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Original article

Correlation between inflammatory cytokines released from the lumbar facet joint tissue and symptoms in degenerative lumbar spinal disorders

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Abstract

Background. Lumbar facet joint tissue has inflammatory cytokines. However, no reports have shown whether inflammatory cytokines in the facet joint leads to pain. This study was designed to characterize the correlation between inflammatory cytokines released from facet joint tissue and symptoms in degenerative lumbar spinal disorders. The purpose of this study was to seek involvement of inflammatory facet joint for radiculopathy in lumbar spinal canal stenosis with clinical and anatomical studies.

Methods. Lumbar facet joint cartilage and synovial tissues in 40 cases of posterior lumbar surgery were harvested to measure tumor necrotizing factor-α (TNFα), interleukin-1β (IL-1β), and interleukin-6 (IL-6) during operation. The visual analogue scale (VAS) and Roland-Morris disability questionnaire (RDQ) were used to examine the correlation between cytokine concentration and symptoms. Coloring agent was injected into facet joints of fresh cadavers to find leakage of pigment from the facet joint into the spinal canal.

Results. Inflammatory cytokines were detected in the joint tissues in the lumbar spinal canal stenosis (LSCS) and lumbar disc herniation (LDH) groups. A positive reaction rate of IL-1β was significantly higher in the LSCS group than in the LDH group. IL-1β-positive cases in the LSCS group showed higher VAS scores for leg pain and higher RDQ scores. Intraspinal canal tissues including lumbar nerve root were stained by injection of methylene blue into the facet joints.

Conclusions. IL-1β in facet joint cartilage in LSCS was associated with leg pain and a decline of quality of life. Inflammatory cytokines produced in degenerated facet joint may leak into the intraspinal space through the lateral part of the ventral facet joint capsule. These results suggest the involvement of inflammatory cytokines in degenerated lumbar facet joints regarding the genesis of pain production.

Introduction

Much attention has been focused on the involvement of chemical factors in radiculopathy caused by lumbar disc herniation. It is, meanwhile, reported that osteoarthritic (OA) changes in a facet joint cause pain in degenerative lumbar spinal disorders.[1–6] Moreover, some reports demonstrate that inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), and interleukin-6 (IL-6), as well as inflammatory mediators such as prostaglandins also can be found in the facet joint tissues in degenerative lumbar disorders.[7,8] On the other hand, based on clinical examination of limb joints with OA, local OA joints showed long-lasting, severe inflammatory symptoms and findings similar to those of inflammatory arthritis, such as rheumatoid arthritis (RA).[9–11] Based on these observations, OA produces symptoms similar to those of inflammatory arthritis including RA, resulting in possible involvement of inflammation in the joint cartilage and synovial tissue during joint destruction and pain.[9,12–14] According to these findings, a facet joint with the same anatomy as the limb joints might exhibit painful symptoms due not only to mechanical factors such as arthropathic changes but also to chemical factors due to arthritis. Nevertheless, there have been no reports suggesting that inflammation due to chemical factors, such as inflammatory cytokines, in the lumbar degenerated facet joint also cause pain in degenerative lumbar spinal disorders. The purpose of this study was to determine the involvement of the inflammatory facet joint in lumbar spinal canal stenosis, in addition to mechanical compression, using clinical and anatomical methods.

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Materials and methods

Patient information

A total of 40 patients who underwent posterior lumbar spinal surgery due to degenerative lumbar spinal disorders were enrolled in this study. Informed consent was obtained from all patients. There were 24 men and 16 women in the study group. More particularly, there were 11 cases in the lumbar disc herniation (LDH) group and 29 in the lumbar spinal canal stenosis (LSCS) group. The average age of the patients subjected to operation was 50 years (range 30–66 years) for the LDH group and 67 years (range 48–84 years) for the LSCS group, with no significant difference between the two groups. The average duration of illness for the LDH group was 13 weeks, whereas the duration for the LSCS group was a significantly longer period of 132 weeks.

We determined the number of responsible levels from clinical symptoms, physical findings, neurological findings, various imaging findings including magnetic resonance imaging (MRI), and selective nerve root blocks. The symptoms of all LDH cases were due to radiculopathy caused by a single-disc disorder; therefore, we observed no cases of cauda equina syndrome in the LDH group. The responsible level of the LSCS group amounted to 65.5% for single-disc involvement and 35.5% for multiple-disc involvement. It was found that radiculopathy accounted for 55.2% and cauda equina syndrome/mixed type (i.e., combination of radiculopathy and cauda equina syndrome) for 44.8% in the LSCS group. In cases in which the symptoms appeared in bilateral lower extremities, the side where the facet joint tissue had more severe symptoms was used. Also, in cases in which the responsible level was found at multiple intervertebral levels, the facet joint tissue was chosen where the problem seemed to be most significant according to neurological findings and selective nerve root block.

Determining the quantity of inflammatory cytokines and comparing cytokine levels and clinical symptoms

The cartilage and synovial tissues were harvested with surgical knives and punches from the facet joints at the responsible level during operation. The collected tissues were immediately cooled to –80°C and were kept at that temperature for preservation. Each tissue was homogenized by ice application to prepare a suspension. The tissues were subject to centrifugal separation with 15000 rpm for 30 min at 4°C, and its supernatant was collected to measure the properties. In each tissue, the levels of TNFα and IL-1β were measured as indexes of inflammatory cytokines by enzyme-linked immunosorbent assay (ELISA), and the IL-6 level was measured by chemiluminescent enzyme immunoassay (CLEIA) using human TNFα kit (Japan Immunoresearch Laboratories, Gunma, Japan), human IL-1β EASIA kit (BioSource Europe, Nivelles, Belgium), and human IL-6 kit (Fujirebio, Tokyo, Japan), respectively. The measuring instrument was the EMax Microplate Reader (Molecular Devices, Sunnydale, CA, USA). The detection sensitivities for TNFα, IL-1β, and IL-6 were 5 pg/ml, 10 pg/ml, and 4 pg/ml, respectively, because the serum concentrations of these cytokines in healthy adults were less than those at each detection sensitivity by the supply companies. Each value for these cytokines beyond the sensitivity was regarded as "positive," and each value within the sensitivities were regarded as "negative." The inflammatory cytokine levels for each collected tissue and the correlation with the visual analogue scale (VAS) for low back pain, leg pain, and leg numbness and the Japanese version of the Roland-Morris disability questionnaire (RDQ) were statistically examined. For statistical examination, Student's *t*-test and the Kruskal-Wallis test were used; significant difference was set at less than 5% risk.

Assessing facet joint osteoarthritis on MRI

MRI studies for all patients in both groups were performed on the same 1.5 T imaging system. Each study included T1-weighted and T2-weighted sagittal images. One experienced orthopedic surgeon reviewed all MR images and was masked to any clinical and prior imaging data. Four grades of osteoarthritis of the facet joints were defined using criteria by Weishaupt et al.[15]: grade 0, normal facet joint space (2–4 mm); grade 1, narrowing of the facet joint space (<2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process; grade 2, narrowing of the facet joint space and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions; grade 3, narrowing of the facet joint space and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts.

Two weeks later, the same person evaluated the facet joints on MRI using the same grading to assess intraobserver variability. Weighted kappa statistics were used to describe intraobserver agreement for MRI. The value of weighted kappa coefficients for intraobserver agreement for MRI here was considered to be "good" when the score was >0.8.

Anatomical study of joint fluid leakage from degenerated lumbar facet joints

A total of 24 lumbar facet joints from three fresh male cadavers — ages 63, 65, and 85 years — were used for

the macroscopic study. None of the cadavers had undergone any lumbar surgery during their lifetimes. The causes of death were colon cancer, heart failure, and pneumonia, respectively. According to lumbar plain radiographic examination, degeneration changes were observed in lumbar facet joints in all cases.

The bodies were placed in prone position, and a medial skin incision was made on the lumbar part. Paravertebral muscles were detached, and dorsal capsules of bilateral L1/2, 2/3, 3/4, 4/5 facet joints were exposed. Agar jelly was injected into the subdural and epidural space through inter-raminal space. This jelly injection procedure was to prevent cauda equina avulsion and to keep the nerve and connective tissue structures in the spinal canal fixed when the vertebral body was removed. Methylene blue was injected into the lumbar facet joints using a 20-gauge needle and syringe under direct vision to detect any leakage of the coloring agent toward the intraspinal canal tissue including the lumbar nerve root. The methylene blue volume injected into each facet joint was 0.5 ml in this study because the dosage of contrast medium for lumbar facet joint block is generally 0.5 ml, and it is reported that the lumbar facet joint capacity is approximately 1–2 ml.[16] A block of lumbar spine was then removed in one piece and kept frozen. Each lumbar vertebral body was cut in a level of each facet joint and a slice section was prepared.

Extraarticular leakage of the coloring agent was classified into four categories to discuss the extent of its leakage. Specifically, leakage localized in the joint cartilage and joint capsule was defined as type C (cartilage); staining of the joint cartilage, joint capsule, and subsequently ligamentum flavum was defined as type F (flavum); staining of the ligamentum flavum and further soft tissue in epidural space was defined as type E (epidural tissue); and staining of nerve roots was defined as type R (root). By definition, types C and F are localized in the joint, and types E and R are subject to extraarticular leakage. All experiments in this study were approved by the Fukushima Medical University Investigation Review Committee.

Results

Correlation between inflammatory cytokine concentration and clinical symptoms

Each inflammatory cytokine concentration in the synovial and cartilage tissue was examined in the LDH and LSCS groups. The collected volumes of cartilage tissue and synovial tissues in the LDH group were 201 ± 105 mg and 123 ± 121 mg, respectively, and those in the LSCS group were 287 ± 208 mg and 200 ± 151 mg, respectively. There was no significant difference in collection volume of either tissue between the two groups.

In both groups, the positive reaction rate of inflammatory cytokines in each tissue was determined. In the LDH group, no TNFα was detected from either the cartilage or synovial tissues. The positive reaction rate of TNFα for cartilage tissue was 0% and for synovial tissue it was 3.7% (1/27 cases) in the LSCS group. Whereas this value for IL-1β expressed in cartilage tissue in the LDH group was 11.1% (1/9), the positive reaction rate was 34.5% (10/29) in the LSCS group. As for IL-1β, the synovial tissue had a positive rate of 0% in the LDH group, but the value was 38.5% (10/26) in the LSCS group. IL-1β had significantly higher positive reaction rates in the LSCS group than in the LDH group ($P < 0.05$). The detection rate of IL-6 was higher for both tissues in both groups than the detection rates for TNFα or IL-1β ($P < 0.05$). The positive reaction rates in the cartilage and synovial tissues in the LDH group were 90.0% (9/10) and 90.9% (10/11), respectively; and they were 100% for all the cases in both tissues in the LSCS group (Fig. 1). More specifically, the highest positive rate was obtained for IL-6, followed by IL-1β and

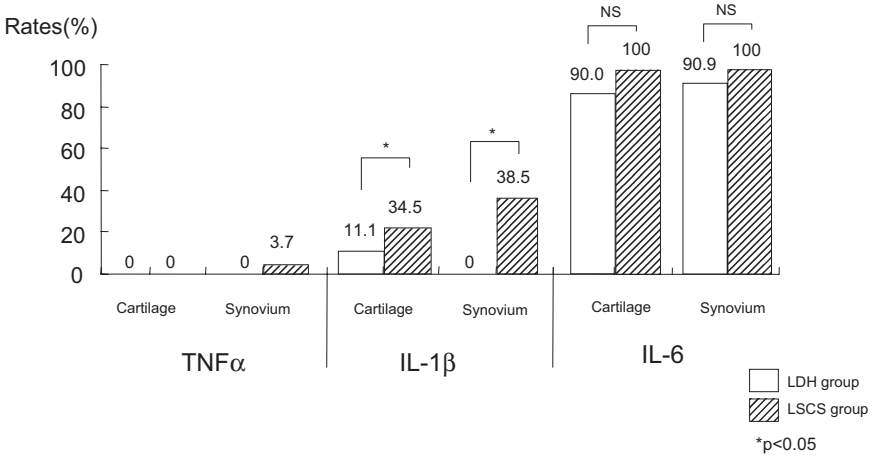


Fig. 1. Positive reaction rates for each inflammatory cytokine in the lumbar disc herniation (*LDH*) and lumbar spinal canal stenosis (*LSCS*) groups. The positive reaction rate was the greatest for interleukin-6 (IL-6), followed by IL-1β, and tumor necrosis factor-α (TNFα) for both tissues in both groups. The IL-1β-positive rate was significantly higher in the LSCS group than in the LDH group. IL-6 was observed at a high rate for both tissues in both groups

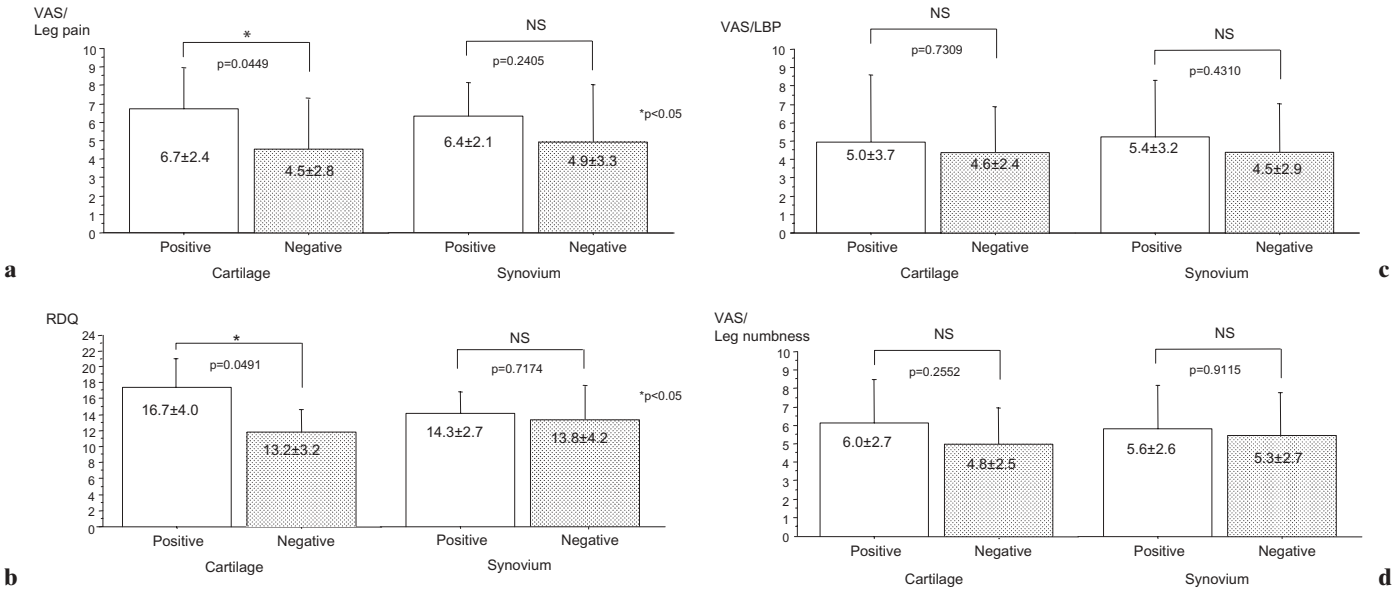


Fig. 2. As for IL-1β, the LSCS group was divided into a positive group and negative group to explore the extent of clinical symptoms. With regard to cartilage tissue, the IL-1β-positive group showed a significantly higher Visual Analogue Scale (VAS) score for leg pain (**a**) and the Roland-Morris disability questionnaire (RDQ) (**b**) compared to the IL-1β-negative group. On the other hand, IL-1β expression in synovial tissue indicated no statistically significant difference in the VAS for leg pain or the RDQ between the IL-1β-positive group and the IL-1β-negative group. The VAS value for low back pain (*LBP*) and leg numbness indicated no significant difference in the tissues between the two groups (**c**, **d**)

TNFα for both tissues in both the LDH and LSCS groups.

Moreover, for IL-1β, the LSCS group was divided into a positive group and negative group to discuss the extent of clinical symptoms. In the LSCS group, the IL-1β-positive group in the facet joint cartilage at the responsible level had VAS for leg pain and RDQ values of 6.7 ± 2.4 and 16.7 ± 4.0, respectively. In contrast, the IL-1β-negative group had VAS and RDQ values of 4.5 ± 2.8 and 13.2 ± 3.2, respectively. There was a statistically significant difference between the two groups (Fig. 2a,b). The IL-1β-positive group had VAS for low back pain and leg numbness and RDQ values of 5.0 ± 3.7 and 6.0 ± 2.7, respectively, and the IL-1β-negative group had values of 4.6 ± 2.4 and 4.8 ± 2.5, respectively. There was no statistically significant difference between the groups, as there was for cartilage tissue (Fig. 2c,d). Specifically, as for the cartilage tissue, the IL-1β-positive group showed significantly higher VAS for leg pain and RDQ scores than the IL-1β-negative group. In addition, the VAS for low back pain and leg numbness indicated no significant difference between these two groups for both tissues. Thus, lumbar spinal canal stenosis provided an association of IL-1β that was found in the facet joint cartilage with leg pain and diminished quality of life.

Assessing facet joint osteoarthritis on MRI and its IL-1β production

The weighted kappa coefficient for intraobserver agreement for MRI was 0.85. The degree of OA change of the lumbar facet joints at the responsible level was grade 2 or 3 in all cases of the LSCS group (Fig. 3). IL-1β-positive cases in cartilage tissue numbered 4 of 12 (33.3%) in grade 2 and 6 of 17 (35.3%) in grade 3. There were no cases of OA change of grade 0 or 1 in facet joints in the LSCS group. In contrast, some degree of OA change was seen in all of the lumbar facet joints in the LDH group. The degree of OA change for most cases was grade 1 in the LDH group. The degree of OA change for the only case that was IL-1β-positive in the cartilage in the LDH group was grade 2.

Leakage of coloring agent inside the facet joint from the intraspinal canal space

In the anatomical study with fresh cadavers, methylene blue, which was injected into the facet joints from the dorsal joint capsule, was used and stained the joint cartilage, ventral capsule, and ligamentum flavum in all three cases (Table 1). The injection of methylene blue into the left L4/5 facet joint in case 2 was incomplete because the joint space was too narrow to put the needle into capsule owing to severe OA changes. The epidural space, including the vertebral foramen, dura

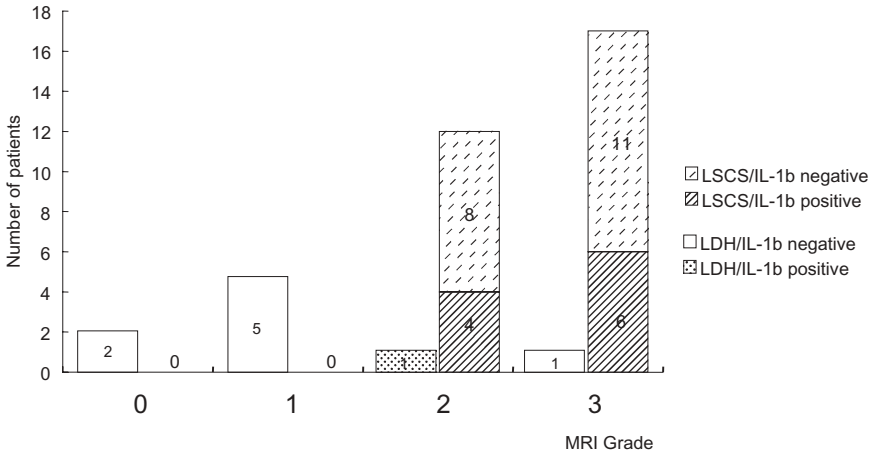
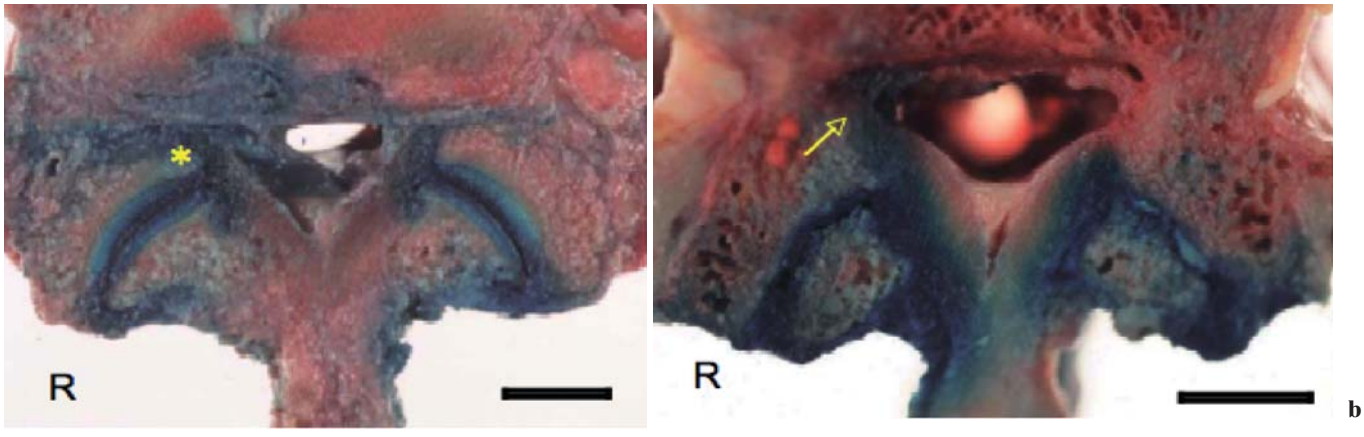


Fig. 3. Assessment of facet joint osteoarthritis (OA) by magnetic resonance imaging (MRI) and IL-1β production. The degree of OA change of the lumbar facet joints in the level was grade 2 or 3 in all cases in the LSCS group. Cartilage tissue was IL-1β-positive in 4 of 12 (33.3%) grade 2 cases and in 6 of 17 (35.3%) grade 3 cases



a **b**

Fig. 4. **a** Bilateral L4/5 facet joint of case 1. Methylene blue injected from the dorsal joint capsule into the facet joint stained joint cartilage, the ventral joint capsule, and the lateral part of the ligamentum flavum. The epidural space, including the foraminal space, dura mater, and nerve root, were also stained (*asterisk*). **b** Bilateral L4/5 facet joint of case 3. Not only the ventral joint capsule and lateral part of the ligamentum flavum but also the dura mater and epidural space were stained (*arrow*). Elderly patients and the lower level of the lumbar spine showed considerably more cartilage degeneration. *Bar* 1 cm

Table 1. Classification of leakage

Type	Description
C (cartilage)	Coloring agent is localized in the joint cartilage and joint capsule
F (flavum)	Staining of joint cartilage, joint capsule, and ligamentum flavum
E (epidural tissue)	Staining of ligamentum flavum and soft tissue of epidural space
R (root)	Staining of nerve roots

By definition, types C and F are localized in the joint, and types E and R are subject to extra-articular leakage

mater, and nerve roots, was also stained. The most lateral part of the ventral joint capsule, including the ligamentum flavum, was stained by methylene blue injected from the posterior capsule in type F; this was also found in types E and R, which shows that connective tissues in the epidural space and nerve root were also stained by methylene blue (Fig. 4). Considerable cartilage degeneration (e.g., reduction of cartilage, uneven cartilage surface, subchondral bone exposure) was more marked in the more elderly case than in the younger cadavers; and more severe coloring agent leakage was found at the lower lumbar vertebral level, especially the L4/5 level, than at the upper level. It suggests that inflammatory cytokines produced in degenerated facet joints may

leak into the intraspinal space through the most lateral part of the ventral facet joint capsule.

Discussion

In recent studies, inflammatory cytokines produced in the cartilage or synovial cells might involve the development of OA and the genesis of pain.[17,18] However, it is still unknown if inflammatory mediators (e.g., cytokines) modify inflammation in a complicated manner or if chemical factors are involved in osteoarthritis. In a previous study, it was reported that inflammatory cytokines are released from lumbar facet joints with OA changes in degenerative lumbar spinal disorders.[7] Nevertheless, there have been no reports that inflammation in the lumbar facet joint due to chemical mediators such as inflammatory cytokines causes pain and a declining quality of life (QOL). This study found that the LSCS group had a higher positive reaction rate of inflammatory cytokines than did the LDH group. Specifically, the LSCS group is characterized by a higher positive reaction rate of IL-1β in the lumbar facet joint cartilage and synovial tissue. The concentrations of IL-1β and IL-6 in lumbar facet joint cartilage and synovial tissue were higher in the LSCS group than in the LDH group.

Pain seriously affects QOL. There are various methods for evaluating pain, with the VAS approach being widely used as a measurement of the extent of pain. Because low back pain-related functions are affected primarily by the extent of leg pain, a greater extent of low back and leg pain worsens low back pain-related functions.[19] The Roland-Morris disability questionnaire is one of the most widely used indexes of low back pain-related functions.[20–22] In this study, those with IL-1β-positivity at the responsible level of the lumbar facet joint in the LSCS group showed significantly higher VAS for leg pain and RDQ scores than those with no IL-1β expression. This result indicates that IL-1β in the facet joint cartilage was associated with leg pain and declining QOL in the LSCS group.

There were no statistically significant differences between IL-1β expression and the VAS for low back pain and leg numbness. The reason for this result seems to be that low back pain may not be related to chemical mediators such as inflammatory cytokines derived from the facet joint. Instead, repeated mechanical stress or trauma and spinal deformity by secondary overload on a degenerated facet joint may be a more important factor for low back pain in degenerated lumbar disorders. Although the correlation between IL-1β and leg numbness is still uncertain, the influence on lumbar nerve roots by inflammatory cytokines from degenerated facet joint cartilage would induce nerve root injury, which causes leg pain more than leg numbness.

It is largely agreed that the first stage of OA results from mechanical stress against cartilage due to aging, genetic factors, and environmental factors, followed by secondary synovitis. Also, it is thought that the presence of synovial inflammation, which is often associated with the OA process, is believed to be a secondary phenomenon related to the destruction of cartilage and the release of cartilage breakdown products in the synovial fluid.[11] That would be why IL-1β in facet joint cartilage was more associated with leg pain and a declining QOL than that in synovial tissue in the series of this study.

The reason IL-1β was not detected at a high rate in either tissue in the LDH group and was not as closely associated with symptoms is thought to be due to the fact that the LDH group comprised younger subjects, and there is likely less degeneration in their facet joints. Moreover, the inflammation associated with symptoms might be derived not from facet joint tissues but from herniated nucleus pulposus.

IL-6 was highly detected in both groups but was not significantly associated with symptoms. IL-6 has been known to be both a proinflammatory and antiinflammatory cytokine that controls and maintains inflammation not only in an acute state but also a chronic state, even when the inflammation has subsided.[23,24] It is thought that IL-6 might not be closely related to symptoms or QOL because continuous local inflammation in the facet joint tissues would help produce IL-6 even after inflammation has subsided in the LSCS group. Therefore, inflammatory cytokines that express in the lumbar facet joint at a responsible level contribute to leg pain and the declining QOL because of the pain-related function.

In this MRI study of lumbar facet joint, the degree of facet joint degeneration for the cases in the LSCS group was “moderate” or “severe.” This suggests that inflammatory cytokines might be produced in highly degenerated facet joint tissues, which should be different from that in normal or less degenerated facet joint tissues in LSCS and from that in the LDH group.

An anatomical study with fresh cadavers was performed to identify how inflammatory cytokines in degenerated lumbar facet joints could be transmitted to the intraspinal space, even to the nerve root. As a result, a coloring agent was injected from the dorsal capsule into the facet joint. It stained not only joint cartilage, the ventral capsule, and the lateral part of the ligamentum flavum but also the extraarticular epidural space, dura mater, and lumbar nerve roots. It is suggested that inflammatory cytokines, which can be produced in facet joint cartilage and synovial tissue, may leak out of the facet joint capsule, especially into the intraspinal space through the lateral part of the ventral facet joint capsule, owing to OA changes in the lumbar facet joint.

It has been reported that the ends of the ventral facet joint capsule in the lumbar spine are attached to the ridge of facet joint surface, whereas the ends of the posterior facet joint capsule are attached over the ridges of the facet joint surface.[25] These authors also reported that the thickness of the ventral joint capsule was thicker than that of the posterior capsule at every lumbar level because the ventral capsule and ligamentum flavum become united and cannot be distinguished from each other. These findings support the belief that a degenerated ventral joint capsule, which would be even thicker together with the ligamentum flavum, may be torn minutely at the most lateral part by mechanical stress because a degenerated lateral ventral joint capsule may not have enough tissue margin to be stretched but be structurally defective. Therefore, it is possible that inflammatory cytokines produced in the facet joint leak into the intraspinal space through the lateral part of the ventral joint capsule tear and affect the lumbar nerve root through an inflammatory process.

Conclusions

These results in this study indicate the possible involvement of inflammation of the lumbar facet joint in clinical symptoms. Moreover, we explored the possibility that inflammation of a degenerated lumbar facet joint may cause the radiculopathy that is involved in the etiology of lumbar spinal canal stenosis.

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