Tumor necrosis factor- α , interleukin-1 β , and interleukin-6 in the cerebrospinal fluid of patients with cervical myelopathy and lumbar radiculopathy

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Abstract There have been few reports describing cytokines in the cerebrospinal fluid (CSF) of patients with spinal degenerative disorders. This study investigated whether interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) could be detected in CSF of patients with cervical myelopathy or lumbar radiculopathy and whether the concentrations of those cytokines correlated with the severity of disease conditions. CSF samples were obtained from 21 patients with cervical myelopathy (Group M) and 19 patients with lumbar radiculopathy (Group R), and six volunteers (control). The concentration of IL-6 was significantly higher in Groups M and R than in the control, possibly demonstrating spinal cord and nerve root damage, respectively. However, TNF- α was lower than the detection limit. IL-1 β was detected in only five samples from three patients in Group M and two volunteers in the control. The concentrations of IL-6 did not show any correlation with symptom duration, the scoring system by the Japanese Orthopaedic Association, or the duration of nerve root block. There is a possibility that the concentration of inflammatory cytokines in CSF

can indicate certain pathological aspects of cervical myelopathy or lumbar radiculopathy.

Keywords Cytokine · Cerebrospinal fluid · Cervical myelopathy · Lumbar radiculopathy

Introduction

Cervical myelopathy arises as a result of compression of the spinal cord in patients with cervical spondylosis, ossification of the posterior longitudinal ligament, or disk herniation. Lumbar radiculopathy results from compression of the nerve root by herniated disk material, osteophytes, and/or ligamentum flavum. Under these conditions, neural tissue damage can occur, and specific cytokines are produced from the nerve and glial cells, and released into the cerebrospinal fluid (CSF) [11, 12, 21, 22]. Moreover, the cytokine concentration in the CSF is elevated by the increased permeability of the blood–nerve barrier caused by spinal degenerative disorders [1, 26, 27].

Many authors have studied the cytokines in the CSF of patients with neurologic diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, and transverse myelitis [11, 12, 21, 22]; however, to our knowledge, there have been a few clinical reports [2, 6] regarding the cytokines in the CSF of patients with spinal degenerative disorders such as cervical spondylotic myelopathy and lumbar canal stenosis.

This study investigated whether interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) could be detected in the CSF of patients with cervical myelopathy or lumbar radiculopathy, and whether the concentrations of these cytokines in the CSF differed between patients with spinal degenerative disorders and

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controls. We further studied the relationships between the concentrations of these cytokines and the severity of symptoms, and in patients with lumbar radiculopathy, the relationships between three cytokines and the duration of nerve root block.

Materials and methods

CSF samples were obtained from 21 patients with cervical myelopathy (Group M) and 19 patients with lumbar radiculopathy (Group R) by lumbar puncture prior to myelography, and six volunteers (control) who underwent lumbar spinal anesthesia for the removal of devices after osteosynthesis. None of the patients in the control group had any type of spinal disorder. The mean ages were 66.2 (range 46–80 years), 53.5 (range 25–85), and 41.5 years (range 15–81) in Groups M, R, and the control, respectively. Group M was older than Group R ($P = 0.023$); however, there was no significant difference in age between Group M and the control ($P = 0.057$) or between Group R and the control ($P = 0.221$). There were 17 men and four women in Group M, 15 men and four women in Group R, and five men and one woman in the control. In Group M, there were 16 patients with cervical spondylotic myelopathy, four with ossification of the posterior longitudinal ligament, and one with cervical disk herniation. Group R consisted of 15 patients with lumbar disk herniation and four with lumbar canal stenosis. In Group R, the L4, L5, and S1 nerve roots were involved in 2, 13, and 4 patients, respectively.

The samples were stored immediately at -80°C . All specimens were clear and transparent without any precipitation or suspended materials. Therefore, the analysis was carried out without further treatment of the specimens. No patients took any medicine at least 6 h before the CSF sampling. IL-1 β , IL-6, and TNF- α production were measured by a company providing comprehensive laboratory testing services (SRL Inc., Tokyo, Japan) using the enzyme-linked immunosorbent assay technique, who were blinded to the groups of the patients. The detection limits were 0.12, 0.16, and 0.5 pg/ml for IL-1 β , IL-6 and TNF- α , respectively.

We evaluated the differences in the concentrations of three cytokines among the three groups. Also, the relationships between the three cytokines and the severity of conditions or symptom durations were evaluated. The mean symptom durations were 28.9 months (range 2–144 months) and 46.9 months (range 2–120 months) in Groups M and R, respectively. The severity of cervical myelopathy was evaluated with a scoring system for cervical myelopathy by the Japanese Orthopaedic Association (JOA score-C) [30]. The highest possible JOA score-C is

17 points. The mean JOA score-C was 10.0 points (range 5.5–14.0). The severity of lumbar radiculopathy was evaluated with the assessment of treatment for low back pain by the Japanese Orthopaedic Association (JOA score-L) [7]. The highest possible JOA score-L is 29 points. The mean JOA score-L was 12.4 points (range 3–22). To evaluate the relationships between neurological deficits and the concentrations of the cytokines, the sum of motor disturbance and the sensory disturbance of JOA score-L (neurological deficits score) was calculated. The highest possible score is 4 points. The mean neurological deficits score was 2.2 points (range 0–4). In addition, the relationships between the three cytokines and the duration of nerve root block were evaluated in Group R. Just after CSF collection, a 22-gauge spinal needle was inserted into the involved nerve root sleeve with an image intensifier, and 1 ml of 1.0% lidocaine HCl (Xylocaine[®], Astra Zeneca, London, UK) and 2 mg of betamethasone (Rinderon[®], Shionogi Co. & Ltd., Osaka, Japan) were injected after radiculography in order to ensure appropriate insertion. The interval until a patient first required an analgetic after selective nerve root block was defined as the duration of nerve root block.

The Mann–Whitney U test was used for intergroup comparisons. Correlations were evaluated with Spearman's rank sum test. A probability value less than 0.05 was considered significant. All statistical analyses were performed on SPSS.

Results

IL-1 β was detected in only five samples from three patients in Group M and two volunteers in the control. IL-1 β was not detected in Group R. The mean concentrations of IL-1 β were 0.35 and 1.17 pg/ml in the three patients in Group M and two in the control group, respectively (Table 1). In Group M, there were no significant differences in age, symptom duration, JOA score-C, or the concentrations of IL-6 between patients with and without IL-1 β in their CSF.

IL-6 was detected in all CSF samples from Groups M and R, and the control. The mean concentrations of IL-6 were 4.58, 5.14, and 1.96 pg/ml in Groups M and R, and the control, respectively (Table 1). There were significant differences between Group M and the control ($P = 0.031$) and between Group R and the control ($P = 0.017$). However, there was no significant difference between Groups M and R ($P = 0.893$).

TNF- α was lower than the detection limit of 0.5 pg/ml in all samples.

In Group M, the symptom duration did not correlate with the concentrations of IL-6. JOA score-C did not show any correlation with the concentrations of IL-6 (Table 2).

Table 1 Concentration of cytokines in the cerebrospinal fluid

Group	IL-1 β (pg/ml)	IL-6 (pg/ml)*	TNF- α (pg/ml)
M	0.35 $\pm$ 0.14 ^a	4.58 $\pm$ 2.74	— ^d
R	— ^b	5.14 $\pm$ 3.64	— ^d
Control	1.17 $\pm$ 0.67 ^c	1.96 $\pm$ 1.63	— ^d

Values are given as mean $\pm$ SD

* There were significant differences between Group M and the control ($P = 0.031$) and between Group R and the control ($P = 0.017$)

^a IL-1 β was detected in only three of 21 patients in Group M. The value was calculated from samples in these three patients

^b IL-1 β was not detected in Group R

^c IL-1 β was detected in only two of six volunteers in control. The value was calculated from samples in these two volunteers

^d TNF- α was lower than the detection limit of 0.5 pg/ml in all samples

Table 2 Correlation coefficients (a probability value) between concentration of cytokines and parameters in the patients with cervical myelopathy

Parameter	IL-6
Age	0.198 ($P = 0.389$)
Symptom duration	0.086 ($P = 0.710$)
JOA score-C	−0.085 ($P = 0.715$)

IL-1 β was detected in only three patients in Group M. TNF- α was lower than the detection limit of 0.5 pg/ml in all samples

Table 3 Correlation coefficients (a probability value) between concentration of cytokines and parameters in the patients with lumbar radiculopathy

Parameter	IL-6
Age	−0.036 ($P = 0.885$)
Symptom duration	−0.248 ($P = 0.305$)
JOA score-L	−0.142 ($P = 0.563$)
Neurological deficits score	0.115 ($P = 0.639$)
Duration of nerve root block	0.392 ($P = 0.120$)

IL-1 β and TNF- α were lower than the detection limits in all patients in Group R

There were no differences in the concentrations of IL-6 among patients with ossification of the posterior ligament, those with cervical spondylosis, and those with disk herniation.

In Group R, symptom duration, JOA score-L, neurological deficits score, and duration of nerve root block did not show any correlation with the concentrations of IL-6 (Table 3). There was no difference in the concentration of IL-6 between the patients with disk herniation and those with spinal canal stenosis.

Discussion

Our study has several limitations. First, the CSF samples were obtained only from patients undergoing myelography. Myelography was performed for all patients who were candidates for surgery. Therefore, the patients in this study had moderate to severe symptoms, and so the current study may contain bias. We confirmed that the volunteers in the control group had neither neck, back, or lower back pain, nor neurological symptoms. Moreover, they showed negative findings for neurological and tension signs. However, we did not perform MRI studies to confirm that the volunteers did not have asymptomatic disk herniation or disk degeneration. Second, the age difference between Groups M and R was significant. The removal of devices after osteosynthesis is generally indicated for younger patients. Furthermore, the patients with lumbar radiculopathy caused by disk herniation were younger than those with cervical myelopathy. A previous cadaveric study demonstrated that the correlation between anular TNF- α and age was highly significant [29]. Therefore, there is a possibility that the differences in cytokines among the three groups were attributable to age. We checked the relationships between age and the three cytokines for all patients in all three groups; however, there were no significant correlations.

Previous reports showed proinflammatory cytokines such as IL-1 β , IL-6, and TNF were expressed in human herniated disk specimens [8, 28]. Intervertebral disk cells may produce TNF- α , IL-1 β , and monocyte chemoattractant protein-1 immediately after the onset of disk herniation [32]. Local application of nucleus pulposus induced an acute inflammatory reaction at the surface of the dorsal root ganglion [13, 14, 16]. Also the application of a higher concentration of TNF to the L4 dorsal root ganglion induced allodynia and a hyperalgesia response [15]. Application of TNF- α antibodies to the nerve root partially prevented nucleus pulposus-induced abnormal nociceptive responses [20]. TNF- α induced axonal and myelin injuries similar to those observed after nucleus pulposus application [10, 17–19]. The pain in patients with lumbar radiculopathy is probably caused by a combination of mechanical deformation in lumbar tissues and biochemical changes [23]. Selective nerve root block including steroids can have anti-inflammatory effects. In the current study, duration of nerve root block showed no correlation with the concentrations of IL-6. However, the relationship between the concentration of cytokines in CSF and the duration of nerve root block could be demonstrated after the method of measurement of cytokines could be improved.

As described above, there have been many studies showing cytokines in the lumbar disk; however, to our knowledge, there are few papers describing the cytokines in the CSF of patients with lumbar radiculopathy. Scuderi

et al. [24] studied various cytokines in the epidural space lavage obtained from patients with lumbar disk herniation and radiculopathy. The cytokines included IL-1 β , IL-1 α , IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-13, IL-15, IL-17, TNF- α , IFN- α , IFN- γ , GM-CSF, MIP-1 α , MIP-1 β , IP-10, MIG, Eotaxin, RANTES, and MCP-1; however, none of the cytokines were isolated. Brisby et al. [2] investigated the CSF and serum concentrations of IL-1 β , IL-6, IL-8, interferon (IFN)- γ , and TNF- α in patients with lumbar disk herniation and sciatica. They demonstrated that the concentration of IL-8 in the CSF was increased in approximately one-third of patients and that these increased levels of IL-8 correlated to a short duration of pain, which supports the concept of the initial involvement of inflammatory mechanisms after a disk herniation. In their series, however, the concentrations of IL-1 β , IL-6, IFN- γ , and TNF- α were normal both in the CSF and serum. One of the possible reasons for the different results between their and our study could be the differences in the detection limits. The detection limits in their study were 1 pg/ml for IL-1 β and IL-6 and 5 pg/ml for TNF- α , which were approximately ten times higher than those in our study. Another possible reason could be the difference in the timing of observation. Another study analyzed neurofilaments, S-100, glial fibrillary acidic protein, neuron-specific enolase, IL-8, nociceptin, and substance P endopeptidase activity in the CSF obtained from pig models with experimental spinal nerve root injuries induced using mechanical compression [3]. The concentrations of neurofilament and nociceptin were increased in the experimental spinal nerve root injury group; however, there were no intergroup differences in glial fibrillary acidic protein, neuron-specific enolase, S-100, IL-8, or substance P endopeptidase activity. DeLeo et al. [4] demonstrated that IL-6 was produced both locally and centrally in response to nerve damage. The elevated IL-6 levels in the patients with lumbar radiculopathy were ascribed to nerve damage rather than nucleus pulposus. Our study showed that the IL-6 concentration in the CSF of patients with lumbar radiculopathy was significantly higher than that in the control, which indicated that nerve root damage had occurred in the patients with lumbar radiculopathy.

To our knowledge, reports of the cytokines in the CSF of patients with cervical myelopathy are also rare. Regarding other spinal cord disorders, Kaplin et al. [9] indicated that the IL-6 levels were dramatically elevated in the CSF of patients with transverse myelitis and correlated with markers of tissue injury and clinical disability. In multiple sclerosis, Gruol and Nelson [5] reported indirect evidence that elevated IL-6 potentiated neural injury. Moreover, Sekizawa et al. [25] found that the IL-6 levels in the CSF from patients with amyotrophic lateral sclerosis were significantly higher than those in multiple sclerosis or

HTLV-1-associated myelopathy. In the current study, the IL-6 in CSF was significantly higher in patients with cervical myelopathy than in the controls, suggesting that neural damage occurred in patients with cervical myelopathy. However, the TNF- α levels in the CSF of all the patients with cervical myelopathy were under the detection limit, and IL-1 β was detected in only three of 21 patients. Recently, Ito et al. [6] studied IL-8, IL-10, and TNF- α in the CSF of patients with cervical myelopathy, and described that the concentration of IL-8 was significantly higher in patients with cervical myelopathy than in the control. However, IL-10 and TNF- α were not detected in all cases. Based on these studies, IL-6 and IL-8 might be elevated in the CSF of patients with cervical myelopathy; however, IL-10, IL-1 β , or TNF- α are not affected. IL-1 β , IL-6, IL-8, and TNF- α are considered to stimulate brain repair processes and astroglial scarring [3]. A previous autopsy study of traumatic spinal cord injury [31] indicated that IL-1 β , IL-6, and TNF- α were detected in neurons 30 min after injury, indicating that the expression of these cytokines had declined sharply, returning to the baseline by 2 days after injury. This discrepancy of our data might be attributed to cross-sectional analysis of the inflammatory process or different types of nerve tissue injury/inflammation.

Conclusions

Unfortunately, we could not find a relationship between these three cytokines and the severity of the condition, symptom duration, or the duration of nerve root block. However, the concentration of IL-6 in the CSF was significantly higher in the patients with cervical myelopathy and lumbar radiculopathy than in the controls, suggesting that IL-6 is an indicator of neural damage.

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