Clinical Factors that Predict the Surgical Outcome of Ossification of Ligamentum Flavum of Spine – Series of 31 Cases

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ABSTRACT

Introduction: Ossification of the Ligamentum Flavum (OLF) is a pathological ailment that affects the ligament and causes slowly progressive myeloradiculopathy in adults. Current studies have aimed to elucidate the pathogenic and pathological factors associated with OLF.

Material and Methods: A prospective study of 31 patients with OLF was conducted. The study included a review of literature on OLF, along with pathological and clinical factors.

Results: The study revealed that OLF can be diagnosed through lateral radiographs, and the associated factors were identified. OLF was diagnosed in 20 patients, and the remaining cases were confirmed through pathological analysis.

Conclusion: The study concludes that the factors associated with OLF can be classified as clinical, radiological, and pathological. The diagnosis of OLF is crucial for identifying the associated factors and planning surgical interventions.

Keywords: Ossification of Ligamentum Flavum, Modified JOA Score, CPPD Crystals, Sato’s Classification, Pseudo Gout, Prognostic Factors

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was thought a relevant factor in patients with herniated thoracic discs, the surgical outcomes were weaker than those in patients without OLF. However, outside Japan, unlike OPLL in the cervical spine, thoracic myelopathy secondary to OLF is seldom neglected or misdiagnosed as degenerative overgrowth by the posterior spinal portion consisting of the superior articular processes. This error occurs from a lack of knowledge about this pathological condition. OLF has been seen as a composite lesion because of the sequence of ossification of the spinal ligaments with hyperostotic changes. Small degrees of OLF may be considered a degenerative transformation, as its incidence in radiographic studies of the spinal columns of aged persons has ranged from 4.5% to 25.0%. It has been suggested that the mechanism of hypertrophy, overgrowth, and progression of ossification of the ligaments plays a vital role in the pathological process of myelopathy. Study aimed to identify clinical factors that is predictive of the surgical outcome of patients with OLF.

**MATERIAL AND METHODS**

This was a prospective study, which was done on patients suffering from Ossified Ligamentum Flavum of Spine. This study was conducted over the period from February 2013 to February 2016. Due clearance was obtained from the ethical committee of Government Rajaji Hospital and Madurai Medical College, Madurai before this study. Exclusion criteria: Patients with significant anterior compressive lesions causing thecal sac indentation and also those patients with spondylotic compressive myelo-radiculopathy. Thirty-one patients consecutively diagnosed with Ossified Ligamentum Flavum of Spine with Myelopathy. They were diagnosed on the basis of clinical Examination, Radiological Imaging and Histopathological Confirmation. All the surgeries were done at the same Operation theatre in Government Rajaji Hospital, Madurai

Following data were collected; Age, Gender, Level of the Spine involved, Coexisting other spinal disorders, Duration of symptoms, Preoperative modified JOA neurological score.

**RESULTS**

During the period from Feb 2013 to Feb 2016, following 31 patients who underwent surgical management, were analyzed for these following six clinical factors and their significance in predicting the outcome of surgery. Mean age of these patients were 50.1 years with range of 19 to 70 years, and standard deviation of 12.2 years. 48% of these patients were above 50 years of age as shown in figure 4.

Among these 31 patients, 24 were male patients comprising 77.4% of cases and 7 were female patients comprising 22.6% of cases.

Patients were grouped according to the level of spine involvement. Cervical spines were involved in 10 cases (32%) and dorsal spines were involved in 21 cases (68%). None of the case involves lumbar spine as shown in figure 5. Co-existing other spinal disorders like Ossified posterior longitudinal ligament, facetal hypertrophy, disc prolapsed were analyzed whether it predicts the surgical outcome in these cases. It was positive in 72% of cases and negative in 28% of cases as shown in figure 6.
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The most common initial symptom was a tingling sensation, numbness, or pain in the lower extremities, which was present in 49% of the patients. Twenty-five percent of patients complained of gait disturbance due to lower-limb weakness or spasticity, and 11% complained of back pain. The mean preoperative duration of symptoms was 3.5 months, with the range of 1 to 8 months and standard deviation of 1.8 months. Out of Total 31 cases; up to 4 months are 16 cases (51.6%), 4 to 6 months are 14 cases (45.2%), more than 6 months is 1 case (3.2%).

Using “modified Japanese Orthopedic Association” scoring system which has the maximum score of 18, each patient's pre and post-operative neurological deficit was measured. Range was 4-17, mean 13 with standard deviation 2.89. They are group into 4 as in figure 4.

Recovery rate from symptoms was calculated using the following formula;

\[
\text{Recovery Rate} (%) = \frac{\text{Post operative mJOA Score} - \text{Pre operative mJOA score}}{11 - \text{Pre operative mJOA score}}
\]

Based on the results the patients were grouped into 4 types of Recovery. They are Excellent (>75%), Good (50% - 75%), Fair (25% - 50%) and Poor (<25%) as shown in figure 8.

All the patients were followed up post operatively at OPD. Out of 31 patients, 14 cases (14%) for less than 3 months, 15 cases (48%) for 4 to 6 months, 1 case (3%) for 7 to 12 months and 1 case (3%) for more than a year done. Only short term follow up were possible for most cases. We need to continue the follow up for longer term for more accurate prediction of surgical outcome for OLF of Spine.

**Relationship between Recovery and Clinical Factors**

All the above six clinical factors analyzed were statistically evaluated and determined whether it has significant influence in predicting the surgical outcome of OLF of Spine. The results were as follows:

1. Recovery and Age of the patients; p value - 0.5509; Not Significant
2. Recovery and Gender of the patients; p value - 0.4606; Not Significant
3. Recovery and Level of the Spines involved; p value - 0.5696; Not Significant
4. Recovery and Coexisting spinal disorders; p value - 0.4676; Not significant
5. Recovery and Duration of symptoms; p value - 0.0062; Significant as shown in figure 9.
6. Recovery and Preoperative modified JOA neurological score; p value - 0.0011; Significant as shown in figure 10 Above statistical analysis results shows that among the six Clinical Factors, that likely to predict the Outcome for surgery for OLF spine are duration of preoperative symptoms and pre-operative neurological score.

DISCUSSION

Development of OLF
In most OLF cases, the initial changes in the Ligamentum Flavum occur at the site of attachment of the cephalic portions (figure 1), and ossification extends from the lateral aspect to the center along the superficial layer of the hypertrophied Ligamentum Flavum and then above to the anterior parts of cephalic portions. Ossification of the cephalic portions progresses to the cephalic portions, and hyperostosis of the pedicle occurs, resulting in nodular formations. However, the cephalic and caudal parts of OLF never unite completely in the intervening space, even in specimens with thickened nodular OLF in the fibrocartilaginous matrix.

Histopathology of the Ligamentum Flavum
Anatomically, the ligamentum flavum exists in the interlaminar space and supporting tissue, forming part of the posterior wall of the spinal canal. The Ligamentum Flavum has two portions at each intervertebral disc level: the central (inter-laminar) and lateral (capsular) portions. The average composition of the fibers is 80% elastin and 20% collagen, as described by Yong-Hing et al. This composition changes with age, however, and it has been reported that collagen increases in relation to decreasing elastin (Figure 2). The bony attachment of the Ligamentum Flavum is a four-layered structure, the enthesis, as described by Niepel and Sitaj. The four layers are the ossification layer, calcified cartilage, non-mineralized cartilage, and ligament. The enthesis also occupies a key position in the pathological process of the diseases or so-called enthesopathy. It is well known that the enthesis has a rich vascular supply, highly active metabolism, an ample and specialized nerve supply, and a few scattered fibrocartilage cells with reserved activity, among other structures. With aging, small osteophytes develop in the Ligamentum Flavum at the ligamento-osseous junction (enthesis), which shows marked intraligamentous calcification, swelling, and hyalinization of the collagen fibers, the appearance of fibrocartilaginous cells, and a reduction in the elastic fibers (Figure 2). It is thought that this small OLF is a degenerative enthesopathy that developed from the enthesis.

Differentiation between Degenerative Osteophytes and OLF
To understand the cause of the overgrowth of cartilaginous tissue that precedes the development of OLF, we investigated the changes in the enthesis of the Ligamentum Flavum immunohistochemically using type-specific human monoclonal anti-collagen antibodies I-VI. Collagen types I, III, and VI were found in the unossified ligaments. Type II collagen was demonstrated only in the ossified cartilage and non-mineralized cartilage layers of the enthesis (Figure 2). There was no significant difference in the width of the ossified cartilage layer, but the difference in the width of the non-mineralized layer between the OLF group and the controls was substantial. Active production of type II collagen by the chondrocytes was revealed in the hyperplastic extracellular matrix. Therefore, it was thought that proliferation of type II collagen at the enthesis resulted in the formation of a hypertrophied ligament before it developed into OLF.

Pathology of Ossification of the Ligamentum Flavum
The OLF extended along the superficial layer of the hypertrophied ligament, as in OPLL. However, numerous fibro-cartilaginous cells with abundant matrices including type II collagen were seen more abundantly in OLF than in OPLL. At the transitional areas adjacent to the ossified areas, there were various morphological phenomena: irregular arrangement of the fibrous structures; abundant collagen fibers; irregular, ruptured, and fewer elastic fibers; numerous cartilage cells; calcified tissues; premature ostens; and proliferating vessels. These characteristic histological findings suggest that numerous Fibro cartilaginous cells existed in the abundant collagen fibers and produced a large amount of type II collagen. Thus, the developmental mode of OLF was confirmed to be mainly endochondral ossification. The accompanying hypertrophic cartilaginous proliferation, however, showed additional intramembranous ossification at the margin of the thickened OLF.

Factors Related to the Development of Ossification
Role of Mechanical Stress
When considering the mechanism of ossification development, the theory states that both dynamic and static mechanical stresses act as local factors in the development of OLF under a general ossifying diathesis. Yamazaki et al. described disc degeneration and vertebral wedging acting as local factors that increase the tension of the Ligamentum Flavum. They, therefore, indicated that localized mechanical stress that affected the Ligamentum Flavum was a contributing factor to ossification development. Anatomically, the Ligamentum Flavum in the thoracic region is subjected to static stress continuously, and it is greater in flexion than in extension. Therefore, it is thought that the development of OLF depends on mechanical stress. However, the formation of the ossified tissue at the enthesis (enthesisopathy) is self-limited, and massive ossification is uncommon. OLF is therefore due to something more than enthesisopathy.

Role of Growth Factors
Growth factors are believed to be important in the pathogenesis of the ossification of both the posterior longitudinal ligament and the Ligamentum Flavum. Bone morphogenetic proteins (BMPs) and transforming growth factor-β (TGF-β) may have important roles in the pathogenesis of OPLL and OLF. BMPs initiate cartilage and bone differentiation and induce new cartilage and bone formation in vivo, whereas TGF-β stimulates cartilage and bone formation via determined chondroprogenitor and
osteoprogenitor cells in vivo. On the other hand, Ono et al. examined the appearance and localization of TGFβ1, fibronectin, and bone alkaline phosphatase in OLF lesions from four patients. Based on these results, it is believed that TGFβ1 and fibronectin may contribute to the hypertrophy and ossification of the ligamentum flavum. Recently, a key molecule called cartilage-derived morphogenetic protein (CDMP)-1 and has been identified as a member of the TGFβ super family. Nakase et al. reported that CDMP-1 was immunolocalized in spindle-shaped cells distant from the ossification front.

**CONCLUSION**

Clinical factors that are likely to predict short-term outcome include the duration of symptoms and preoperative neurological status. Thus early and correct diagnosis is required to avoid poorer results. Long-term follow up needed to determine the factors that predict the surgical outcome.

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