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Interleukin-6 Serum Levels Are Elevated in Individuals with Degenerative Cervical Myelopathy and Are Correlated with Symptom Severity

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Background: Few studies have investigated systemic inflammation levels in degenerative cervical myelopathy (DCM). This study evaluated the concentration of inflammatory cytokines in DCM patients and assessed whether they can predict symptom severity.

Material/Methods: A total of 40 consecutive DCM patients and 10 healthy volunteers were included in this study. Concentrations of interleukin (IL)-1β, IL-6, interferon-γ, and tumor necrosis factor-α were compared between DCM patients and normal controls. Spearman's correlation coefficient was used to examine relationships of cytokines with age, body mass index (BMI), symptom duration, and symptom severity. A DCM compression rat model was established to examine the levels of inflammatory cytokines in serum and cerebrospinal fluid (CSF).

Results: Serum level of IL-6 is significantly higher in DCM patients compared with normal people (0.8±0.5 pg/ml *vs.* 0.5±0.3 pg/ml, *P*=0.036). Positive correlations were found between IL-6 levels with BMI (ρ=0.519; *P*=0.001) and symptom severity (ρ=–0.556, P<0.001). In DCM compression model rats, IL-6 was elevated in CSF (40.5±3.3 *vs.* 13.2±2.4 pg/ml, P<0.001) and serum (7.1±1.7 *vs.* 2.9±1.6 pg/ml, P<0.001) samples from rats in the compression operation group compared with the sham operation group. Infusion of IL-6 in rats receiving the sham operation also led to motor function damage and mechanical allodynia threshold decline.

Conclusions: Serum IL-6 level was elevated in DCM patients and its concentration can predict symptom severity. Local infusion of IL-6 led to myelopathy symptoms in model rats, which suggests that anti-inflammation can effectively treat DCM.

MeSH Keywords: Inflammation • Receptors, Interleukin-6 • Spinal Cord Compression

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Background

With aging of the population and changes in people's lifestyles, the number of patients affected by spinal degenerative diseases is rising. It is estimated that the incidence and prevalence of degenerative cervical myelopathy (DCM) in the North American region is at least 41 and 605 per million, respectively [1]. DCM arises as a result of compression of the spinal cord in patients with cervical spondylosis, ossification of the posterior longitudinal ligament, or disk herniation [1]. Patients with DCM can present with a variety of clinical signs and symptoms, including hand numbness, loss of manual dexterity, and impaired gait pain [2]. Based on recent evidence, surgical decompression is effective at halting disease progression and improving functional status for the majority (>80%) of patients [3]. However, a significant portion of patients (9.3%) may experience delayed neurological deterioration and complications [4] and no medical treatment is available to improve the neurological status in patients with worsening symptoms of compression myelopathy.

Gaps in the knowledge of the disease pathophysiology have historically limited therapeutic advances in DCM. Current studies are actively investigating the disease pathogenesis and inflammation is found to be of vital importance for development of neural degeneration and potentially irreversible spinal cord damage. Evidence from experimental and human DCM studies clearly shows that the chronic compression of the cervical spinal cord induces activation of microglia and the recruitment of macrophages at the site of the compression [5,6]. Inflammatory cytokines produced by these recruited cells lead to tissue damage, demyelination, and neurological dysfunction [7], as well as apoptosis of neurons and oligodendrocytes [8]. However, it remains unknown whether their presence and activity have the potential to act as markers of severity of clinical signs of DCM.

Concentrations of proinflammatory cytokines are elevated in compressed lesions of the spinal cord [9,10], and it was also confirmed that some proinflammatory factors are elevated in cerebrospinal fluid (CSF) of cases with DCM [10,11]. Many authors have studied cytokines in serum of patients with low back pain and lumbar intervertebral disc diseases [12,13]; however, to the best of our knowledge, there is no report on cytokines in the serum of patients with DCM. Recent studies showed that the blood–spinal cord (SC) barrier is disrupted by chronic SC compression [6] and loss of blood–SC barrier integrity can facilitate local inflammation factors entering the circulation system.

The goal of this study was to investigate changes in serum cytokine concentrations in patients with DCM and their associations with the severity of SC compression. We also verified these changes in a DCM rat model in CSF and serum.

Material and Methods

Participants

This study was approved by the Institutional Review Board of the Sixth People's Hospital affiliated to Shanghai Jiao Tong University. We collected whole blood from a total of 40 consecutive patients with DCM before surgery and 10 healthy volunteers as normal controls. Another 10 DCM patients were included as an independent validation. Written informed consent was obtained from all participants before enrollment. For each participant, serum was isolated by centrifugation and aliquots were stored at -80°C until biochemical analysis. Clinical data, including basic demographic information, underlying diagnosis, duration of symptoms, and imaging data, were collected from the participants and their medical records. The severity of cervical myelopathy was evaluated with a scoring system for cervical myelopathy by the Japanese Orthopaedic Association (JOA score-C) [14]. Briefly, the JOA scoring system evaluates the severity of myelopathy by assigning scores based on degree of dysfunction in 7 categories: motor function of fingers, shoulder and elbow, and lower extremity; sensory function of upper extremity, trunk, and lower extremity; and bladder function. The total score in this system for normal people was 17 and patients with more severe symptoms had lower scores.

DCM Compression rat model design

Male Sprague-Dawley rats (8–12 weeks of age) were obtained from the Experimental Animal Center of the Sixth People's Hospital affiliated to Shanghai Jiao Tong University (license number: SCXK-Shanghai: 2004-0007). All rats were maintained in a clean facility and were housed under standard conditions, and all animal procedures were approved by the Institutional Ethics Committee. The methods used to induce chronic compression in the cervical cord have been described in detail elsewhere [15]. A sheet of expandable polyvinyl alcohol compound polymer (size 3×5×0.7 mm, kindly provided by the Institute of Polymer Chemistry and Physics, School of Chemistry, Beijing Normal University) was inserted between the C5–C6 laminae. The volume of the sheet expands over more than 30 h after implantation by absorbing water from the tissues, reaches 200% of the original volume, and then remains constant. This model reproduces the characteristic course and features of clinical DCM.

Thirty rats were allocated to the following 3 groups: in group A (sham operation) the rats underwent sham surgery (sublaminar placement and immediate removal of the implanted polymer sheet); in group B (compression operation) the rats underwent polymer sheet implantation; and in group C (sham operation+IL-6) the rats underwent sham surgery and an absorbable gel sponge soaked in IL-6 (Rat IL-6 Recombinant

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Protein, Invitrogen, RP-8670) was deposited on the C5–C6 laminae.

Biochemical analysis

A Meso Scale Discovery multiplex cytokine immunoassay panel (catalog no.: K15009B) was used to quantify serum concentrations of proinflammatory cytokines in participants, including IFN-γ, IL-1β, IL-6, and TNF-α. The assay was performed according to the manufacturer's recommendations. The detection limits were IFN-γ: 2.2 pg/mL, IL-1β: 0.3 pg/mL, IL-6: 0.19 pg/mL, and TNF-α: 0.56 pg/mL.

CSF and serum samples from model rats were collected under general anesthesia before sacrifice. IL-6 concentration was determined using a rat IL-6 ELISA kit (ThermoScientific, Rockford, IL) following the manufacturer's instructions. Concentrations of IL-6 in CSF and serum are reported in pg/ml and averaged for each group.

Behavior test

Motor function of rats was evaluated using the Basso-Beattie-Bresnahan (BBB) motor rating scale [16]. This is a 22-point scale (scores 0–21) that systematically and logically records recovery of hind-limb function from a score of 0, indicative of no observed hind-limb movements, to a score of 21, representative of a normal ambulating rodent. The rats were tested for functional deficits weekly after surgery by the same examiner who was blind to the treatment each animal had received.

Mechanical allodynia was assessed by paw withdrawal threshold (PWT) in response to mechanical stimuli on the plantar surface of the right hind paw [17]. Before each test, animals were accustomed to a wired chamber for at least 30 min (12×20×17 cm). The test consisted of evoking a hind paw flexion reflex with a hand-held force transducer fitted with a 0.5-mm^2 polypropylene tip (electronic von Frey hair; IITC Life Science, Woodland Hills, CA). An abrupt withdrawal of the right hind paw during stimulation or after stimulus removal was considered as positive. The 2.04-g filament was applied as the first stimulus. The results are reported as the Δ withdrawal threshold (in g) that was calculated by subtracting the average of the last 3 measurements after the treatments from the average of 3 measurements before the treatments.

All behavioral tests were performed by the same examiner without knowing the experimental group of the animal. Observations were performed on the day before surgery and weekly during the postoperative period according to the experimental group. The animals were evaluated once a week for 10 weeks after surgery.

Histological assessment

At 10 weeks after surgery, all rats were perfused transcardially with 4% paraformaldehyde in phosphate-buffered saline (PBS). The C5–C6 segment of the spinal cord was dissected from each animal, embedded in paraffin, and sectioned at a slice thickness of 5 mm and a gap interval of 5 mm over a 1-mm length. One hundred histological sections were analyzed from the C5–C6 cord segment for each rat. The specimens were stained with hematoxylin and eosin.

TUNEL staining

We investigated apoptotic cell death at 10 weeks after surgery. The 30 rats for this investigation were perfused transcardially with 4% paraformaldehyde in PBS. The C5–C6 segment of the spinal cord was dissected from each animal, embedded in paraffin, and sectioned. Three cross-sections (thickness ¼ 5 mm, gap interval ¼ 50 mm) per rat were stained with the In-Situ Cell Death Detection Kit, POD (Roche, Basel, Switzerland) according to the manufacturer's recommendations. The TUNEL signal was observed under an FV300 confocal microscope (Olympus, Tokyo, Japan). Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI, 1: 5000 in PBS) (Molecular Probes, Eugene, OR). The means of the ratios of apoptotic to total nuclei were calculated in the anterior horn of each animal.

Statistical analysis

Data are expressed as the means ± standard error of the mean. Age was compared using the Mann-Whitney U test. The chi-square test was applied to analyze sex distribution in the control and DCM cohorts. The *t* test was used to compare the BMI and concentration of inflammatory cytokines between control and DCM cohorts. The BBB score and paw withdrawal threshold were tested with two-way repeated-measures analysis of variance (ANOVA). One-way ANOVA was performed to compare the means among all groups each week. Statistical analyses were performed using SPSS Statistics 17.0 (SPSS, Inc., Chicago, IL). P values of less than 0.05 were regarded as statistically significant.

Results

Participant characteristics

We recruited 40 DCM patients and 10 healthy volunteers as normal control in this study. The baseline characteristics of all participants are shown in Table 1. The distribution of age, sex, and BMI were well balanced between DCM patients and control group. The media ages for DCM patients and the control groups were 52 y (range: 35–68 y) and 60 y (range: 41–67 y),

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Table 1. The baseline characteristics of participants.

Variables	DCM patients (N=40)	Controls (N=10)	P value
Age (median, range)	52 (35–68)	60 (41–67)	0.168
Sex			1.000
Male	18 (45.0%)	5 (50.0%)	
Female	22 (55.0%)	5 (50.0%)	
BMI (kg/m^2) (mean ±SD)	25.2±3.1	23.6±2.6	0.160

DCM – degenerative cervical myelopathy; BMI – body mass index.

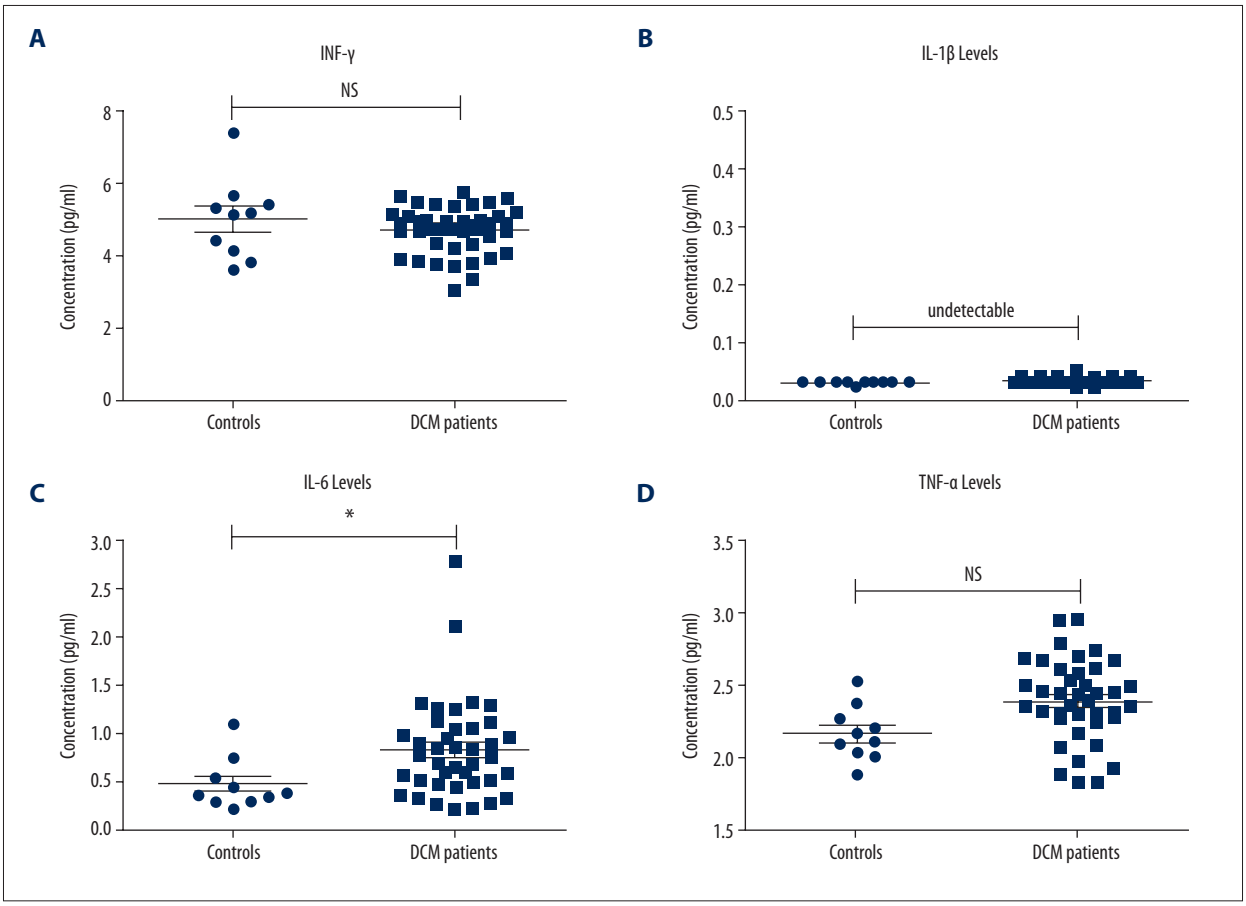

Figure 1. Comparison of serum levels of inflammatory cytokines between control subjects and participants with degenerative cervical myelopathy (DCM). (**A**) interferon (INF)-γ; (**B**) interleukin (IL)-1β; (**C**) IL-6; (**D**) tumor necrosis factor (TNF)-α. Each symbol represents values from a single subject; midline represents the mean; and error bars represent the standard error. * *P*<0.05.

respectively (*P*=0.168). The control cohort had 50.0% females and 50.0% males, and the DCM cohort had 55.0% females and 45.0% males (*P*=1.000). The mean BMIs for the DCM patients and control groups were 25.2±3.1 kg/m^2 and 23.6±2.6 kg/m^2 (*P*=0.162). For the 40 DCM patients, the mean symptom duration time was 26.0 months (range: 8–42 months) and the mean JOA score for myelopathy severity was 10.6.

Biochemical factors in DCM patients and control groups

Serum levels of IFN-γ, IL-6, and TNF-α were detectable in all participants. IL-1β was almost undetectable (test results were under detection limits) (Figure 1B). DCM patients had serum IL-6 levels (0.8 ± 0.5 pg/ml) higher than those of control participants (0.5±0.3 pg/ml) (*P*=0.036) (Figure 1C). Serum levels of IFN-γ (4.7±0.7 *vs.* 5.0±1.1 pg/ml, *P*=0.270) and TNF-α (2.4±0.3 *vs.* 2.2±0.2 pg/ml, *P*=0.068) had no significant difference

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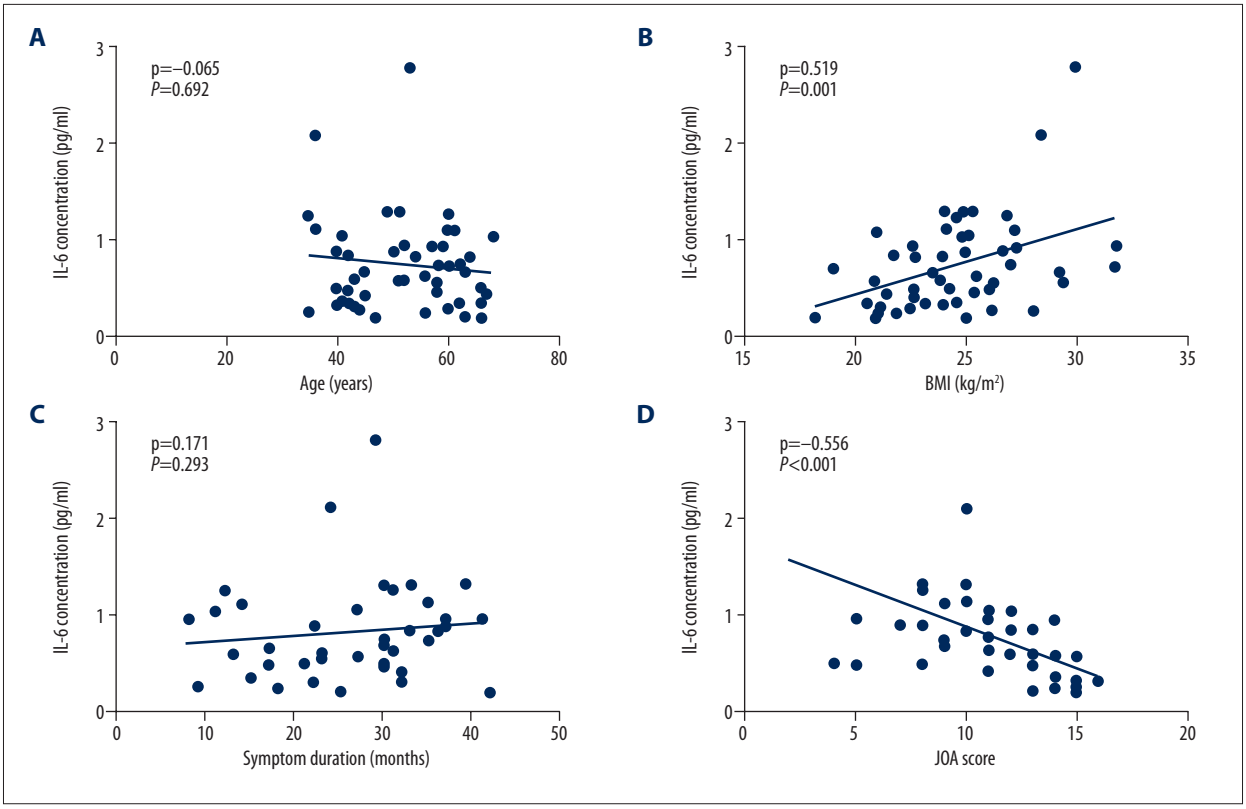

Figure 2. Spearman's correlation coefficients between interleukin (IL)-6 levels and (**A**) age, (**B**) body mass index (BMI), (**C**) symptom duration, and (**D**) Japanese Orthopaedic Association (JOA) score. The resulting Spearman's correlation coefficient (ρ) and corresponding p value are reported.

between DCM patients and control groups (Figure 1A, 1D). We then detected the serum level of IL-6 in an independent validation group of DCM patients. The results showed that the validation group had similar serum IL-6 levels (0.8±0.4 pg/ml) as in the DCM patient group (*P*=0.916), and both were higher than in the control group (validation group *vs.* control group, *P*=0.011) (Supplementary Figure 1).

Since serum IL-6 level was significantly elevated in DCM patients, we then analyzed the correlations between IL-6 levels with age, BMI, symptom duration, and JOA scores in the DCM patient group. Spearman's correlation results showed that IL-6 levels were significantly correlated with BMI (ρ=0.519; *P*=0.001) and JOA score (ρ=-0.556, P<0.001) (Figure 2B, 2D). No significant correlation was observed between IL-6 and age (ρ=–0.065; *P*=0.692) or symptom duration (ρ=0.171; *P*=0.293) (Figure 2A, 2C).

Assessment of the DCM compression rats model

Motor function of the rats was evaluated using the BBB motor rating scale. The scores declined 2 weeks after surgery in all 3 groups, but recovered in the sham operation group after 2 weeks. Motor function was significantly decreased from 4 weeks after surgery in the compression operation group compared with the sham operation group (P<0.001) (Figure 1). In contrast, motor function in the sham operation+IL-6 group was similar to that of the compression operation group throughout the 10 weeks after surgery, but deteriorated faster within 3 weeks and then decreased less (Figure 3A).

Mechanical allodynia was assessed by paw withdrawal threshold (PWT) in response to mechanical stimuli on the plantar surface of the right hind paw. The withdrawal threshold remained fairly constant in the sham operation group, but declined gradually in the compression operation group and sham operation+IL-6 group. The mechanical allodynia worsened faster in the first 5 weeks after surgery than in the compression group. Both groups had a significantly decreased withdrawal threshold compared to the sham operation group (Figure 3B).

The IL-6 concentration in CSF and serum samples from the sham operation and compression operation groups were also tested. The results showed that IL-6 was significantly upregulated in CSF (40.5±3.3 *vs.* 13.2±2.4 pg/ml, P<0.001, Figure 4A) and serum (7.1±1.7 *vs.* 2.9±1.6 pg/ml, P<0.001, Figure 4B) samples in the compression group compared to the sham operation group.

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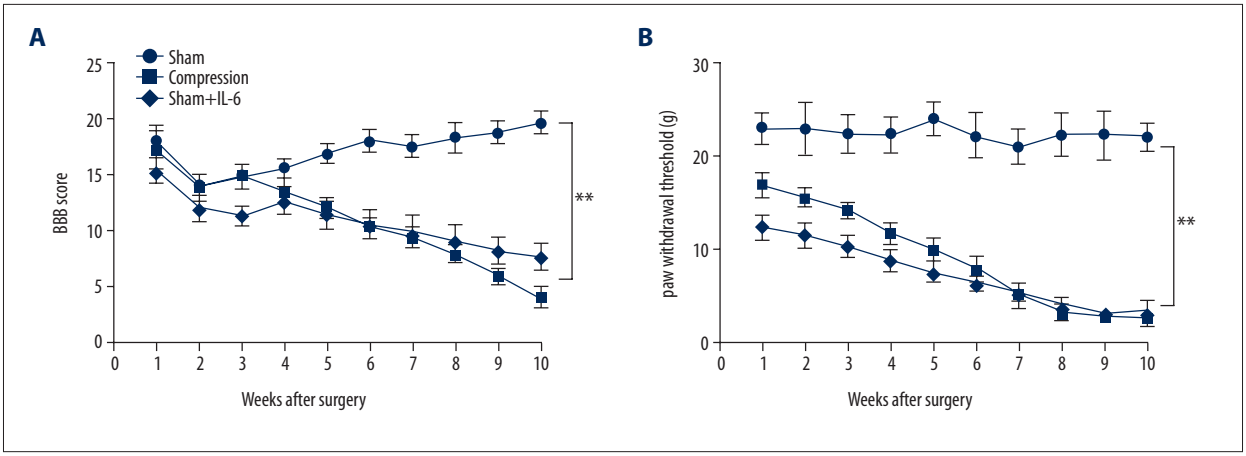

Figure 3. Time course of (**A**) Basso-Beattie-Bresnahan (BBB) motor rating scores and (**B**) paw withdrawal threshold (PWT) of the right hind paw in response to mechanical stimuli in 3 groups in compression model rats. IL-6 indicates interleukin-6. * $P<0.05$, ** $P<0.001$.

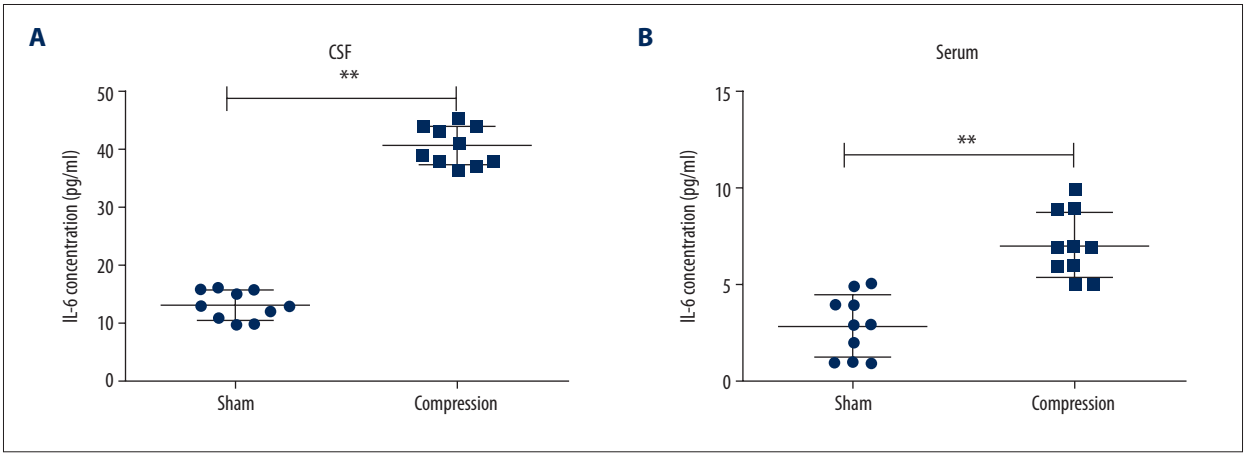

Figure 4. Comparison of IL-6 concentration between sham operation group and compression operation group rats in (**A**) cerebrospinal fluid (CSF) samples and (**B**) serum samples. Each symbol represents values from a single subject, midline represents the mean, and error bars represent the standard error. * $P<0.05$, ** $P<0.001$.

Histological assessment and TUNEL staining were performed with C5–C6 segments of the spinal cord for rats from each group. At 10 weeks after surgery, the cross-sectional structure of the spinal cord was dense and intact in the sham operation group (Figure 5A), but in the compression operation group, the white matter structure was spongy and the gray matter was disintegrated (Figure 5B). Slightly damaged structure was also observed in the sham operation+IL-6 group (Figure 5C). Compared with the sham operation group, TUNEL-positive cells were mainly detected in the compression operation group (Figure 5D, 5E). We also detected some apoptotic cell death in the sham operation+IL-6 group (Figure 5F).

Discussion

The goals of this study were to examine circulating levels of inflammatory factors in DCM patients and to evaluate the association between their changes with clinical factors, including age, BMI, symptom duration, and the severity of cervical myelopathy. Our findings indicate that the serum level of IL-6 is significantly higher in DCM patients compared with normal people. Positive correlations were found between IL-6 levels with BMI and JOA score. These results were also validated in subsequent DCM compression model rats. IL-6 was elevated in CSF and serum samples from rats in the compression operation group compared with the sham operation group. Infusion of IL-6 in rats receiving sham operation also led to motor function damage and mechanical allodynia threshold decline. Histological examination showed spinal cord structure destruction and neuronal apoptosis in rats in the compression operation group and sham operation+IL-6 group.

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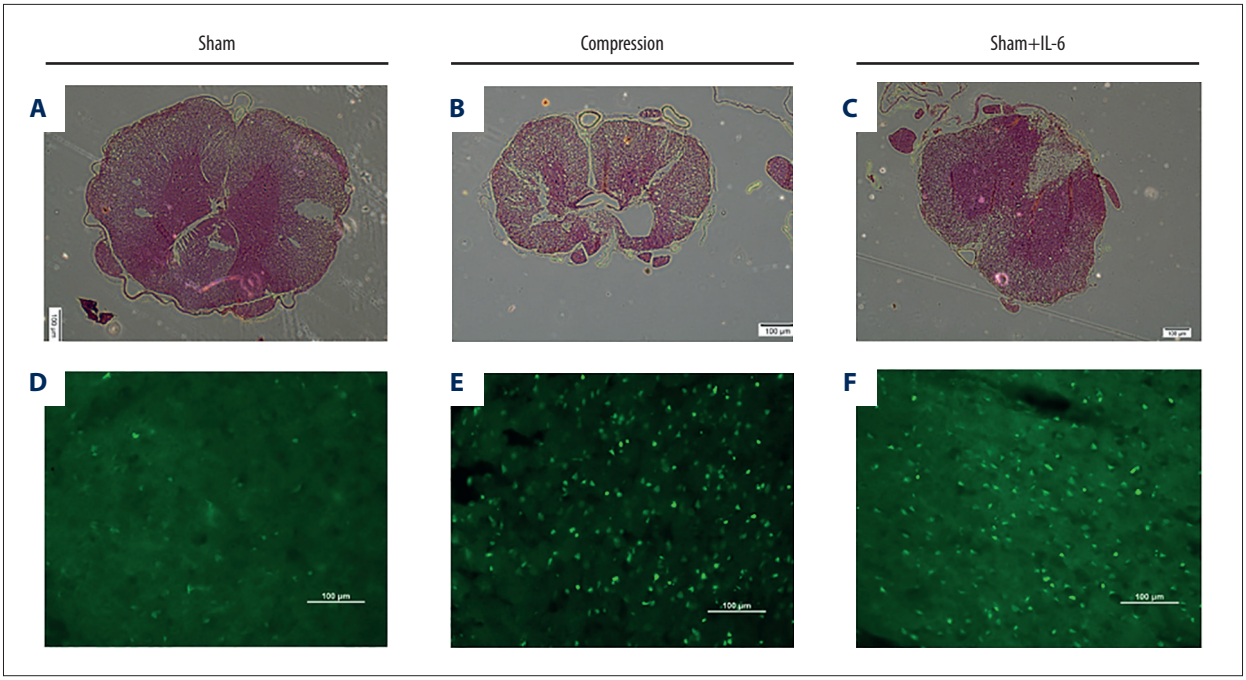

Figure 5. Photomicrographs of cervical cord sections at C5–C6 at 10 weeks after surgery in the compression model rats. Hematoxylin and eosin staining of (**A**) sham operation group, (**B**) compression operation group, and (**C**) sham operation+IL-6 group; TUNEL staining to detect apoptotic cell death in the anterior horn of (**D**) sham operation group, (**E**) compression operation group, and (**F**) sham operation+IL-6 group. IL-6 indicates interleukin-6. Bar=100 mm.

Investigators are trying to identify systemic factors that can be used to aid diagnosis, stage severity, and indicate prognosis. For spine degenerative diseases, many studies have been performed focusing on cytokines in serum of patients with low back pain and lumbar intervertebral disc diseases [12,13,18–20], but little is known about cytokines in serum of patients with DCM. Inflammation occurs in compressed lesions of spinal cords [9,10]. For DCM, it was also confirmed that some pro-inflammatory factors are elevated in CSF [10,11]. Our study demonstrates for the first time that serum levels of IL-6 are significantly elevated in individuals with DCM in comparison to the control group, suggesting that DCM subjects have low-grade systemic inflammation. Importantly, the study subjects were well-balanced for age, sex, and BMI, minimizing any influence of these parameters on outcomes.

Il-6 was an important inflammatory factor in spinal cord disease. Previous studies found that IL-6 can be spontaneously produced *in vitro* by human herniated and degenerated discs [21,22]. IL-6 can also sensitize dorsal root ganglia to painful stimuli in preclinical models by increasing production of TNF-α by neurons [23,24]. Serum and CSF IL-6 levels increase in response to spinal cord injury [25,26], and the concentration of IL-6 in CSF can be used to stratify injury severity and predict outcome in traumatic spinal cord injury [27]. Similarly, the results of our study showed that serum IL-6 levels were significantly elevated in DCM patients and the concentration of IL-6 was correlated with severity of myelopathy. IL-6 was also elevated in CSF in DCM compression model rats, and local infusion of IL-6 at C5–C6 laminae can also lead to motor function damage and mechanical allodynia threshold decline. These results indicated that IL-6 plays an important role in DCM.

Many inflammatory cytokines are locally elevated after nerve injury, and IL-6 is one of the most important factors involved [28–30]. In our study, the concentration of IL-6 also increased in CSF from rats undergoing the compression operation. Elevation of IL-6 has long been known to be associated with algesia. It was reported that intrathecally administered human recombinant IL-6 elicited touch-evoked hyperalgesia in normal rats [31]. Similarly, local infusion of IL-6 at C5–C6 laminae led to mechanical allodynia threshold decline in the sham operation+IL-6 group. In addition, we observed slight neuron apoptosis in the sham operation+IL-6 group. Given that reduction of inflammation by glucocorticoids or rh-erythropoietin (EPO) can also decrease motor neuron apoptosis in spinal cord injury [32,33], we hypothesize that IL-6 neutralization affects DCM treatment.

Our study has several limitations. Firstly, it was a single-center study with a small number of DMC cases. Although the baseline characteristics of DMC patients and normal control were well balanced, a larger sample size is needed to validate the results. Secondly, only 4 inflammatory cytokines were included

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in first-step screening, which may leave out some other factors important for diagnosis of DCM. Thirdly, our study did not have a long follow-up period, so it was impossible to determine whether and how the inflammation levels change after treatment. Finally, although IL-6 levels were higher than normal in the control group, the levels of IL-6 measured in the DCM patients are within the reported range for normal human. Serum cytokine levels may vary by age, sex, sample type, and type of assay used; therefore, it is still difficult to determine the range of serum IL-6 levels for DCM patients, which may limit the routine clinical application of this biomarker.

Conclusions

In conclusion, our study showed that the serum levels of IL-6 were significantly higher in DCM patients compared with normal people. Positive correlations were found between IL-6 levels with BMI and JOA score. In DCM compression model rats, IL-6 was elevated in CSF and serum samples from rats in the compression operation group compared with the sham operation group. Infusion of IL-6 in rats undergoing the sham operation also led to motor function damage and mechanical allodynia threshold declined. Histological examination showed spinal cord structure damage and neuronal apoptosis in rats in the compression operation group and sham operation+IL-6 group.

Acknowledgement

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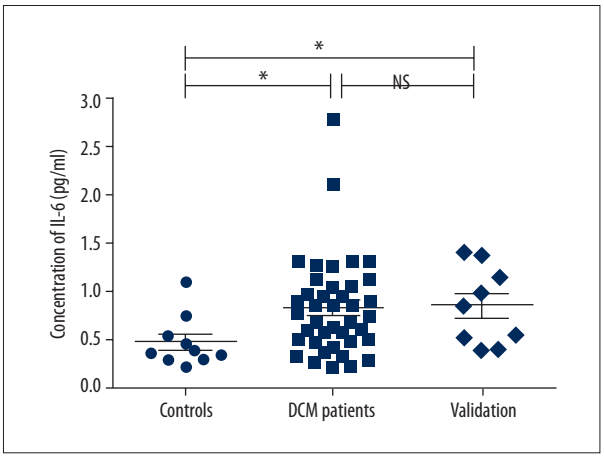
Conflict of Interest

None.

Supplementary Figure



Supplementary Figure 1. Serum levels of IL-6 in control subjects, participants with degenerative cervical myelopathy (DCM), and validation group patients. Each symbol represents values from a single subject; midline represents the mean; and error bars represent the standard error. * $P<0.05$.

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