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# Macrophage Tissue Infiltration, Clinical Symptoms, and Signs in Patients with Lumbar Disc Herniation. A Clinicopathological Study on 179 Patients

**R. Rothoerl**[1], **C. Woertgen**[1], **M. Holzschuh**[1], **K. Brehme**[2], **J. Rüschoff**[3] and **A. Brawanski**[1]

[1] Department of Neurosurgery, University of Regensburg, Germany
[2] Department of Anaesthesiology, University of Regensburg, Germany
[3] Department of Pathology, University of Regensburg, Germany

## Summary

It is postulated that in addition to nerve-root compression, an inflammatory stimulus of the herniated lumbar disc is responsible for sciatic pain and radiculopathy. The clinical relevance of the histologically described inflammatory infiltrates is, however, not clearly defined [8, 22]. It was the aim of this study to assess the clinical relevance of inflammatory cells in herniated lumbar disc specimens. The presence of inflammatory cells was examined immunohistochemically in routinely processed resection specimens of the lumbar disc. The histological results were compared to prospectively obtained clinical data. Disc specimens of 179 patients who underwent surgery for lumbar disc herniation were studied immunohistologically. Preoperatively each patient received a visual analogue scale for classification of the pain level and general clinical data were recorded prospectively. Varying amounts of inflammatory cells could be demonstrated in the resected disc tissue. In the statistical workup no statistically significant correlation between the histological evidence of macrophage infiltrates and the pain grading scale or the clinical data could be found.

In our study there is no statistically significant correlation between macrophage infiltrates in herniated lumbar disc specimen and the obtained clinical data.

*Keywords:* Lumbar disc herniation; inflammation; sciatic pain.

## Introduction

The pathogenesis of sciatica with lumbar disc herniation is not yet clearly defined. Mixter and Barr suggested that tissue of the intervertebral disc protruded into the spinal canal compresses thereby irritating the nerve root and causing sciatic pain [17] Although this concept is widely accepted, the mechanical nerve root compression itself does not explain sciatic pain and radiculopathy alone [11, 21]. Several authors [7, 8, 13, 16, 24, 32] state that inflammation of the nerve root and or intervertebral disc tissue may be a major factor in radiculopathy and sciatic pain. Animal studies have shown that nucleus pulposus could promote the inflammatory phenomenon in the nerve roots. Additionally a local release of biochemical agents or the antigenicity of the disc tissue itself might account for nerve root inflammation and thus for radiculopathy and sciatic pain [19, 1, 15]. It has been suggested that the herniated nucleus pulposus would induce a foreign body reaction when exposed to the systemic circulation [30]. This foreign body reaction is thought to result in a macrophage infiltration in the herniated lumbar disc [28].

However less is known about the clinical significance of this phenomenon. The aim of this study was to compare pre-operatively obtained clinical data of patients pain ratings to immunohistochemical findings in herniated lumbar disc tissue.

## Method and Patients

In this prospective study, intervertebral disc specimens of 179 patients were studied. All patients underwent surgery for monosegmental lumbar disc herniation for the first time. The standard operation procedure was a conventional discectomy via an extended interlaminar fenestration. All patients showed nerve root compression intra-operatively. The complete material was embedded and processed further. The weight of the resected tissue was not estimated. A decalcification procedure was not necessary due to only a small amount of bony structures in some specimens. Due to the routinely performed specimen fixation and paraffin-embedding, the exact topographical relationship between specimen and nerve root could not be specified. 61 patients were female and 118 male. The mean age was 43 years with a range from 23 to 76 years. One to two days prior to surgery each patient received a visual analogue rating scale (VAS, 0 = no pain, to 100 = worst pain patient could imagine) for the classification of the individual pain level. The patients were asked to describe the average pain over the last few weeks without considering how the pain was distributed. General clinical data, such as level of disc herniation, reflex deficit, length of symptoms, paresis, sensory deficit, pain distribution, straight-leg raising test, were recorded.

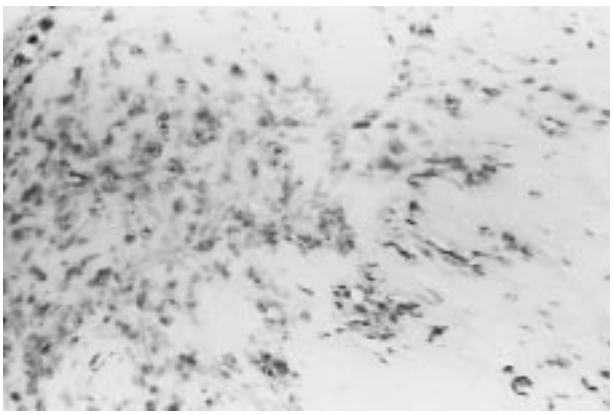

Fig. 1. Example for a CD68 positive infiltrate

Systemic inflammation was ruled out by obtaining erythrocyte sedimentation rates, white blood counts and c-reactive protein.

The herniated disc specimens were routinely fixed in a 10 percent buffered formaline solution and paraffin-embedded, 5 µm thin sections were stained with monoclonal antibodies obtained commercially from Dako A/S Denmark using an indirect immunoperoxidase method: Antihuman macrophage antibody (Dako CD 68), Positive and negative control tissue was used in each staining procedure. The immunohistochemical staining was performed according to the recommendations of the manufacturer [14].

The specimen were microscopically examined and classified blindly by two examiners independently of each other. According to the amount of inflammatory cells, specimens with no or only solitary positive cells were classified as showing no evidence for inflammation. All specimens in which cellular infiltrates could be observed were classified as confirming inflammation. See Fig. 1.

Clinical data as well as the results of the pain grading scale were statistically correlated with these groups.

The statstical workup was performed by using the computer programs StatView 4.5® and SuperANOVA$^{TM}$®, especially the Fisher's Protected Least Significant Difference post hoc test, Scheffe and Bonferroni/Dunn test.

## Results

### *History, Symptoms and Signs*

Between the patients showing no infiltrate in their specimens and the patients showing a positive macrophage infiltrate, no difference concerning erythrocyte sedimentation rates, white blood counts and c-reactive protein could be demonstrated. 9 Patients rated their pre-operative pain on the visual analogue rating scale between 0% and 25%, 17 between 26 and 50%, 62 between 51% and 75%, and 82 between 76% and 100%. For details and other symptoms and signs see Table 1.

### *Comparison Toimmunohistochemical Data*

Varying amounts of inflammatory cells could be demonstrated in the resected disc tissue. According to the classification 43% [77] of the specimen were classified as showing evidence of inflammation. 102 specimens (57%) showed no or only solitary positive cells in the CD68 macrophage staining. No significant difference between these two groups concerning age, sex, length of pre-operative symptoms, pre-operative pain distribution, straight leg sign, paresis and level of pain on the visual analogue grading scale (VAS) on admission could be found. For details see Table 1.

## Discussion

Several authors state that inflammation in disc tissue resulting from injury may be a major factor in radiculopathy and sciatic pain [3, 7, 8, 12, 13, 16, 24, 25, 29, 32].

The intra-operative finding that mechanically com-

Table 1. *Preoperative Clinical Findings*

| Parameter | No inflammation | Inflammation | Total | Significance |
|---|---|---|---|---|
| Mean age in years | 43 | 44 | 43 | n.s. |
| Women | 30% | 39% | 34% | n.s. |
| Men | 70% | 61% | 66% | n.s. |
| Mean duration of symptoms | 79 days | 63 days | 72 days | n.s. |
| Range duration of symptoms | 1–731 days | 1–295 days | 1–731 days | n.s. |
| Sensory deficit | 89% | 83% | 86% | n.s. |
| Paresis | 63% | 57% | 60% | n.s. |
| Negative SLR | 10% | 13% | 11% | n.s. |
| SLR $\geq 30°$ | 31% | 30% | 30% | n.s. |
| SLR $< 30°$ | 59% | 57% | 59% | n.s. |
| VAS O-25 | 1% | 3% | 2% | n.s. |
| VAS 26–50 | 10% | 16% | 13% | n.s. |
| VAS 51–75 | 30% | 28% | 29% | n.s. |
| VAS 76–100 | 59% | 53% | 56% | n.s. |
| Smokers | 39% | 39% | 39% | n.s. |
| Hyperuraecemia | 9% | 16% | 11% | n.s. |
| Diabetes | 8% | 13% | 10% | n.s. |

*VAS* Means the rating on the visual analogue rating scale; *SLR* means straight leg raising test.

pressed nerve roots become tender [2, 11, 26] and recent histological and biochemical studies on herniated lumbar disc tissue led to the notion of inflammatorily induced sciatic pain [3, 7, 8, 12, 13, 16, 24, 25, 29, 32]. A recent study supports that nucleus pulposus itself may have inflammatogenic properities [28]. But there seem to be different mechanisms of nerve root injury [4]. One is induced by the nucleus pulposus itself and the other is induced by chronic compression and irritation of the nerve root, both seem to differ from each other according to the mode and composition of the histochemical reactions [4].

In most studies, a cellular reaction composed of macrophage and T-lymphocyte tissue infiltration has been described, since herniated lumbar discs are usually operated on in the more chronic state. Compared to other inflammatory tissues [9] in the early stages, a neutrophil-infiltration and, in the chronic stages, a macrophage dominated immuno-reaction could be expected [8, 28].

Groenblad *et al.* studied 24 patients. By using immunohistochemical methods, inflammatory cells such as macrophages, T-lymphocytes, B-lymphocytes and neutrophils were distinguished. The inflammatory infiltrate was mainly composed out of macrophages. It was not indicated whether the clinical material in question was obtained prospectively or retrospectively. Due to the small number of disc materials examined the authors could only point out some trends concerning clinical data and inflammatory cell occurrence. A statistically significant correlation between clinical data and immunhistologically verified infiltrates could not be found [8].

Doita *et al.* found granulation tissue in herniated lumbar disc specimen in 14 of 21 patients (66.7%). They found no correlation between inflammatory changes and duration of symptomś. Other symptoms and signs were not compared [5].

Virri *et al.* studied macrophages in 20 herniated and protuded lumbar disc specimen. The authors found macrophages in 55% of the specimen. Only the duration of the pre-operative symptoms were compared in both groups. A statistically significant correlation could not be found [31].

Our experience with herniated lumbar disc specimen of 44 patients and prospectively obtained clinical data show that the inflammatory infiltrate is mainly composed of macrophages. B- and T Lymphocytes could only be observed in specimen with positive CD 68 macrophage stains. In the patients with no macrophage infiltrates in the herniated lumbar disc tissue the straight-leg raising test was statistically positively significant at lesser degrees. But this might simply be a chance observation [20].

However, to our knowledge there is no detailed prospective study, which compares pre-operative symptoms and signs to the evidence of macrophage infiltrates in herniated lumbar disc specimen in a larger population.

Due to our previous experience only macrophage stains were made in the present study. We could confirm macrophage infiltrates in 43% (77) of the 179 herniated lumbar disc specimen. Although in earlier studies the clinical importance of the inflammatory changes in herniated lumbar disc tissue is pronounced [8, 22, 24] we could not find any statistical correlation with the clinical data. In our opinion there seems to be no clinical significance of the well described phenomenon of the macrophage tissue infiltration in herniated lumbar disc tissue.

## Conclusion

The findings of the present study support the observations of an inflammatory reaction in herniated lumbar disc specimens [6, 16, 22].

A correlation between the macrophage tissue infiltration and the pre-operative symptoms and signs as well as the patients' pain ratings could not be found.

In our opinion there seems to be no correlation of the well described phenomenon of the macrophage tissue infiltration in herniated lumbar disc tissue to preoperatively obtained data.

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## Comments

This paper, documents in a prospective manner that the degree of "clinical pain" and frequency of inflammatory cells in lumbar disc tissue has no correlation. The clinical relevance of inflammatory cells in lumbar disc specimens is thus still a matter of dispute. The "negative" conclusion is absolutely of interest.

*J. Haase*

The authors have investigated in a prospective study 179 patients undergoing surgery for lumbar disc herniation. Macrophage (CD68+) infiltration of resected tissue was conelated with clinical data, in particular the individual pain level.

This work was stimulated by previous studies which revealed abundant macrophage infiltration of herniating disc tissue (Gronblad M *et al* (1994) Spine 19, p 2744) and suggested biochemical in addition to mechanical factors as inflaming stimuli (Olmarker K *et al* (1995) Spine 20, p 665. Saal JS (1995) Spine 20, p 1821).

The authors did not find any statistical correlation between histological findings and the clinical parameters. The study does not really provide novel information on this clinically relevant issue, compared to their previous study.

It would also be of interest to analyse a potential relationship between inflammatory reactions in lumbar disc tissue and the development of postdiscectomy syndromes.

*O. Wiestler*

*Authors' Reply*

In a previous study only 44 patients were included. A sufficient statistical analysis could not be performed due to the small number of patients. Therefore this previous report describes only preliminary results. In the present study 179 patients were included. A sufficient statistical analysis is now performed. In the literature there is no study published which compares clinical material and immunohistochemical findings in a prospective manner in a larger population.

Concerning the reviewers comment that a relationship between inflammatory reactions in lumbar disc tissue and the development of postdiscectomy syndromes would be interesting.

We agree that a follow up study would be of interest. However the aim of this study was to assess the clinical relevance of inflammatory cells in herniated lumbar disc specimens concerning pre-operatively obtained clinical data. This correlation was suggested in previous studies (e.g. Groenblad 1994). A follow up study would be beyond the scope of this article.

Correspondence: Ralf D. Rothoerl, M.D., Department of Neurosurgery, Klinikum der Universität Regensburg, Franz Josef Strauss Allee 11, 93053 Regensburg, Germany.