Title

Predictive factors for a poor surgical outcome with Thoracic Ossification of the Ligamentum Flavum by multivariate analysis: a multicenter study

Running title: Surgery for thoracic myelopathy caused by ossified ligamentum flavum and anterior longitudinal ligament –report of 96 patients-

Kei Ando, [1] Shiro Imagama, [1] Zenya Ito, [1] Kenichi Hirano, [1] Ryoji Tauchi, [1] Akio Muramoto, [1] Fumihiko Kato, [2] Yasutsugu Yukawa, [2] Noriaki Kawakami, [3] Koji Sato, [4] Yuji Matsubara, [5] Tokumi Kanemura, [6] Yukihiro Matsuyama, [7] and Naoki Ishiguro, [1]

[1] Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; [2] Department of Orthopedic Surgery, Chubu Rosai Hospital, Nagoya City; [3] Department of Orthopedic Surgery, Meijo Hospital, Nagoya City; [4] Department of Orthopedic Surgery, Nagoya 2nd red cross Hospital, Nagoya City; [5] Department of Orthopedic Surgery, Kariya-Toyota General Hospital, Kariya City; [6] Department of Orthopedic Surgery, Konan Kosei Hospital, Konan City; [7] Department of Orthopedic Surgery, Hamamatsu Medical University, Hamamatsu City, Japan

Authors informations

Kei Ando PhD
Department of Orthopedic Surgery, Nagoya University School of Medicine, 65 Tsurumai Showa-ward, Aichi 466-8550, Japan
phone:+81-52-744-1908 fax:+81-52-744-2674
mail: keikeiando@hotmail.co.jp

Acknowledgments: I am grateful to all the staff of Nagoya Spine Group for allowing me to study their patients, and I also wish to thank M. Kamiya, H. Yoshihara, M. Yanase, Y. Sakai, Y. Katayama, N. Wakao, and Ms S. Horiuchi for their assistance with data collection.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Introduction

Thoracic ossification of the ligamentum flavum (T-OLF) is relatively rare spinal disorder that generally requires surgical intervention due to its progressive nature and its poor response to conservative therapy. The prevalence of OLF has been reported at 3.8% to 26% [1-3], which is very similar to the prevalence of cervical ossification of the posterior longitudinal ligament (OPLL) [4]. However, predictive factors for OLF are unclear because of the paucity of reports on this condition unlike cervical OPLL [1,5-15] . Since obtaining detailed data and analysis from a single center study on this topic has been insufficient and difficult, we investigated clinical features, radiologic findings, and surgical outcomes of OLF in a multicenter study. We reported surgical results of 63 patients who underwent single level surgery for thoracic OLF-induced myelopathy in a multiinstitutional retrospective survey[16]. That study classified any ossified anterior longitudinal ligament (OALL) that was adjacent to or at the same vertebral level as a patient's OLF using sagittal CT images and identified patients with OALL discontinuous type which exists either immediately rostral or caudal to the OLF but not at the OLF intervertebral level. Discontinuous had more preoperative severe symptoms and poorer surgical outcomes. Therefore, we conducted a study on an expanded number of patients, including those with multilevel or single level T-OLF who had undergone surgery, and analyzed their pre- and postoperative symptoms, radiological findings and intraoperative findings. The aim of this multicenter study is to determine factors related to the surgical outcomes including any types of OALL that may have been present in the OLF patients by the multivariate logistic regression analysis. This study had the largest sample size which described the surgical outcomes of thoracic OLF.

Methods

Patient population

Between 2000 and 2008, 19364 patients who underwent spinal surgery were registered in the database of the research group, a study group for spinal diseases. We excluded patients who underwent surgery for cervical and thoracic ossified posterior longitudinal ligament (OPLL) or cervical spondylosis myelopathy (CSM) before their OLF surgery or during follow-up. We identified 107 patients who underwent surgery for thoracic OLF-induced myelopathy and who were then observed for a minimum of 2 years postoperatively. Preoperative symptoms, severity of symptoms and myelopathy, disease duration, MR imaging and CT findings, surgical procedure, intraoperative findings,

complications, and postoperative recovery were investigated in these patients. Ninety-six patients were ultimately included in the study because 11 patients were excluded from analysis due to a lack of detailed follow-up data. There were 77 men and 19 women with a mean age at surgery of 63.4 ± 10.3 years (range 36-83 years). The mean disease duration from onset to surgery was 16.6 ± 22.1 months (range 0.5-120 months) (Table 1). We evaluated the severity of a patient's myelopathy before and after surgery using the Japanese Orthopaedic Association (JOA) scoring system for thoracic myelopathy (total of 11 points), which was derived from the JOA scoring system for cervical myelopathy by eliminating the motor and sensory scores for the upper extremities [16,17]. We evaluated postoperative improvement of symptoms using the recovery ratio of the JOA score and the Hirabayashi method ([postoperative JOA score – preoperative JOA score] / [17 – preoperative JOA score] × 100%), with a recovery ratio of 100% indicating the best postoperative improvement. This study was approved by the ethics committee of each institution, and all patients were informed that the data from their cases would be used for the study.

Axial CT classification of OLF

We used Sato's classification which evaluates CT images [18], and found the following 4 types of OLF in our subjects: lateral, extended and enlarged, fused, and tuberous (Fig. 1).

Sagittal CT image classification of OALL relative to the OLF

We classified any OALL that was adjacent to or at the same vertebral level as a patient's the most severe OLF level using sagittal CT images[16]. We found 4 types according to where the OALL was located relative to the most severe OLF level (Fig. 2). No discernible OALL immediately rostral or caudal to the most severe OLF level (Type N); One sided (Type O), in which the OALL exists either immediately rostral or caudal to the most severe OLF level but not at the most severe OLF intervertebral level; Discontinuous (Type D), in which the OALL is present both rostrally and caudally to the most severe OLF level but not at the same level as the most severe OLF level; and Continuous (Type C), in which the OALL extends from the rostral to the caudal levels, including the most severe OLF level. Two board-certified orthopedic spine surgeons reviewed all images twice. These orthopedic surgeons had worked mainly as spine surgeries and had interpreted spine CT and MR images as their daily clinical and research practice. The two reviewers identified and characterized the abnormalities by

consensus. Neither orthopedic spine surgeon had received information pertaining to age, sex, clinical history, symptoms and/or surgical outcomes at the time of the interpretation. They identified each thoracic OLF in the 96 patients and assessed its axial and sagittal CT classification.

Statistical analysis

Data were analyzed using the SPSS version 19 software package. The mean values are presented as mean ± SD. Statistical analysis was performed by Tukey multiple comparison tests and one-way ANOVA. The multivariate logistic regression analysis were used to compute odds ratios (OR) and a 95% confidence interval (CI) to identify the risk factors associated with surgical outcomes. A recovery rate of JOA scale scores 50% or higher was considered to be a good outcome as reported previously[19]. A p value < 0.05 was considered statistically significant. Intra- and inter observer reliability on axial CT classification of OLF and sagittal CT image classification of OALL relative to the OLF was assessed using weighted kappa statistics[20].

Results

Radiographic findings

MRI and CT were performed to all patients. There were only 3 patients (3.1%) decompressed at middle thoracic spine (T5-9), and the majority of the affected levels (84 patients (87.5%)) in the lower thoracic region (T9-12). The numbers of decompressed level were single level in 63 patients (65.6%), 2 levels in 26 (27.1%), and > 2 levels in 7 (7.3%). Intramedullary signal intensity change on MR images was observed in 81 patients (84.4%). Morphologically classifications, as determined by axial CT images, were lateral in 14 patients (14.6%), extended and enlarged in 31 (32.3%), fused in 41 (42.7%), and tuberous in 10 (10.4%). We classified the morphology of the OALLs as seen in sagittal CT images as Type N in 38 patients (39.6%), Type O in 32

(33.3%), Type D in 15 (15.6%), and Type C in 11 (11.5%) (Table 2). The intraobserver and interobserver reliabilities were 0.939 (observer 1), 0.924 (observer 2), and 0.939 (interobserver) for axial CT classification of OLF; 0.970, 0.985, and 0.964 for sagittal CT image classification.

Surgical methods and outcomes

The mean JOA score was 5.6 points preoperatively, and 7.8 points at 2 years postoperatively, yielding a mean recovery rate of 44.6%. Thus, a statistically significant improvement in the JOA score was obtained at 2 years follow-up examination ($p<0.01$, paired t-test) (Table 1). Laminectomy was performed in 32 patients (33.3%), laminoplasty in 55 (57.3%), and posterior decompression and fusion with instrumentation in 9 (9.4%). OLF patients in whom bilateral ossification of the ligamentum flavum was not fused in the middle of the spinal canal were basically treated with laminoplasty whereby a high-speed drill and punch were used to cut the laminae bilaterally located over the level of the OLF. The laminar flap was lifted up with a clamp and the interspinous and supraspinous ligaments in the rostral and caudal portions of the laminar flap were cut with a knife and punch. After removing the OLF, the laminar flap was repositioned over the original site with suture. Laminectomies were performed at a single level above and below the area of the OLF. The extent of facet joint resection was under half of joint for both procedures. Surgeries with instrumentation had facet resection of over half a joint. Evaluation of the surgical procedures performed with the various morphologic OLF types were showed that the lateral type was most frequently treated with laminoplasty, the extended and enlarged type and the fused type with laminectomy and laminoplasty, and the tuberous type with fusion. There was no tendency for a particular type of surgery to be performed relative to the type of OALL (Table 2). Intraoperatively, we found adhesions to the dura mater (ossification of the dura mater) in 43 patients (44.8%). Of these 43 patients with ossified dura mater, 7 (16.3%) experienced a dural tear during surgery, which was repaired with 5-0 silk suture, fibrin glue sprayed directly onto the dura mater and a gelatin sponge placed over the repaired site. Fortunately, there were no neurological complications associated with the dural tears.

Relationship of recovery rate to various factors

There were no statistically significant differences between the recovery rate and sex,

diabetes mellitus, OLF level, OLF number CT axial classification, and surgical methods. The factors which had statistically significant were age, disease duration, CT sagittal classification, signal intensity on T2WI, and ossification of dura mater. Especially, the recovery rate of type D in CT sagittal classification was significantly lower than that in three other groups (Table 3).

Factors related to the surgical outcomes

The recovery rate was 50% or higher in 47 patients (50.0%). Preoperative factors related to the surgical outcomes (recovery rate of 50%) were assessed, including age, disease duration, CT axial classification, CT sagittal classification, signal intensity on T2WI, and ossification of dura mater which had statistically significant relationship of recovery rate. The cut-off value of 50% was used, because the recovery rate of 50% or higher has been considered to be good to excellent surgical outcomes in the previous literature[21]. As a result, disease duration [odds ratio; 1 for < 6 months vs. 2.53 (95% confidence interval; 4.84-13.2, P = 0.001) for 6 to 12 months and 3.02 (3.99-22.9, P = 0.001) for 12 months or higher], Type D in CT sagittal classification [odds ratio; 1 for Type N vs. 0.068 (0.005-0.852, P = 0.037) for Type D], and presence of ossification of dura mater [odds ratio; 1 for presence of ossification of dura mater vs. 0.104 (0.018-0.602, P = 0.011) for absence of ossification of dura mater] were significantly associated with the surgical outcomes (Table 4).

Discussion

Ossification of the ligamentum flavum has been recognized as a cause of myeloradiculopathy since Polgar et al[22]. first reported in 1920. It is possible to diagnose thoracic OLF by MRI and CT [1,15]. The incidence of thoracic OLF has been reported at 3.8% to 25% including asymptomatic cases [1,2]. However, these are limited reports without sufficient numbers of patients that is, at least 20 or more [1,5,6,8-15]. Reported cases of thoracic OLF occurred most commonly in the lower thoracic spine, followed by upper thoracic spine [1,2,10,23]. Similar to previous studies, we had 9 patients with upper level, 3 patients with middle level, and 84 patients with lower level lesions, The reasons for the high frequency of OLF at lower thoracic levels include increased mechanical stress where the thoracic vertebrae form the junction between the rigid rib cage and the elastic lumbar spine [24], a direct correlation between increased mobility of the spine and

repetitive mild trauma [25], and high tensile force present in the posterior column [26]. Although duration of symptoms, age, and signal intensity change of the spinal cord have been studied as important factors at cervical myelopathy[27], there have been only a few reports on predictive factors for poor surgical outcome in OLF surgery, including older age, midthoracic OLF, more than two segments of OLF, coexisting OPLL or other spinal disorders, a lower preoperative JOA score, intramedullary high signal intensity on MR imaging [10], and a longer duration of symptoms before surgical intervention [8]. There have been the only one report about the OALL around OLF segments[16]. In the present study, duration of symptoms, ossification of dura mater, and discontinuous type of OALL on sagittal CT images were significantly important factors. A long duration of symptoms may make the injured spinal cord due to compression irreversible same as the reports in cervical myelopathy. There have been reported tuberous type of OLF frequently adhere to the dura mater. Tuberous type tended to have poor outcome in this study. Moreover, the ossification of dura mater may have relationship with multiple factors, duration of symptoms, difficulty in surgical technique, and postoperative instability because laminectomy is usually chosen to treat this type of OLF[8].

Resnick et al [28] has used the term OALL interchangeably with diffuse idiopathic skeletal hypertrophy (DISH), which is characterized by flowing calcification/ossification of ligaments, particularly along the anterolateral aspect of the axial skeleton across contiguous vertebral bodies with preservation of intervertebral disc height. Although the rate of progression of OALL may be related to increased cervical motion [29,30], there is still a high incidence in the thoracic spine which is a relatively immobile segment [31]. We found a correlation between OALL present around vertebral levels affected by OLF in the past study[16]. This report suggested the correlation due to the mechanical stress arising from the OALL as well as the OLF[16]. In the current study, CT sagittal classification, Type D was significantly important factor as poorer outcomes after their OLF surgeries, although multivariate analysis including multilevel OLF was done because the subject was the only single level OLF to be easy to classify. This increased symptom severity and the poorer outcome may be due to the focusing of mechanical stress when the OALL is present both rostrally and caudally to the OLF (Type D), and the addition of micro-motion on the vulnerable spinal cord, even within the relatively stiff thoracic spine segments. In contrast, patients with Type C had a good postoperative recovery, possibly because the continuous segment of the OALL still present after decompression may have prevented additional micro-motion on the spinal cord. There was no significant difference in the surgical outcomes among the 3 methods

in the present study. Unlike thoracic OPLL, it is possible to decompress the spinal cord directly by the removal of OLF from the posterior side. Therefore, it has been thought to be able to require good outcomes without using instrumentation unless the facet have been preserved during decompression. However, we speculate that it may be possible for patients with OALL type D to get better outcomes using instrumentation which can make the environment to recover the vulnerable spinal cord. Unfortunately, there was only one patient with OALL type D who underwent the posterior fusion in the present study. Further prospective studies on a greater number of patients are needed for a better determination of the effects of surgical procedures on surgical outcomes for OLF and to compare fusion and non-fusion surgery; however, we believe that OALL occurring around the OLF level is an important factor for predicting surgical outcome if there have been some myelopathic symptoms as OALL and OLF can be asymptomatic.

Conclusions

Ninety-six patients with thoracic OLF were evaluated in a multicenter study. Symptoms of thoracic OLF improved with surgery, but patients with longer duration of symptoms, the ossification of dura mater, and Type D OALL had poorer surgical outcomes. A prospective study on the predictive factors for poor surgical outcome in thoracic OLF surgery will be necessary in the future.

TABLE 1: Summary of demographic data in 96 patients with T-OLF

TABLE 2: Type of ossification and surgical methods

TABLE 3: Relationship of recovery rate to various patient factors

TABLE 4: Factors related to surgical outcomes by the multivariate logistic regression analysis

Fig. 1: The CT axial classification of OLF, with scans obtained at the middle of the facet joint. A: Lateral type. The ossified ligamentum flavum is located only in the capsular portion of ligamentum flavum, which can be detected at the lateral edge of the spinal canal. B: Entended and Enlarged type. The ossified ligamentum flavum is located at the surface of the ligamentum flavum and protrudes into the spinal canal. C: Fused type. Bilateral ossified ligament flavum fuse at the middle of the ossified ligamentum flavum. D: Tuberous type. Fused ossified ligament flavum make a tuberous mass at the middle of the spinal canal.

Fig. 2: The CT sagittal classification of OALL at the OLF level. No discernible OALL immediately rostral or caudal to the most severe OLF level (Type N); One sided (Type O), in which the OALL exists either immediately rostral or caudal to the most severe OLF level but not at the most severe OLF intervertebral level; Discontinuous (Type D), in which the OALL is present both rostrally and caudally to the most severe OLF level but not at the same level as the most severe OLF level; and Continuous (Type C), in which the OALL extends from the rostral to the caudal levels, including the most severe OLF level.

1. Guo JJ, Luk KD, Karppinen J, et al. Prevalence, distribution, and morphology of ossification of the ligamentum flavum: a population study of one thousand seven hundred thirty-six magnetic resonance imaging scans. *Spine (Phila Pa 1976)* 2010;35:51-6.

2. Kudo S, Ono M, Russell WJ. Ossification of thoracic ligamenta flava. *AJR Am J Roentgenol* 1983;141:117-21.

3. Williams DM, Gabrielsen TO, Latack JT, et al. Ossification in the cephalic attachment of the ligamentum flavum. An anatomical and CT study. *Radiology* 1984;150:423-6.

4. Ohtsuka K, Terayama K, Yanagihara M, et al. A radiological population study on the ossification of the posterior longitudinal ligament in the spine. *Arch Orthop Trauma Surg* 1987;106:89-93.

5. Yayama T, Uchida K, Kobayashi S, et al. Thoracic ossification of the human ligamentum flavum: histopathological and immunohistochemical findings around the ossified lesion. *J Neurosurg Spine* 2007;7:184-93.

6. Wang W, Kong L, Zhao H, et al. Thoracic ossification of ligamentum flavum caused by skeletal fluorosis. *Eur Spine J* 2007;16:1119-28.

7. Wang W, Kong L, Zhao H, et al. Thoracic myelopathy caused by ossification of ligamentum flavum of which fluorosis as an etiology factor. *J Orthop Surg Res* 2007;2:6.

8. Aizawa T, Sato T, Sasaki H, et al. Thoracic myelopathy caused by ossification of the ligamentum flavum: clinical features and surgical results in the Japanese population. *J Neurosurg Spine* 2006;5:514-9.

9. Li F, Chen Q, Xu K. Surgical treatment of 40 patients with thoracic ossification of the ligamentum flavum. *J Neurosurg Spine* 2006;4:191-7.

10. Inamasu J, Guiot BH. A review of factors predictive of surgical outcome for ossification of the ligamentum flavum of the thoracic spine. *J Neurosurg Spine* 2006;5:133-9.

11. Liao CC, Chen TY, Jung SM, et al. Surgical experience with symptomatic thoracic ossification of the ligamentum flavum. *J Neurosurg Spine* 2005;2:34-9.

12. He S, Hussain N, Li S, et al. Clinical and prognostic analysis of ossified ligamentum flavum in a Chinese population. *J Neurosurg Spine* 2005;3:348-54.

13. Miyakoshi N, Shimada Y, Suzuki T, et al. Factors related to long-term outcome after decompressive surgery for ossification of the ligamentum flavum of the thoracic spine. *J Neurosurg* 2003;99:251-6.

14. Shiokawa K, Hanakita J, Suwa H, et al. Clinical analysis and prognostic study of ossified ligamentum flavum of the thoracic spine. *J Neurosurg* 2001;94:221-6.

15. Nishiura I, Isozumi T, Nishihara K, et al. Surgical approach to ossification of the thoracic yellow ligament. *Surg Neurol* 1999;51:368-72.

16. Ando K, Imagama S, Wakao N, et al. Examination of the influence of ossification of the anterior longitudinal ligament on symptom progression and surgical outcome of ossification of the thoracic ligamentum flavum: a multicenter study. *J Neurosurg Spine*

2012;16:147-53.

17. Association JO. Scoring system for cervical myelopathy. *J Jpn Orthop Assoc* 1994;68:490–503.

18. Sato T, Kokubun S, Tanaka Y, et al. Thoracic myelopathy in the Japanese: epidemiological and clinical observations on the cases in Miyagi Prefecture. *Tohoku J Exp Med* 1998;184:1-11.

19. Matsumoto M, Chiba K, Toyama Y, et al. Surgical results and related factors for ossification of posterior longitudinal ligament of the thoracic spine: a multi-institutional retrospective study. *Spine (Phila Pa 1976)* 2008;33:1034-41.

20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74.

21. Ogawa Y, Toyama Y, Chiba K, et al. Long-term results of expansive open-door laminoplasty for ossification of the posterior longitudinal ligament of the cervical spine. *J Neurosurg Spine* 2004;1:168-74.

22. F P.： Über interarkuelle Wirbelverkalkung. . *Fortschr Geb*

Rontgenstr Nuklearmed Erganzungsband 1920;40:292–8.

23. Park BC, Min WK, Oh CW, et al. Surgical outcome of thoracic myelopathy secondary to ossification of ligamentum flavum. *Joint Bone Spine* 2007;74:600-5.

24. Okada K, Oka S, Tohge K, et al. Thoracic myelopathy caused by ossification of the ligamentum flavum. Clinicopathologic study and surgical treatment. *Spine (Phila Pa 1976)* 1991;16:280-7.

25. Maigne JY, Ayral X, Guerin-Surville H. Frequency and size of ossifications in the caudal attachments of the ligamentum flavum of the thoracic spine. Role of rotatory strains in their development. An anatomic study of 121 spines. *Surg Radiol Anat* 1992;14:119-24.

26. Smith DE, Godersky JC. Thoracic spondylosis: an unusual cause of myelopathy. *Neurosurgery* 1987;20:589-93.

27. Yagi M, Ninomiya K, Kihara M, et al. Long-term surgical outcome and risk factors

in patients with cervical myelopathy and a change in signal intensity of intramedullary spinal cord on Magnetic Resonance imaging. *J Neurosurg Spine* 2010;12:59-65.

28. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. *Radiology* 1975;115:513-24.

29. Suzuki K, Ishida Y, Ohmori K. Long term follow-up of diffuse idiopathic skeletal hyperostosis in the cervical spine. Analysis of progression of ossification. *Neuroradiology* 1991;33:427-31.

30. Oga M, Mashima T, Iwakuma T, et al. Dysphagia complications in ankylosing spinal hyperostosis and ossification of the posterior longitudinal ligament. Roentgenographic findings of the developmental process of cervical osteophytes causing dysphagia. *Spine (Phila Pa 1976)* 1993;18:391-4.

31. McCafferty RR, Harrison MJ, Tamas LB, et al. Ossification of the anterior longitudinal ligament and Forestier's disease: an analysis of seven cases. *J Neurosurg* 1995;83:13-7.