Ossification of the ligamentum flavum

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Abstract:

Ossification of the ligamentum flavum (OLF or OYL: ossification of the yellow ligament) usually occurs at the lower thoracic level and causes various types of neurological symptoms in accordance with the compression level of the spinal cord, the nerve roots, the conus medullaris, and the cauda equina. Although the greatest compression level to the nerve tissues is thought to be the most pathognomonic one, it is difficult to diagnose it in some cases. The effectiveness of conservative treatment such as applying a corset is small. Early surgical treatment is strongly recommended for the patients with spastic gait, severe decrease of muscle power in the lower extremities, bladder-bowel disturbance, combined ossification of the posterior longitudinal ligament at the same level, and severe compression to the spinal cord due to thickly hypertrophied ossification. However, numbness of the lower extremities and spastic gait tend to remain even after surgery. **Keywords:**

ossification of the ligamentum flavum (OLF), thoracic spine, neurological findings, surgical treatment

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This review article is based on the contents of the author's previous paper concerning ossification of the ligamentum flavum (OLF) that appeared in Japanese as a chapter in a book named *Evidence-Based Guidance in the Treatment of Cerebrovascular and Neurological Disease*, 4th Edition, edited by Tamura A et al., Medical View Co., Ltd, 2016¹⁾. Some information is added here, especially concerning genetic studies, recent etiological studies, and surgical results. This article is being permitted to be published as an updated second version by the editors on both sides.

Concept

The ligamentum flavum locates within the spinal canal posterolaterally connecting two adjacent laminae and is divided into two portions: capsular portion and interlaminar portion²). It is composed of 80% elastic fiber and 20% collagen fiber³). OLF is a neurological disease in which the ligamentum flavum is chronically ossified and compresses the spinal cord, the nerve roots, the conus medullaris, and cauda equine to various degrees and extents. It can be said that it is a presentation of degenerative changes of the whole spinal column due to aging, and at the same time, it is one of the presentations of systematic ossification trait of the vertebral ligaments. It usually occurs at the lower thoracic level com-

bined with ossification of the posterior longitudinal ligament (OPLL) at the cervical and/or thoracic levels.

Cause

Although the cause of the ossification of the vertebral ligaments is yet unclear, two factors are conjectured: systematic factors and local factors. The former includes heredity, abnormal metabolism of carbohydrate, abnormal metabolism of calcium, abnormal secretion of gender hormone, and degeneration of the ligament, and so on. The latter includes mechanical stress to the enthesis where the ligament attaches to the bone, especially at the capsular portion.

The chondrocytes are activated by mechanical stress and produce high volume of type-II collagen, and that type-II collagen is then transformed into type-I collagen in the course of endochondral ossification, resulting in formation of bone within the vertebral ligament⁴). Concerning OPLL, it is reported that collagen 11A2 gene and collagen 6A1 gene are related to its formation⁵). It is also reported that in OPLL, growth factors and transcription factors such as cartilage-derived morphogenetic protein-1, promyelocytic leukemia zinc finger, and tumor necrosis factor-alpha-stimulated gene 6 are related to the course of the transformation of the undifferentiated mesenchymal cell to the os-

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teoblastic cell^{6,7)}. Among Chinese populations, Runt-related transcription factor 2s can be responsible for ectopic bone formation in spinal ligaments such as OLF and OPLL⁸⁾.

At the lower thoracic level with kyphotic spinal alignment, strong traction force tends to act on the ligamentum flavum due to rotational flexion movement of the thoracolumbar spine because it locates far from the center of movement. The traction force is thought to influence the ossification mechanism^{9,10}. In contrast, within the ligamentum flavum at the cervical and lumbar spines with lordotic spinal alignment, not ossification but calcification without trabecular structure tends to be formed. At these levels, it is not thought that traction force acts strongly. This is the important difference concerning calcium metabolism in relation to the vertebral level, sagittal alignment of the spine, and probably the strength of traction force.

Etiology

In Japanese populations, OLF is found in about 4.5% of the outpatient X-ray films taken at clinics. Almost all of these patients are at fifty decades and older, and there are no differences between male and female in the incidence. In contrast, there are few patients of OLF in western countries, therefore, OLF and OPLL are called "Japanese disease"^{11,12}. However, whether OLF is statistically more common in Japanese people or not and whether this difference in the prevalence based on the racial difference or not is unclear because previous papers concerning OLF have mainly been written by Japanese researchers, and it is possible that the difference in the prevalence between Japan and western countries is based on the difference in the recognition by researchers on OLF¹³.

Wada et al.¹⁴⁾ reported that 48.7% of 254 patients with cervical OPLL were combined with thoracic OLF. Kawaguchi et al.¹⁵⁾ analyzed the whole spine of 178 patients using multidetector computed tomography (CT) and reported that 64.6 % of the patients with cervical OPLL had OLF, mainly in the thoracic spine. Sato et al.¹⁶⁾ analyzed 265 patients who underwent surgery for thoracic myelopathy and reported that (1) the degenerative changes of vertebral column causing thoracic myelopathy were OLF in 52%, OPLL in 12%, disc herniation in 11%, and OLF combined with OPLL in 9% and (2) sixty-five percent of OLF was located at the tenth thoracic (T10)/T11 or T11/T12.

Fujimori et al. investigated the prevalence, concomitance, and distribution of ossification of the spinal ligaments of 1,500 Japanese people using CT. They revealed that the average prevalence of thoracic OLF was 12% (15% in men and 7.7% in women), the most common level was T11, and 34% of cervical OPLL also had thoracic OLF¹⁷. Mori et al.¹⁸ also investigated 3,013 patients using CT and reported that the prevalence of thoracic OLF in Japanese was 36%, and the distribution formed two peaks with the highest peak at T10/T11 and the second highest peak at T4/T5.

Moon et al.¹⁹⁾ reported that the prevalence rate of thoracic

OLF was 16.9%, and T10/11 segment was most affected level in 2,134 Korean people.

Symptoms

As OLF is one of the degenerative changes of the spinal column with aging, the patients with OLF often have other changes at the vertebral body, intervertebral disc, facet joint, vertebral ligaments, and paravertebral muscles. Therefore, the local symptoms include not only constriction-like discomfort due to probable irritation of intercostal nerves by OLF itself but also back pain, stiffness of back muscle, and pain on movement, probably caused by degenerative changes of spinal column structures other than OLF.

Also, the systemic symptoms such as numbness, pain, and muscle weakness in the lower extremities, gait disturbance, and bladder-bowel disturbance occur due to compression of the spinal cord and spinal nerves by OLF. As almost all OLFs are formed at the lower thoracic level where the spinal cord gradually transforms to the conus medullaris and the cauda equina, various types of symptoms occur in accordance with the affected nerve tissues at various levels, that is, spastic or flaccid paralysis at the lower extremities, supra-conus medullaris syndrome, and conus medullaris syndrome.

Diagnosis

Ordinarily, the diagnosis of the pathognomonic level is based on the neurological findings, imaging examinations using X-ray films and CT and magnetic resonance imaging (MRI). To clarify the level more precisely, spinal cord monitoring is sometimes performed as one of the functional examinations.

1. Neurological findings

At the cervical and lumbar levels, the pathognomonic level can be determined by the neurological findings consisted of the degree of power of the affected muscle, the level of sensory disturbance, and the degree of deep tendon reflex because the relationship between the spinal segmental sign and the affected level is relatively clear. However, at the thoracic level, its relationship is unclear. It can be said that among neurological findings, the change in deep tendon reflexes is the single and only index. In patients whose deep tendon reflexes of the lower extremities are dominantly higher than those at the upper extremities, thoracic myelopathy is strongly suspected, and imaging examinations must be performed from the upper to lower thoracic levels. In patients with flaccid paralysis of the lower extremities, especially with severe muscle atrophy and muscle weakness, wide imaging examinations must be performed at not only the lumbar but also the lower thoracic level because disorders at the lower thoracic level such as OLF and/or OPLL are suspected.

In supra-conus medullaris syndrome, the spinal cord seg-

ments between the fourth lumbar (L4) and the second sacral (S2) located at about the T12 vertebral level are affected. The characteristic signs are muscle atrophy and weakness below the knee and drop foot. Sensory disturbance occurs at various regions from the level below the knee to the perianal, but there is ordinarily no root pain nor bladder-bowel disturbance.

In conus medullaris syndrome, the spinal cord segments lower than S3 located at about the L1 vertebral level are affected. In genuine conus medullaris syndrome without root effect around the conus medullaris below the L2 vertebral level, there is no muscle weakness nor abnormality of deep tendon reflexes. However, characteristically, saddle-shaped sensory disturbance around the perianal and severe bladderbowel disturbance occur early due to severe lower neuron effect^{20,21}).

2. Imaging technologies

Although OLF at the middle and lower thoracic levels can be examined even in lateral X-ray films, that at the upper thoracic level is difficult to reveal because of overlap of shadow of the shoulders. In contrast, horizontal and reconstructed sagittal CT images are the most useful as OLF can clearly be examined at almost all levels. The classification of OLF had previously been made based on lateral X-ray films at the thoracic level, but at present, it is based on CT images made at the middle level of the facet joint. Sato et al. divided the configuration of OLF into five types. Among them, in the lateral, extended, and enlarged types, bilateral ossifications are not fused at the center of the lamina, whereas in the fused and tuberous types, bilateral ossifications are fused at the center. In the fused and tuberous types, ossification spreads to multiple levels and combines with ossification of the dura mater in about 60% of cases²²⁾.

The most important matter to be discussed before surgery is which OLF is pathognomonic, especially in patients with OLF at multiple levels. Ordinarily, the level where OLF is most prominent and the spinal cord and nerves are most severely compressed is thought to be the most pathognomonic, and MRI is a safer and more convenient imaging modality for best imaging of soft tissues. However, in general, in diseases compressing the spinal cord, there are not always correlations between the degree of compression and the severity of neurological findings. Even in cases with severe compression of the spinal cord, some patients have little or no neurological findings at all²³⁾. This is an important point to be recognized in diagnosis.

3. Electrophysiological examinations

To clarify the pathognomonic level more precisely, spinal cord monitoring is sometimes performed as one of the functional examinations. However, even now, problems concerning the reliability of spinal cord monitoring remain, that is, there is some doubt regarding the accuracy of interpretation of the changes of waves, and there is some discrepancy between electrophysiological findings and imaging findings. Satomi et al. reported that in three of the four patients, there were discrepancies between the level of most prominent OLF in images and the level of positive waves that usually indicate as pathognomonic in monitoring. In the other one patient, surgery was performed at the thoracic level of positive wave in monitoring, but no neurological effect was gained after surgery. Finally, good effect was gained for that patient only after decompression surgery at the cervical level²⁴.

Kaneko et al. reported a patient with severe thoracic myelopathy due to OPLL and OLF in whom spinal cord monitoring resulted in false negative. The amplitude on spinal cord stimulation transiently decreased to within 50% and finally recovered to the control level. However, the patient showed complete motor paralysis just after surgery²⁵⁾.

Matsuyama et al.²⁶⁾ pointed out the unsteadiness of the level of alarm point in the monitoring of compound muscle action potential because the conditions of stimulation and the number of recorded muscles are different in each institute.

Treatment

1. Conservative treatment

In general, myelopathy due to OPLL and OLF is caused by static and/or dynamic compression mechanisms. The effectiveness of treatment using orthoses for cervical myelopathy is the result of decreasing dynamic compression force caused by cervical vertebral movement. However, at the thoracic spine where the vertebral movement is smaller than that of the cervical spine due to the rigid connection with the thoracic cage, almost all of compression mechanism is thought to be not dynamic but static. Therefore, the effectiveness of outer orthoses such as corset for OLF is small.

Tanaka et al.²⁷⁾ examined the histological changes of the lamina resected en bloc and reported that in 10 of the 11 patients, the facet joints were degenerated, the joint spaces were narrowed, and the movement was decreased, and in 8 patients, the adjacent inferior and superior articular processes were completely fused, and severe paralysis tended to occur in such a patient. This report means that the degree of myelopathy due to OLF depends on not dynamic but static mechanism in which a large space-occupying lesion compresses the spinal cord.

Ordinarily, for symptoms such as back pain and numbness and pain in the lower extremities, nonsteroidal antiinflammatory drugs, muscle relaxants, and vitamin B12 are administered combined with outer compress and cream. For the symptoms of severe neuralgic pain in the lower extremities, palliative drugs are additionally administered. As back pain in patients with OLF is caused by not only constriction-like discomfort due to probable irritation of intercostal nerves by OLF itself but also stiffness of back muscle and pain on movement probably caused by degenerative changes of spinal structures such as intervertebral body and facet joints, physical therapy is recommended at an early stage. Hot therapy to improve local blood circulation and walking are effective. However, dynamic moving therapy of the vertebral column such as massage and stretch by others is contraindicated because they possibly afford more stress to the lesion at OLF.

2. Surgical treatment

Decompression surgery is recommended for patients in whom conservative treatment is ineffective and patients with severe spastic gait, severe muscle weakness of the lower extremities, and bladder-bowel disturbance. As OLF is one of the presentations of systematic ossification trait of the vertebral ligaments and it is a static compression disease in which symptoms may progress in accordance with extension of ossification, early decompression surgery is recommended without continuing aimless conservative treatment. Especially in patients in whom OLF and OPLL occur at the same thoracic level, early surgery is strongly recommended because the spinal cord is severely compressed both anteriorly and posteriorly, resulting in severe thoracic myelopathy.

The region of ossification and the affected lamina is resected via posterior approach. The surgical methods include open-door type laminectomy, en bloc laminectomy, fenestration, and hemilaminectomy^{22,27,32)}. In patients in whom the dura mater is ossified and adhered to the OLF, both the ossified dura mater and OLF are resected en bloc with preserving arachnoid.

Despite a wide resection of the posterior skeletal structures including a medial part of the facet joint, postoperative instability of the vertebral column does not tend to occur, and therefore, additional instrumentation surgery for argumentation is unnecessary.

Surgical results

Recently, surgeries have been performed more safely because of precise and voluminous preoperative intelligence gained by various imaging modalities, improvement of surgical skill of surgeons, and the introduction of intraoperative imaging modalities such as navigation systems. However, even now, the condition of adhesion between OLF and the dura mater and the existence of ossified dura mater cannot precisely be diagnosed preoperatively. Therefore, in some patients, the arachnoid is ruptured at the time of resecting OLF and cerebrospinal fluid (CSF) spouts out during surgery. The process of surgery may be interrupted by the spouting CSF and blood from adjacent extradural space, resulting in damaging the fragile spinal cord through rough procedure. Sato et al.²²⁾ reported good results of prophylactic treatment of opening of the dura mater starting from the normal caudal and cranial sides to protect the arachnoid in patients with OLF of fused and prominent types where the dura mater tends to be ossified.

Tanaka et al. reported the results of surgical treatment of 16 patients who underwent en bloc laminectomy based on

the classification of surgical results according to the motor function of Japanese Orthopaedic Association (JOA) score for myelopathy. Excellent is assessed where postoperative motor function of the lower extremities improves by two ranks or more in contrast to the preoperative one. Good is assessed when postoperative motor function improves by one rank, and fair is assessed when improvement is less than one rank. Of 16 patients, 2 patients were assessed as excellent, 7 good, 4 fair, and 3 worse. The results of OLF without OPLL were better than those combined with OPLL²⁷⁾.

Zhong et al. reported the results of 22 patients who underwent posterior decompressive laminectomy. Evaluated using a modified JOA score, 9 patients were excellent, 8 good, 4 fair, and 1 unchanged. The mean Hirabayashi recovery rate was 65.49%. However, surgical complications occurred such as dural tear in five patients and CSF leakage, immediate postoperative neurologic deterioration, epidural hematoma, and wound infection in one patient each, respectively³⁰.

Ando et al.³¹⁾ reported that the risk factors related to surgical outcomes were duration of the disease, combined ossification of the dura mater, and the presence of discontinuous type ossification of the anterior longitudinal ligament (OALL). Aizawa et al.³²⁾ reported the surgical results of 72 patients and concluded that the preoperative results statistically depended on the preoperative severity of myelopathy.

It is well known that numbness of the lower extremities and spastic gait hardly improve and these remain even after surgery. Therefore, before surgery, informed consent must be obtained from patients and their families on these points.

Important points in treatment

The general clinical courses of OLF are variable. In some cases, there are no symptoms despite large prominent OLF in imaging examination, and in other cases, the neurological findings and symptoms are progressively getting worse. As OLF is one of the presentations of systematic ossification trait of the vertebral ligaments, and it is one of the compression diseases that may progress chronically, the appearance of *de novo* neurological findings must be recognized by imaging examinations at cervical, thoracic, and lumbar spines.

Summary

1. OLF is one of the presentations of systematic ossification trait of the ligaments and sometimes combined with OPLL at the cervical and/or thoracic levels. It usually occurs at the lower thoracic level and causes various types of neurological symptoms in accordance with the compression level of the spinal cord, the nerve roots, the conus medullaris, and the cauda equina.

2. Imaging techniques such as CT and MRI are very useful to diagnose this disease. Although the most compressed level to the nerve tissues is thought to be the most pathognomonic one, it is difficult to diagnose it in some cases.

3. Among the two compression mechanisms of nerve tissues causing symptoms, that is static and dynamic, the static mechanism mainly acts in OLF and the influence of the dynamic mechanism is small because the thoracic vertebral column moves little due to the rigid connection with the thoracic cage. Therefore, the effect of conservative treatment such as stabilization using outer orthoses to decrease the dynamic mechanism is limited.

4. Early surgical treatment is strongly recommended for patients with spastic gait, severe decrease of muscle power in the lower extremities, bladder-bowel disturbance, combined OPLL at the same level, and severe compression to the spinal cord due to thickly hypertrophied ossification.

5. Because numbness of the lower extremities and spastic gait hardly improve even after surgery, informed consent must be obtained regarding these points before surgery.

Conflicts of Interest: The author declares that there are no conflicts of interest.

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