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Clinical Study

Cytokine profile in degenerated painful intervertebral disc: variability with respect to duration of symptoms and type of disease

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Abstract

BACKGROUND CONTEXT: Neuroinflammation is supposed to play a crucial role in the generation of chronic pain. Numerous trials have documented the contribution of proinflammatory cytokines in the pathophysiology of pain associated with peripheral and central nociception. Local and systemic expressions of proinflammatory cytokines have been implicated as mediators of pain. Among these cytokines, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are especially notable because of their hyperalgesic impacts after nerve damage.

PURPOSE: The aim of the present study was to evaluate and compare the tissue levels of IL-1β, IL-6, interleukin-10 (IL-10), and TNF-α in subligamentous and free fragment types of degenerated intervertebral disc in acute and chronic periods.

STUDY DESIGN: This was a cross-sectional study.

PATIENT SAMPLE: A cross-sectional study was implemented on a total of 49 patients (24 women, 25 men) with an average age of 38.2±4.9 treated surgically by means of microdiscectomy.

OUTCOME MEASURES: Of these cases, 19 had complaints for less than 6 months, whereas 30 patients had been suffering from low back pain and leg pain for more than 6 months. Thirty-eight patients have been diagnosed with subligamentous type and 11 patients had free fragment type of disc degeneration.

METHODS: The levels of IL-1β, IL-6, IL-10, and TNF-α were assessed in tissue samples prepared from nucleus pulposus tissue obtained during microdiscectomy. Results were compared in patients with acute and chronic duration of complaints, as well as subligamentous and free fragment types of intervertebral disc degeneration.

RESULTS: The levels of IL-1β ($p<.001$), IL-6 ($p<.001$), IL-10 ($p<.001$), and TNF-α ($p<.001$) were significantly higher in patients with acute duration of complaints. Similarly, free fragment type of intervertebral disc degeneration displayed remarkably higher levels of IL-1β ($p=.009$), IL-6 ($p<.001$), IL-10 ($p=.024$), and TNF-α ($p=.017$) compared with the subligamentous type.

CONCLUSIONS: Inflammatory cytokines seem to have a more apparent role in intervertebral disc degeneration especially in acute period and in free fragment type. Further trials should be performed for elucidation of pathophysiology at the molecular level and the development of more effective diagnostic and therapeutic measures.

Keywords: Cytokines; Duration of symptoms; IL-1β; IL-6; IL-10; Intervertebral disc, degeneration; Low back pain; Nucleus pulposus; TNF-α

Introduction

The intervertebral disc (IVD) is an avascular and aneural tissue composed of a central gelatinous region called nucleus pulposus. A fibrous ring of highly organized collagen fibers termed annulus fibrosus surrounds it [1].

The primary functions of the IVD are shock absorption, stabilization, movement, and flexibility of the spine. These tasks can be fulfilled properly because of the appropriate composition and interaction of its nucleus pulposus and annulus

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EVIDENCE & METHODS

Context

While inflammatory cytokines are known to play a role in the degenerative process, their influence and role in various stages of disc degeneration remains to be defined. The authors sought to evaluate this using disc material from 49 patients with various stages of disc degeneration obtained during lumbar discectomy.

Contribution

The authors report that inflammatory cytokines play an important role in the degenerative process particularly in the acute period and in the presence of free disc fragments. Cytokines considered in this analysis included IL-1β, IL-6, IL-10 and TNF-α.

Implications

This study includes a small number of patients with limited heterogeneity in terms of the variety of disc degeneration present. In addition, disc material was only obtained following lumbar discectomy and this excludes the possibility of comparing the cytokines to normal in vivo controls. While the information presented is somewhat useful, it cannot characterize the changes in cytokines profiles over the course of the degenerative process. As the authors recognize, it is limited as a cross-sectional study. In light of these shortcomings the evidence presented here should be considered Level III.

—The Editors

fibrosus. If one or both of these structures bulge or migrate out of the normal intervertebral space, a herniated disc occurs. In case of a disc herniation, the protrusion from the disc may compress the nerve roots or the spinal cord itself, resulting in a variety of clinical symptoms [2]. The symptomatology linked with IVD degeneration that generates a painful sensation radiating into the leg is defined as sciatica [3]. The treatment modalities for sciatic pain consist of non-surgical measures (such as physiotherapy and medication) and surgery. Usually, the conservative therapy should be administered during the initial 6 to 8 weeks from the onset of symptoms. Increasing muscle weakness, alterations of the urinary bladder function, or opioid-resistant pain constitute absolute surgical indications [4]. It has been postulated that mechanisms other than pure mechanical compression may be responsible in the pathophysiology of sciatic pain in IVD degeneration [2].

Disorders of the IVD like herniation and chronic degenerative disease are frequently accompanied by acute or chronic pain. Degeneration of IVD is elicited by an impairment of the normal homeostatic mechanisms that favor the catabolic metabolism and subsequently result in loss of disc height. This process is a common entity that affects approximately 80% of adults at some stage of their life. The concept for pathophysiological basis of low back pain associated with IVD has recently changed. A more complex mechanism involving both mechanical and biochemical mechanisms has been considered rather than the assumption of a sole mechanical compression of the nerve root [5,6].

With respect to preoperative radiological findings derived from magnetic resonance imaging (MRI), IVD disease can be in the form of a sequestrated free fragment, a subligamentous disc sequestration, or disc protrusion [7].

Neuroinflammation is supposed to play a crucial role in the generation of chronic pain, and experimental studies have supported the contribution of proinflammatory cytokines to peripheral and central nociception [2,5]. Local and systemically expressed proinflammatory cytokines have been implicated as mediators of pain, and tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) were noteworthy for their hyperalgesic effects after neural injury [5]. Even though the role of TNF-α in painful disorders has been well demonstrated, scarce data exist on the functions of IL-1β, IL-6, and interleukin-10 (IL-10) in IVD degeneration.

To sum up, several publications had been made on the individual cytokine profiles distinguishing between acute and chronic painful conditions [1,2,5]. To the best of our knowledge, no reports have been published on the levels of cytokines for different pathologic types of disc disease. The aim of the present study was to evaluate and compare the tissue levels of IL-1β, IL-6, IL-10, and TNF-α in subligamentous and free fragment types of degenerated IVD in acute and chronic periods.

Patients and methods

This cross-sectional study was implemented in the neurosurgery department of our tertiary care center between February 2014 and August 2015. A total of 49 patients diagnosed with IVD degeneration who were scheduled for surgical treatment were included. Approval of local institutional review board and written informed consents were obtained before the start of the study. This trial was implemented in accordance with the principles in the Declaration of Helsinki and good clinical practice guidelines.

Samples of degenerate nucleus pulposus were derived from patients whose diagnoses and clinical examination findings had been confirmed by MRI. Patients who had been suffering from low back pain and leg pain were surgically treated. Microsurgical sequestrectomy was applied for herniated and degenerated discs with radiculopathy as the routine procedure, and all patients were operated for the first time. Samples were collected from nucleus pulposus in accordance with the description in previous literature [8]. Immediately upon collection, samples were stored at −80°C in liquid nitrogen.

The following were the exclusion criteria: age below 18 or above 65 years, previous diagnoses of systemic disease (diabetes mellitus, collagen vascular disease, and hepatic or renal insufficiency), and previous surgery for IVD degeneration. Healthy adults without a diagnosis of osteoporosis or