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Gadolinium enhancement in newly diagnosed patients with lumbar disc herniations are associated with inflammatory peridiscal tissue reactions – Evidence of fragment degradation?

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ABSTRACT

Objective: It is debatable whether a local inflammatory tissue response caused by herniated disc material contributes to sciatic pain and/or sensorimotor deficits. The impact of inflammatory changes on local tissue remodelling, the healing process and the clinical course of disease remains unclear.
Methods: In this prospective observational study, we included a total of 31 patients with a single-level, unilateral lumbar disc herniation. The diagnosis was confirmed by magnetic resonance imaging (MRI) ± gadolinium. The presence of peridiscal contrast enhancement was correlated with the extent of inflammatory reactions in the herniated fragments as confirmed by immunohistochemistry; clinical symptoms, including the duration of radicular pain; and the incidence of sensorimotor deficits.
Results: Peridiscal contrast enhancement was found in 17 patients (55%) and was encasing the adjacent rootlet in 4 cases. There was no significant correlation between gadolinium uptake and the presence of sensorimotor deficits or the duration of radicular symptoms. Degenerative changes were observed in all 31 disc specimens. Overall, 18 cases exhibited increased cellularity in the marginal areas, which were mostly populated by $CD68^+$ macrophages and fibroblasts. Additionally, these areas displayed a limited number of $CD3^+$ T-lymphocytes and different degrees of concomitant neovascularisation, which represented a chronic and unspecific immune response. Peridiscal contrast enhancement on MRI was significantly correlated with the histopathological characteristics of tissue inflammation. However, no correlation was found between the histological evidence and the degree of inflammation and neurological symptoms.
Conclusion: Gadolinium-enhanced MRI is a sensitive method to detect unspecific inflammatory reactions in therapy-naïve disc herniations. However, the neuroradiological and histological evidence of peridiscal inflammation was not correlated with the severity of pain or sensorimotor deficits in our patients. Additional research is needed because the occurrence of local inflammation may indicate an ongoing degradation of herniated fragments and thus be helpful in therapeutic decision-making.

1. Introduction

Despite its high prevalence and significant socio-economic impact, the causes of radicular pain in a lumbar disc herniation and the endogenous mechanisms that affect the natural course of the disease are not sufficiently understood. The mechanical concept of nerve root damage by a disc prolapse (considering that compression and a deformation of the radix are the underlying

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causes of sciatica) has been widely accepted for several decades [1]. However, some authors have proposed that local inflammation associated with the herniated disc is a significant additional factor that leads to pain and neurological deficits by inducing inflammatory radiculopathy. In addition, this inflammation may induce tissue remodelling and repair [2,3]. Therefore, detecting inflammation may have clinical and prognostic merit in patients who suffer from lumbar disc herniations. Viable disc tissue is directly involved in macrophage recruitment, whereas devitalised annulus fibrosus and nucleus pulposus tissue does not initiate an inflammatory response [4].

Gadolinium-DTPA (Gd)-enhanced herniated disc material, as seen on preoperative magnetic resonance imaging (MRI), represents epidural vascularised granulation tissue [2,5], which has an additional inflammatory impact on the compressed nerve root. Several studies have demonstrated a correlation between peridiscal Gd enhancement adjacent to the nerve root in previous non-operated lumbar disc herniations and the duration of sciatic symptoms [5] and sensorimotor deficits [6]. However, the presence of an inflammatory tissue reaction as the underlying cause of Gd uptake and its specific characteristics were not confirmed by histological data in these studies.

In contrast, the prognostic significance of a peridiscal inflammatory reaction was not associated with patient history and neurological findings in studies that confirmed inflammation by a histological workup of herniated disc tissue. A statistically significant correlation has not been found between the incidence of motor weakness, sensory deficits and the duration of radicular symptoms [3,7,8]. To the best of our knowledge, only two studies have reported on a systematic histological investigation of surgically removed Gd-enhanced and nonenhanced lumbar disc herniations [9,10].

Despite these studies, it remains unclear whether a focal inflammatory tissue reaction in therapy-naïve patients with lumbar disc herniations has clinical significance or prognostic merit.

In this study, we hypothesised that there may be associations between the appearance of Gd enhancement in preoperative lumbar MRI, the histopathological characteristics/quantification of presumed inflammatory tissue reactions, and the severity of neurological symptoms, such as pain and paresis.

2. Patients and methods

2.1. Patient characteristics

In this prospective single centre study, a total of 31 patients who had a single-level unilateral lumbar disc herniation with displacement of the nerve root underwent surgery. At the time of patient inclusion and data acquisition all authors worked at the University of Cologne, except for L.L. and F.B. The diagnosis was confirmed by preoperative MRI ± Gd. Indications for surgery were intractable or chronic radicular pain and substantial or progressive paresis. The exclusion criteria included previous spinal surgery, chemonucleolysis, periradicular infiltrations, a history of spinal inflammatory disease, an elevated blood leucocyte count and elevated C-reactive protein levels before surgery. The duration of radicular pain and the presence of paresis, sensory impairment and radiating pain on straight leg raise were recorded during the standardised preoperative neurological examination.

The type of disc displacement, i.e., a contained herniation (an extrusion of disc material through the annulus but not through the posterior longitudinal ligament) or a perforated herniation (an extrusion of disc material that perforated the annulus and the posterior longitudinal ligament) was determined during surgery. Our prospective observational study was performed according to the Declaration of Helsinki.

2.2. Magnetic resonance imaging

All of the MRI studies were performed using 1.5 T scanners and included sagittal and axial T1- and T2-weighted images to depict the relevant disc pathology. Gd-DTPA was administered at a dose of 0.2 ml per kg of body weight in every patient.

The absence or the presence of Gd enhancement and the type of enhancement were assessed by comparing precontrast and postcontrast T1-weighted images. Image interpretation was performed retrospectively in a blinded fashion by an experienced neuroradiologist.

2.3. Tissue sampling and processing

During the surgery, portions of the disc herniations that faced the epidural space and corresponded to the area of Gd uptake were identified and collected for further histological and immunohistochemical work-up. When enhancement was not observed, the marginal fragments of the disc prolapse that were in contact with the spinal dura were obtained and processed in the same manner.

The samples were fixed in 4% formaldehyde and embedded in paraffin blocks. All of the specimens were processed equally. Four-micrometre paraffin sections were stained with haematoxylin and eosin (HE). For immunohistochemistry, 4-μm paraffin sections were prepared for the demonstration of CD68 (macrophages), leucocyte common antigen (LCA), CD20 (B lymphocytes), CD31 (vascular endothelium), smooth muscle actin (SMA) (all from DAKO, Hamburg, Germany), and CD3 (T lymphocytes) (DCS, Hamburg, Germany).

Immunohistochemistry was performed using the avidin–biotin complex technique with the Ventana iVIEW ABC Kit (Ventana, Illkirch, France) and appropriate biotinylated secondary antibodies. The peroxidase reaction product was visualised using 3,3′-diaminobenzidine (Sigma, Munich, Germany) as chromogene and H_2O_2 as cosubstrate with a Benchmark XT Immunostainer (Ventana). The sections were counterstained with haematoxylin. The omission of primary antibodies in the control experiments resulted in the expected absence of any cellular labelling. To determine the extent of macrophage infiltration and/or neovascularisation in a semiquantitative fashion, all of the disc samples were examined independently by two experienced neuropathologists and were classified into the following grades: grade 0 for the absence of macrophage infiltration/neovascularisation, grade 1 for minor macrophage infiltration/neovascularisation, grade 2 for moderate macrophage infiltration/neovascularisation and grade 3 for dense macrophage infiltration/neovascularisation.

2.4. Statistical analysis

The results were expressed as the median values [25–75% percentile]. In several cases, the full range was additionally presented. For non-parametric comparisons of the different groups, we used Fisher's exact test for the nominal variables and the Mann–Whitney *U* test for ordinal and metric variables. Correlations between the different parameters were analysed using Spearman's correlation coefficient. $P < 0.05$ was the level of significance. The statistical analyses were performed using SPSS for Windows (SPSS, Surrey, UK).

3. Results

3.1. Demographic and clinical characteristics of the patients

The median age of the 31 patients enrolled in this study was 54 years [39–67 years]. Twelve patients were female. The median duration of radicular symptoms was 4 weeks [2–14 weeks] (full