a single tertiary care academic medical center. Radiographic measurements were performed on preoperative computed tomography and magnetic resonance imaging images of the cervical spine. Clinical outcomes included pre- and postoperative Nurick scores, 90-day readmission, complication, and revision surgery rates.

Results: The mean age was 66.1 ± 10.9 years with a mean latest follow-up time of 32.7 ± 16.4 months. Most patients had previous diagnoses of obesity (70.7%) and hypertension (55.8%). At least one-quarter of patients were diagnosed with type 2 diabetes (34.9%), hyperlipidemia (41.9%), cardiovascular disease (25.6%), or chronic kidney disease (25.3%). The most common OPLL subtype was segmental (39.5%) and spanned a mean of 3.54 ± 1.48 segments. Myelopathic symptoms were present in 88.4% of patients. All patients experienced significant neurologic improvement at 3-week and latest follow-up ($P < 0.001$ for both).

Conclusions: Obesity, diabetes, and other metabolic derangements in patients with existing cervical spondylosis may be risk factors for a particularly aggressive form of multilevel OPLL. Various operative approaches may be employed to achieve adequate neurologic recovery. Further workup for OPLL in patients with these risk factors may prove beneficial to ensure appropriate operative management.

Keywords: Cervical vertebrae, clinical outcomes, epidemiology, ossification of posterior longitudinal ligament, spine

INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL) is a hyperostotic condition of the spine characterized by ectopic formation of lamellar bone about the posterior longitudinal ligament (PLL). Although first described in Europe in 1838, OPLL has been reported to have the highest incidence in East Asian populations, classically in patients of Japanese descent.[1] The exact etiology of OPLL remains unknown. However, several environmental exposures and genetic factors have been implicated in the pathogenesis of OPLL. Prior studies have identified high body mass index (BMI) and diabetes as independent risk factors for

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OPLL, along with environmental factors such as exposure to high fluoride concentrations.[2-5] In addition, OPLL and other hyperostotic conditions such as diffuse idiopathic skeletal hyperostosis (DISH) and ossification of the yellow ligament (OYL) have been documented as associated diagnoses, indicating that an inflammatory and/or genetic component may be implicated in OPLL formation.[1,4,6,7]

Cervical OPLL represents the most common manifestation of this condition and presents many clinical challenges. Although often asymptomatic, progressive overgrowth and OPLL may occlude the central canal or neural foramina, resulting in cervical radiculopathy and/or myelopathy. Patients with OPLL may be predisposed to spinal cord injury from even minor trauma, raising further concerns for severe morbidity.[8] In addition, anterior cervical decompression performed in the presence of unrecognized OPLL may cause iatrogenic complications due to adherence of the PLL to the dura, emphasizing the need for careful review of imaging during surgical planning.

Many surgeons in North America or European centers will encounter OPLL in non-Asian populations during their practice. However, studies that describe OPLL in North American populations mostly comprise small case series, data pooled from multiple institutions, or on imaging performed regardless of any symptomatic cervical pathology.[2,4,7] Therefore, the objective of this study was to evaluate the clinical, demographic, and radiographic traits of a particularly robust form of multilevel cervical OPLL in patients seen at a North American tertiary academic center presenting for surgical management of symptomatic cervical radiculopathy or myelopathy.

MATERIALS AND METHODS

Study design and demographics

After obtaining institutional review board approval (IRB Control #19D.508), a retrospective review of all patients who received operative management for cervical radiculopathy or myelopathy due to OPLL at a single-center, high-volume academic medical center by 1 of 6 different fellowship-trained orthopedic spine surgeons from October 2011 to July 2020 was performed. Patients of interest were identified through Standardized Query Language search using the current International Classification of Diseases code 723.7 and review of medical records, operative notes, and radiology reports. Patients 18 years or older who underwent anterior, posterior, or combined anterior/posterior surgery for cervical radiculopathy or myelopathy due to compressive OPLL were included in the study. All patients with previous spinal surgery, infectious or malignancy diagnosis, and missing cervical computed tomography (CT) or magnetic resonance imaging (MRI) imaging were excluded.

Patient demographic data including age, sex, BMI, past medical history, history of tobacco and alcohol use, self-identified race, primary preoperative diagnosis, operative approach used, mean levels decompressed, mean levels fused, length of stay, latest follow-up, 90-day readmissions, and revision surgeries were obtained through chart review and retained in a secure database.

Radiographic parameters

Radiographic measurements were obtained on preoperative sagittal and coronal CT and MRI images of the cervical spine using the Sectra Workstation IDS7 21.1 (Sectra AB; Linköping, Sweden). Radiographic parameters included OPLL span in number of segments, mean diameter at the most stenotic point, mean OPLL thickness, and canal stenosis ratio as described by Jayakumar *et al.* [Figure 1].[9] Images were reviewed by board-certified orthopedic spine surgeons, an orthopedic spine surgery fellow, and an orthopedic surgery resident, all of whom were trained to identify and classify OPLL via CT scan and MRI. The diagnosis of OPLL was classified as localized, segmental, continuous, or mixed [Figures 2 and 3], as previously described by the Investigation Committee for Ossification of the Spinal Ligaments and the Japanese Ministry of Health, Labour, and Welfare.[10] Imaging studies were also reviewed for the presence of DISH, OYL, and thoracic involvement.

Clinical outcomes

Patient records were retrospectively reviewed to assess for age at diagnosis, onset of neurologic deficits, precipitating factors, presenting neurologic deficits, and quality of

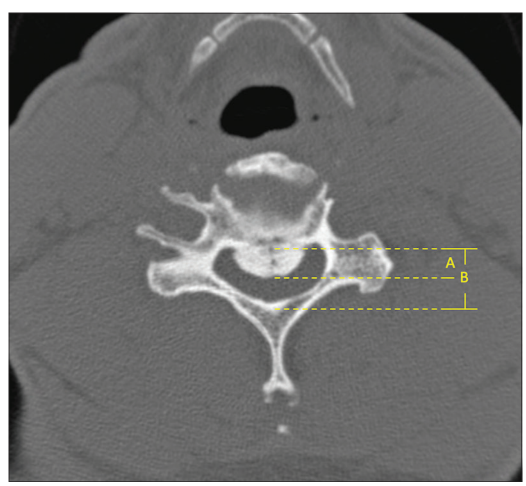

Figure 1: Measurement of canal stenosis ratio, performed on axial computed tomography or magnetic resonance imaging images and defined as the percentage of the ratio of (A) ossification of the posterior longitudinal ligament thickness to (B) axial diameter of the canal at the same level

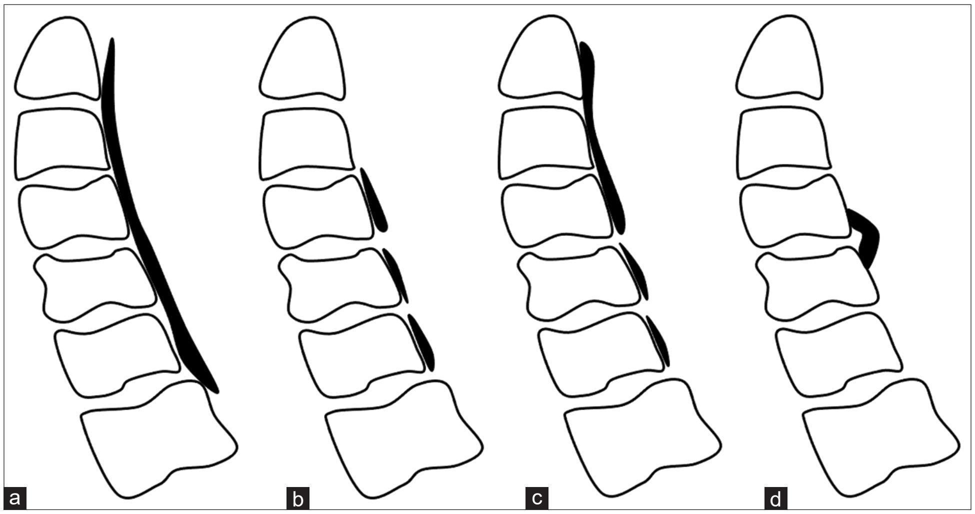

Figure 2: Morphological subtypes of ossification of the posterior longitudinal ligament as described by the Investigation Committee for Ossification of the Spinal Ligaments and the Japanese Ministry of Health, Labour, and Welfare, including (a) Continuous, (b) Segmental, (c) Mixed, and (d) Other subtypes

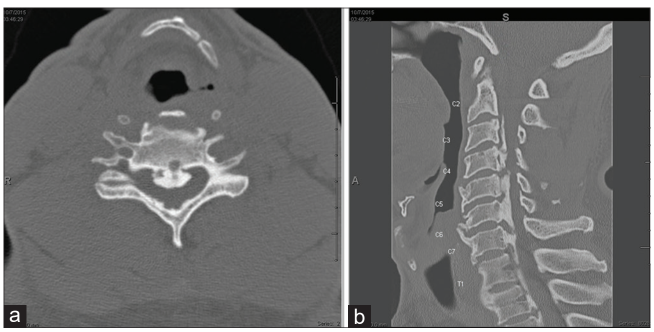

Figure 3: Computed tomography (CT) images of a male patient who presented with progressively worsening gait abnormalities and hand weakness. Axial (a) and sagittal (b) CT images of the cervical spine demonstrate continuous-type ossification of the posterior longitudinal ligament spanning from C2-T2 with >50% canal stenosis

postoperative change. Acute onset was defined as neurologic deterioration occurring in <2 weeks. Precipitant categories included trauma, none, or unavailable for review. Neurologic deficits at presentation were categorized as myelopathy, radiculopathy, or myeloradiculopathy. Postoperative outcomes were described as improvement, no change, or worsening of preoperative symptoms.

Statistical analysis

Statistical analysis was performed using SPSS version 27.0.0 (IBM Corp, Armonk, New York, USA). Normality of distributions was assessed using a Shapiro–Wilk test. One-way analysis of variance and Kruskal–Wallis testing were used to compare means for continuous variables between the four OPLL subtypes as described above.

RESULTS

We identified 43 total patients with OPLL who were included in our study. Patients were on average 66.1 ± 10.9 years of age with a BMI of 34.8 ± 7.53 kg/m^2 [Table 1]. There was a similar proportion of male (n = 22, 51.2%) and female (n = 21, 48.8%) patients. Thirty (70.7%) patients were obese, defined as having a BMI >30.0 kg/m^2. Regarding other medical conditions, 24 (55.8%) patients were diagnosed with hypertension, 15 (34.9%) had type 2 diabetes mellitus, 18 (41.9%) had hyperlipidemia, 11 (25.6%) had cardiovascular disease, 10 (25.3%) had chronic kidney disease, 3 (6.98%) had rheumatoid arthritis, and 5 (11.6%) had DISH. Ten patients reported a history of tobacco use and nine patients reported alcohol use. None of the patients in this case series identified as Asian, while 23 (53.5%) identified as White, and 20 (46.5%) identified as Black.

The most common OPLL subtype was segmental (39.5%), followed by continuous (32.5%), mixed (16.3%), and then others (11.6%) [Table 2]. Cervical OPLL spanned a mean of 3.54 ± 1.48 segments, with the most stenotic level on average occurring at C5-C6 (46.5%). The mean spinal canal diameter at the most stenotic point was 5.84 ± 0.86 mm, and the mean OPLL thickness was 5.31 ± 0.83 mm. The mean canal stenosis ratio across all OPLL subtypes was 46.7% ±9.36%. When compared by subtype, mixed-type OPLL was found to have the highest canal mean stenosis ratio (53.7% ±9.12%), followed by continuous (50.6% ±6.34%), others (42.9% ±6.39%), and then segmental (41.7% ±9.53%, P = 0.004). OPLL most frequently started at C3 (37.2%) and terminated at C7 (46.5%).

Patients in this series presented with a baseline Nurick grade of 3.09 ± 0.81 and improved by an average 1.72 ± 0.93 postoperatively [Table 3]. The majority of patients presented with myelopathy (n = 33, 76.8%), while 5 (11.6%) patients presented each with isolated

Table 1: Patient demographics

Variable	Value, *n* (%)
Total patients	43
Age	66.1±10.9
Sex	
Male	22 (51.2)
Female	21 (48.8)
Self-Identified Race	
White	23 (57.5)
Black	20 (46.5)
BMI	34.8±7.53
Past medical history	
Obesity	30 (70.7)
Hypertension	24 (55.8)
Type 2 diabetes	15 (34.9)
Hyperlipidemia	18 (41.9)
Cardiovascular disease	11 (25.6)
Chronic kidney disease	10 (25.3)
Rheumatoid arthritis	3 (6.98)
DISH	5 (11.6)
Social history	
Tobacco use	10 (23.3)
Alcohol	9 (20.9)
Latest follow-up (months)	32.7±16.4

BMI - Body mass index; DISH - Diffuse idiopathic skeletal hyperostosis

Table 2: Preoperative radiographic parameters

	Total (*n*=43)
Morphology, *n* (%)	
Segmental	17 (39.5)
Continuous	14 (32.6)
Mixed	7 (16.3)
Others	5 (11.6)
Most stenotic level	C5–C6 (46.5)
Mean OPLL span (segments)	3.54±1.48
Mean diameter at the most stenotic point (mm)	5.84±0.86
Mean OPLL thickness (mm)	5.31±0.83
Canal stenosis ratio (%)†	
All subtypes	46.7±9.36
Segmental	41.7±9.53
Continuous	50.6±6.34
Mixed	53.7±9.12
Others	42.9±6.39
P	0.004*
Levels involved, *n* (%)	
OPLL starting at	
C1	1 (2.3)
C2	12 (27.9)
C3	16 (37.2)
C4	6 (14.0)
C5	8 (18.6)
OPLL ending at	
C4	1 (2.3)
C5	4 (9.3)
C6	10 (23.3)
C7	20 (46.5)
T1	6 (14.0)
T2	2 (4.6)

*Significance level established at $P < 0.05$, †Results of one-way ANOVA comparing mean canal stenosis ratio by OPLL subtype. OPLL - Ossification of the posterior longitudinal ligament; ANOVA - Analysis of variance

radiculopathy or concurrent myeloradiculopathy. Operative treatment entailed a fusion of 3.77 ± 2.89 levels and decompression of 3.77 ± 2.23 levels on average. Regarding operative approach, 15 (34.9%) patients underwent an anterior approach, 26 (60.5%) patients underwent a posterior approach, and 2 (4.65%) underwent a combined anterior and posterior approach. The average length of stay postoperatively was 4.36 ± 5.21 days. One patient was readmitted within 90 days due to postoperative cardiac complications. Two patients underwent additional cervical spine surgery within the 1-year postoperative period, one for hardware complications and the other for adjacent-level symptoms. There were no instances of dural tear, postoperative infection, neuropraxia, or dysphagia.

DISCUSSION

Our study evaluates the patient presentation, demographic factors, and outcomes of 43 patients operatively treated for symptomatic OPLL at a single North American urban academic medical center. OPLL is classically considered an Eastern Asian disease, likely due to several interacting factors including environment, health comorbidities, and genetic inheritance patterns.[7,11] However, understanding the implications of this disease in other races is important to increase the generalizability of existing evidence. The cohort of the present study most frequently presented with myelopathic symptoms and nearly 50% canal stenosis at the most stenotic levels, with the mixed subtype being most common. Similar to prior studies, we identified OPLL predominance in the cervical spine, presentation in the sixth and seventh decades of life, male predominance, and varied clinical presentations and degrees of neurologic dysfunction.[12,13] However, this series identified a unique subset of patients presenting with cervical myelopathy and a history of systemic disease and metabolic derangements, found to have multilevel OPLL spanning >3 segments with severe spinal canal stenosis.

The association between systemic and metabolic conditions and ligament ossification has been well documented in the literature. Several studies have reported the impact of obesity and diabetes on cervical OPLL.[3,4,14-16] A recent meta-analysis noted that patients with spinal ligament ossification had significantly higher BMI, and that patients with higher BMI had significantly higher ligament ossification indices and more severe disease presentation compared to those with lower BMI.[14] Kobashi *et al*. noted that a history of diabetes

Table 3: Clinical features, operative characteristics, 90-day readmissions, and revision surgery rate

	Total (*n*=43)
Preoperative Nurick grade	3.09±0.81
Postoperative Nurick grade	1.37±0.69
P	<0.001
Nurick Δ	1.72±0.93
Onset of neurologic deficits, *n* (%)	
Acute	4 (9.3)
Progressive	39 (90.7)
Neurologic deficit, *n* (%)	
Myelopathy	33 (76.8)
Radiculopathy	5 (11.6)
Myeloradiculopathy	5 (11.6)
Operative approach, *n* (%)	
Anterior	15 (34.9)
Posterior	26 (60.5)
Anterior/posterior	2 (4.65)
Length of stay (days)	4.36±5.21
Latest follow-up (months)	32.7±16.4
Mean levels decompressed	3.77±2.23
Mean levels fused	3.74±2.89
90-day readmissions, *n* (%)	1 (2.33)
Revision surgeries, *n* (%)	2 (4.65)

mellitus and maximum BMI >25 kg/m^2 were independent risk factors for the development of OPLL.[3] Although the underlying mechanism driving these associations remains unclear, various cellular signaling pathways have been implicated in the pathogenesis of this condition. Leptin secreted from adipose tissue may be elevated in OPLL patients and can promote the osteogenesis of OPLL cells via pathways including p38 MAPK, ERK1/2, and JNK.[15] In addition, nuclear factor kappa B has been reported to be associated with the onset of OPLL, particularly in cases complicated by noninsulin-dependent diabetes mellitus.[17] A considerable portion of patients in the present study were diagnosed with obesity (70.7%) and type 2 diabetes (34.9%) with a mean BMI nearing severe obesity, further reinforcing the association between these conditions and the development of severe OPLL.

Hyperlipidemia has been studied as a potential driver of spinal ligament ossification.[16,18,19] The proportion of dyslipidemia in OPLL patients has been reported to be 1.6–2.2 times higher compared to controls.[18] Similarly, Fukada *et al*. reported a comorbidity of dyslipidemia in their OPLL group more than twice that of their control group (71.7% vs. 35.4%, respectively), with 64.1% of patients with diffuse OPLL having comorbid dyslipidemia.[16] Interestingly, although diabetes has been more thoroughly established as a risk factor for OPLL, the authors also noted that the relative risk of dyslipidemia was equivalent to or higher than diabetes mellitus. Several cellular mechanisms describing the relationship between dyslipidemia and ligament ossification have been reported. Particularly, high low-density lipoprotein (LDL)-cholesterol may induce a high oxidative stress environment, activate Wnt signaling, and upregulate LDL receptor-related protein 5 resulting in osteoblast proliferation and bone formation.[19] Although the prevalence of hyperlipidemia in the present study's cohort remains lower than that previously reported, our results highlight the relationship between metabolic abnormalities and aberrant ligamentous ossification. Overall, these findings suggest that visceral fat deposition and abnormal lipid metabolism play a significant role in the onset and progression of OPLL, especially in this particularly severe multilevel form as described.

Recently, atlantoaxial instability and subaxial instability have been suggested as a point of pathogenesis for OPLL.[20-23] Chronic instability due to paraspinal muscle weakness or injury has been associated with progressive spinal degeneration, causing biomechanical changes such as excessive and pathologic function of the facet joints.[20,21] Consequently, accelerated degeneration and repetitive microtrauma to the spinal column occur, causing further insult to the already degenerated spine. In an initial series of 29 cases followed by a subsequent series of 52, Goel observed significant clinical improvement in patients diagnosed with myelopathy secondary to cervical OPLL treated with spinal fixation alone without decompression, providing early literature support to this hypothesis.[22,23] Although cervical spine stability was not specifically evaluated in this study, thorough assessment of dynamic radiographs and medical management of any rheumatologic conditions may allow providers to advise their patients more optimally on the prognosis of their condition.

Surgical outcomes

Orthopedic spine surgeons from the authors' institution have anecdotally reported a particularly aggressive form of OPLL characterized by multilevel involvement and severe central stenosis in patients with diabetes or other metabolic derangements. No definitive guidelines exist for the treatment of OPLL, including whether operative treatment should proceed via an anterior or posterior approach. The goal of surgery in patients with myelopathy secondary to OPLL is to decompress neural elements either by resecting OPLL mass or expanding spinal canal volume.[7] Existing literature suggests that the absence of any neurologic symptoms should preclude operative treatment since OPLL may be detected on incidental imaging in asymptomatic individuals. A 30-year study on OPLL individuals demonstrated that up to 71% of individuals with incidentally discovered OPLL will continue to be myelopathy-free at 30-year follow-up.[1] Park *et al*. similarly found that while asymptomatic patients will often demonstrate radiographic progression in OPLL length and thickness over 2-years, only 2.1% developed myelopathic symptoms during that span.[3] However, the risk of future myelopathy and neurologic injury due to OPLL progression remains poorly understood and based on low-quality evidence.[24]

However, operative management of patients without notable cord compression and mild symptoms is most controversial.[7] Many patients with OPLL with minor neurologic deficits may successfully undergo conservative management. Matsunaga *et al*. evaluated 450 patients with OPLL over a 10-year span and found that surgery led to significant long-term improvement only in patients with Nurick grade 3 or 4 myelopathy but that patients with lower Nurick grades did not benefit from surgery.[27] Moreover, 89% of Nurick grade 3 or 4 patients who were treated nonoperatively became wheelchair-bound compared to only 12% of operatively treated patients. In our cohort, patients presented with an average Nurick grade 3 and experienced significant improvement by nearly two grades following surgical treatment.

The efficacy of anterior versus posterior approaches to OPLL surgery is still inconclusive, and efficacy is dependent on several baseline disease characteristics. In our cohort, 15 patients underwent anterior surgical intervention while 26 patients underwent a posterior surgical approach.[26] Originally, the surgical treatment for OPLL favored total or near total resection of the OPLL mass. Anterior surgery allows for direct decompression of the spinal cord through exposure of and resection of OPLL mass. Diskectomies and corpectomies can be performed to further allow for anterior decompression of the spinal canal. Aside from standard complications associated with multilevel anterior cervical surgery, OPLL presents other considerations, primarily in that of dural ossification which may appear in up to 30.2% of OPLL segments.[27] Yamaura *et al*. therefore suggested an anterior fusion with a "floating" technique whereby an overlying vertebral body is resected and only a subtotal resection of the OPLL mass is performed allowing for the thinned OPLL mass to "float" into the space created by the corpectomy.[30] This therefore can reduce the incidence of incidental durotomy for cases of dural ossification that would be difficult to visualize in an anterior approach. For patients who need decompression and/or fusion of more levels, posterior approaches are much less technically challenging. However, posterior surgery precludes OPLL resection, only achieving indirect decompression by expanding canal space so that the cord does not sit upon the OPLL mass.[26] Recommendations previously put forth recommend laminectomy and fusion or laminoplasty for longer segment OPLL while anterior approaches should be reserved for younger patients with focal lesions to decompress the spinal cord by exposing and then removing the ossified or hypertrophic PLL.[29] Our surgical team generally followed these guidelines in surgical decision-making. Multiple studies have compared a posterior laminoplasty to anterior fusion with floating and have found that patients with canal stenosis >60% achieved superior outcomes with the direct decompression offered by an anterior approach.[30-33] In our cohort, the average canal stenosis ratio was 47.2% which may be why similar outcomes in Nurick grade improvement were achieved in both the groups. In properly selected patients, either approach may therefore be effective in achieving adequate postoperative outcomes.

This present study is not without limitations. First, due to this study's observational design, no control cohort was present to perform comparisons or evaluate for any significant associations based on past medical history or surgical approach. Second, only patients with available cross-sectional imaging data were included, presenting a source of selection bias. Third, only history of diagnosis was obtained without any additional laboratory values to further characterize the extent of metabolic disease. Finally, all data collected were from one institution representing a single region in the United States. Thus, these results may not be applicable to other populations.

CONCLUSIONS

This study describes a series of 43 patients presenting to a single North American center for surgical management of severe multilevel OPLL-causing cervical myelopathy. Overall, the majority of patients were obese with a considerably elevated BMI and had concomitant metabolic abnormalities including type 2 diabetes, hypertension, and dyslipidemia, all known risk factors for the development and progression of OPLL. Appropriately selected surgical intervention can effectively address patient symptoms and improve neurologic function. However, future studies are needed to further elucidate potential epidemiologic ties between OPLL and non-Asian populations, along with the mechanisms responsible for the associations between metabolic derangement and spinal ligament ossification.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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