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Basic Science

Elevated levels of tumor necrosis factor-α and TNFR1 in recurrent herniated lumbar discs correlate with chronicity of postoperative sciatic pain

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Abstract

BACKGROUND CONTEXT: Sciatica is a condition characterized by radicular pain that can be secondary to a lumbar disc herniation (LDH). More than 10% of patients report persistent pain after surgery. The underlying mechanisms of postoperative sciatica remain unclear. There is evidence demonstrating that inflammation plays a role in the pathophysiology of sciatica.

PURPOSE: The study aimed to assess if the expression of tumor necrosis factor (TNF)-α and its receptors (TNFR) was correlated with the severity of pre- and postoperative leg pain in LDH patients who underwent single or multiple decompressive discectomies.

SETTING: This is an experimental prospective human study of intraoperative intervertebral disc (IVD) samples, as well as a clinical scores evaluation.

METHODS: We analyzed the mRNA and protein levels of TNF-α, TNFR1, and TNFR2 in IVD biopsies, and correlated them with visual analogue scale (VAS) scores 1 day before surgery to 6 weeks and 6 months postoperatively.

RESULTS: We evaluated the correlation between the inflammation in IVD with pre- and postoperative pain scores after discectomy in LDH patients operated for the first time (fLDH, N=12) and for recurrent cases (rLDH, N=8). This analysis showed that TNF-α and TNFR1 mRNA levels were significantly greater in rLDH patients; there was a twofold increase for TNF-α and a 50% increase for TNFR1. Similarly, protein levels in IVD samples positively correlated with postoperative VAS scores, whereas TNFR2 protein levels negatively correlated with postoperative VAS scores.

CONCLUSIONS: These findings indicate that rLDH patients present higher postoperative VAS scores compared with fLDH patients, and also that these scores are correlated with increased inflammation and may contribute to pain chronicity.

Keywords: Discectomy; Intervertebral disc; Lumbar disc herniation; Sciatica; TNF-α; Neuroinflammation; Chronic pain; Pain; TNF-α receptors; Leg pain

FDA device/drug status. Not applicable.

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Introduction

Sciatica is a condition characterized by radicular pain along the trajectory of the sciatic nerve. The symptoms responsible for this condition arise as a consequence of a single or multiple disc herniations that compress the nerve roots. This condition represents one of the leading causes of chronic pain in adults, with a lifetime incidence of up to 40%, representing a major socioeconomic burden [1]. Epidemiologic studies have demonstrated that the majority of sciatic pain episodes resolve spontaneously or with the help of conventional analgesics and physiotherapy [2,3]. However, in cases where the symptoms persist for more than 6–8 weeks, different approaches are considered for treatment [4]. In cases where the pain is attributed to lumbar disc herniation (LDH), decompressive discectomy is considered one of the best options to relieve the constriction and alleviate the pain. However, the sole mechanical compression of a prolapsed disc cannot explain in all cases the pathogenesis of sciatic pain. More than one in ten patients report a chronic-intractable pain after undergoing single or multiple surgeries to remove the affected disc [5]. These unsuccessful cases suggest that other mechanisms may play an important part in the pathogenesis of chronic sciatic pain.

Inflammation has largely been considered an important factor in the modulation of pain. This concept is based on a large body of preclinical and clinical evidence demonstrating the nociceptive action of proinflammatory cytokines on nervous tissue [6–10]. Among these agents, tumor necrosis factor (TNF)-α has been shown to be a key player in the development and maintenance of pain [11,12]. In addition, in recent years, the participation of both TNF-α receptors (TNFR), TNFR1 and TNFR2, has been associated in pathways that can affect pain sensation [13,14]. After TNF-α stimulation, these TNFRs have been shown to activate independent opposite mechanisms that ultimately result either in apoptosis for TNFR1 or in cell survival for TNFR2 [15]. However, the participation of TNF-α and TNFR as modulators in the generation of pain is not fully understood. In addition, how these different intracellular pathways can influence the severity of pain in patients still remains unclear.

In a previous study from our group, we provided evidence that the presence of TNF-α in disc biopsies from patients operated for LDH could predict the outcome after surgery [16]. Furthermore, increased TNFR1 and decreased TNFR2 levels in these disc biopsies were associated with increased postoperative pain scores. The aim of the present study was to assess if the expressions of TNF-α and TNFR were correlated with the severity of pre- and postoperative leg pain in LDH patients who underwent single or multiple decompressive discectomies. The study also aimed to investigate if TNF-α and TNFR expressions are associated with surgery-resistant cases in regard to chronic pain sensation.

Methods

The ethics committee of Maastricht University Medical Center approved all human procedures included in the study, and informed written consent was obtained from each individual.

Patients and biopsy collection

Patients were diagnosed with LDH after neurologic examination and confirmation of the affected disc level as seen on magnetic resonance imaging. Patients included in the present study suffered from a ruptured sequestered disc; for this purpose, all radiological findings were corroborated intraoperatively. Patients have had leg pain for at least 3 months before undergoing elective spinal surgery. In total, 20 patients with a single-level disc herniation were included in the study. The study has two groups: Group 1 consisted of 12 patients who underwent surgery for LDH for the first time (fLDH), and Group 2 consisted of 8 patients who underwent surgery for LDH for the second time at the same disc level (recurrent cases, rLDH). The latter was considered as recurrent herniation because an unsatisfactory pain outcome was present over 1 year after the previous operation. All rLDH cases benefited from the first surgical procedure initially for a period of 6 months postoperatively, but after 1 year reported scores that were similar to those reported before the first surgery. In all cases, a partial discectomy without laminectomy or hemilaminectomy was initially performed. Patients who had previously undergone spinal surgery for another indication were excluded. Patients had anti-inflammatory medications suspended for at least 1 week before the surgery, and none of the patients received steroid injection for at least 3 months before the procedure. Intraoperative intervertebral disc (IVD) biopsies were collected from each patient during surgery, and were immediately frozen in liquid nitrogen and then stored at −80°C.

Pain score

Patients were evaluated using visual analogue scale (VAS) scores (0=no pain; 10=worst pain ever experienced) to measure their level of leg pain at different pre- and postoperative time points. The scores were recorded 1 day before the operation, and 6 weeks and 6 months after the surgery. In all patients, the leg pain was considered as secondary to a single-disc herniation involvement. As in our previous studies, the cutoff to differentiate patients with good recovery from patients with poor recovery was established a priori at a VAS score of 3.5 out of 10 [16].

Quantitative polymerase chain reaction (qPCR)

All tissue biopsies were cut into two equal parts: one for Western blot analysis (see below) and one for quantitative polymerase chain reaction. A detailed description of the qPCR technique has been reported previously [16]. In brief, total RNA was extracted using the reagent TRIzol (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. One microgram total RNA was reversely transcribed to cDNA using the First Strand cDNA Synthesis Kit (Fermentas International