

Reijo Autio

MRI OF HERNIATED NUCLEUS PULPOSUS

*CORRELATION WITH CLINICAL FINDINGS,
DETERMINANTS OF SPONTANEOUS RESORPTION
AND EFFECTS OF ANTI-INFLAMMATORY
TREATMENTS ON SPONTANEOUS RESORPTION*

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REIJO AUTIO

**MRI OF HERNIATED NUCLEUS
PULPOSUS**

Correlation with clinical findings, determinants of
spontaneous resorption and effects of anti-
inflammatory treatments on spontaneous resorption

Academic Dissertation to be presented with the assent of
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Abstract

The purpose of the current study was to evaluate the intercorrelations of magnetic resonance imaging (MRI) findings and clinical symptoms and signs in sciatic patients. Furthermore, determinants of spontaneous HNP resorption and the effect of anti-inflammatory treatments (periradicular methylprednisolone injection and intravenous infliximab) on spontaneous HNP resorption were evaluated.

MRI follow-up was performed at baseline, after two months, after six months and after one-year for patients with unilateral sciatica to evaluate determinants of spontaneous HNP resorption and the effect of periradicular methylprednisolone injection on spontaneous HNP resorption. At baseline the study population consisted of 160 patients (group A).

MRI follow-up for 21 patients with unilateral sciatica was performed at baseline and after two weeks, after three months and after six months to evaluate the effect of infliximab, a monoclonal TNF α antagonist, infusion on spontaneous HNP resorption (group B).

Patients in group A were randomized to receive either periradicular saline or methylprednisolone. Volume of HNP, extent and thickness of enhancement (in Gd-DTPA MRI) and degree of disc displacement were measured and the symptoms and signs were followed repeatedly.

The extent of rim enhancement correlated significantly with the degree of disc displacement. The duration of sciatic symptoms correlated negatively with enhancement parameters. The clinical symptoms did not correlate significantly with the different enhancement parameters or disc herniation volume. Achilles reflex abnormality correlated significantly with all enhancement parameters for lesions at L5-S1.

Significant decrease in HNP volume occurred from baseline to two months, and even more so during the whole one year follow-up period. Higher baseline scores of rim enhancement thickness, higher degree of HNP displacement in the Komori classification and age category of 41-50 years were associated with a higher resorption rate. Clinical symptoms alleviation occurred concordantly with a faster resorption rate.

No significant difference was noted in the decrease of HNP volume in the saline and methylprednisolone injection groups in follow-up imaging during one year. The enhancement parameters (thickness and extent of rim enhancement) did not differ significantly in the different treatment groups.

In group B, 11 patients received intravenous infliximab and 10 saline. Baseline demographic data, pain scores, and clinical status, did not differ between the treatment groups. HNP volume decreased significantly in both groups ($P < 0.01$). There was no significant difference in HNP volume changes between the treatment groups. By two weeks, enhancement thickness increased significantly in the infliximab compared placebo group ($p = 0.003$). Two patients in each group required back surgery prior to the 6-month assessment.

Keywords: gd-DTPA enhanced MRI, herniated nucleus pulposus, intervertebral disc, magnetic resonance imaging, resorption of disc herniation, sciatica

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Abbreviations

AF	annulus fibrosus
ALL	anterior longitudinal ligament
ANCOVA	analysis of covariance
bFGF	basic fibroblast growth factor
BMI	body mass index
χ	chi
C5a	complement system factor 5a
cd	compact disc
C.I.	confidence interval
cm	centimetre
CSF	cerebrospinal fluid
CT	computed tomography
Δ	delta
DRG	dorsal root ganglion
DTPA	diethylenetriaminepentaacetic acid
EP	end plate
FOV	field of view
FSE	fast spin echo
Gd	gadolinium
GE	gradient echo
GM-CSF	granulocyte –macrophage colony-stimulating factor
HNP	herniated nucleus pulposus
HIZ	high intensity zone
HIV	human immunodeficiency virus
Ig	immunoglobulin
IL	interleukin or Illinois
I.V.	intravenous
IVD	intervertebral disc
κ	kappa
kg	kilogram
L	lumbar disc level

LBP	low back pain
LTB4	leucotriene B4
MCP	monocyte chemoattractant protein
mg	milligram
mm	millimetre
mm ²	square millimetre
mm ³	cubic millimetre
MMP	matrix metalloproteinase
MR	magnetic resonance
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
N	number of patients
NEX	number of excitations
NSAID	non-steroidal anti-inflammatory drug
NO	nitric oxide
NP	nucleus pulposus
P	statistical significance
PG	proteoglycan
PGE2	prostaglandine 2
PLA	phospholipase
PLL	posterior longitudinal ligament
PMN	polymorphonuclear
RCT	randomized controlled trial
RF	radiofrequency
ROC	receiver operating characteristics
ROI	region of interest
S	sacrum
SD	standard deviation
SE	spin echo
Sig.	significance
SLR	straight leg raising
SNR	signal to noise ratio
SPSS®	statistical package for the social sciences
T	tesla
T1	longitudinal relaxation time
T2	transverse relaxation time
TE	time of echo
TGF	tumor growth factor
TNF α	tumor necrosis factor alpha
TR	repetition time
US	ultrasound
USA	United States of America
VAS	visual analog scale
VEGF	vascular endothelial growth factor
vs.	versus
W	weighted

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Autio RA, Karppinen J, Kurunlahti M, Kyllönen E, Vanharanta H, Tervonen O (2002): Gadolinium Diethylenetriaminepentaacetic Acid Enhancement in Magnetic Resonance Imaging in Relation to Symptoms and Signs among Sciatic Patients. *Spine* 27:1433–1337.
- II Autio RA, Karppinen J, Niinimäki J, Ojala R, Kurunlahti M, Haapea M, Vanharanta H, Tervonen O (2006): Determinants of Spontaneous Resorption of Intervertebral Disc Herniations. *Spine*, in press.
- III Autio RA, Karppinen J, Kurunlahti M, Haapea M, Vanharanta H, Tervonen O (2004): Effect of Periradicular Methylprednisolone on Spontaneous Resorption of Intervertebral Disc Herniations. *Spine* 29:1601–1607.
- IV Autio RA, Karppinen J, Niinimäki J, Ojala R, Veeger N, Korhonen T, Hurri H, Tervonen O (2006): Effect of Infliximab, a Monoclonal Antibody against TNF α , on Spontaneous Resorption of Intervertebral Disc Herniations: a randomized controlled study. *Spine*, in press.

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1 Introduction

Herniated nucleus pulposus (HNP) often causes back pain and radicular leg pain, i.e., sciatica. Lumbar disc syndrome, defined as herniated disc or typical sciatica, was diagnosed in 5% of men and 4% of women in a large Finnish survey (Heliövaara *et al.* 1987a). The incidence of herniated lumbar disc or sciatica increased clearly after the age of 19 years according to a Finnish longitudinal birth cohort study (Zitting *et al.* 1998). Unfortunately, the cause of low back pain remains unknown in 70% of primary health care patients (Grönblad 2005). Although there is no single test or clinical finding specific to disc-induced back pain, it is suggested that herniated intervertebral disc is responsible for about 40% of prolonged back pain cases (Schwarzer *et al.* 1995).

Lumbar intervertebral disc herniation is by far the commonest reason for sciatic symptoms, but asymptomatic disc herniations are known to exist. It is also known that disc herniation is not always the reason for sciatica, which has led to the search for molecular transmitters affecting the nerve roots and/or dorsal root ganglions. Tumor necrosis factor alpha (TNF α) is considered the main inflammatory candidate (Olmarker & Larsson 1998, Igarashi *et al.* 2000). It appears that the interaction of activated macrophages with herniated disc tissue leads to the generation of inflammatory cytokines such as TNF α , which in turn are required for the induction of angiogenesis-inducing molecules such as vascular endothelial growth factor (VEGF) and matrix-degrading enzymes such as metalloproteinases and plasmin (Haro *et al.* 2002, Kato *et al.* 2004).

Most lumbar disc herniations regress in size within months. Histological samples have verified the presence of neovascularization and inflammatory cells such as macrophages in the herniated disc tissue. The clinical symptoms of sciatica mostly have a benign course, although residual sciatic or back pain symptoms are not uncommon.

In addition to the usual anti-inflammatory oral medication, methylprednisolone and other corticosteroids are also used to treat low back disorders, mostly by periradicular injection (Gupta *et al.* 1996). Recently, TNF α inhibitors have been introduced as potential therapeutic modalities for HNP-induced sciatica (Karppinen *et al.* 2003). Since only a fraction of patients with HNP need surgery, there is great interest in the effect of various treatments on HNP regression, which is thought to correlate with favorable clinical outcome. Conservative treatments are generally aimed at relieving pain and minimizing disability in the early phases, in the hope that the disease has a favorable course on its own.

However, there is little knowledge about the effects of anti-inflammatory medications on HNP resorption.

Magnetic resonance imaging (MRI), using contrast enhanced T1W fat saturated sequences, enables us to study neovascularization in vivo. The increasing emphasis on inflammation in the etiology of sciatica and the newly introduced concept of rim enhancement around HNP raise doubts about whether the full potential of MRI imaging has been used in the prognostic evaluation of herniations. In the present thesis, the objectives were to evaluate MRI findings with and without gadolinium (Gd) enhancement in the diagnostics of sciatica and as prognostic signs of good spontaneous resorption of HNP. A further aim was to evaluate the effect of some anti-inflammatory treatments (periradicular corticosteroid injection and intravenous infusion of infliximab, a monoclonal antibody against $\text{TNF}\alpha$) on spontaneous HNP regression.

2 Review of the literature

2.1 Anatomy of the intervertebral disc and adjacent structures

2.1.1 Intervertebral disc

Intervertebral disc (IVD) is a flexible structure between bony vertebral bodies. Flexibility of the spine is dependable on disc's ability to reshape according to spine movements. IVD is composed of gelatinous nucleus pulposus (NP) in the centre and lamellar anulus fibrosus (AF) encircling it. Thin vertebral endplates cover the disc lying against vertebral body. (Eyre & Muir 1976, Buckwalter 1995, Antoniou *et al.* 1996.) Normal NP consists of a core of a well-hydrated proteoglycan (PG) matrix in a loose, irregular collagen fiber meshwork. Water can account for over 80% of the weight of NP in children and young adults. Collagen II is the major collagen of human NP (~80%) but collagens VI (~15%), IX (~1–2%), XI (~3%) and III (<1%) have also been found. (Eyre & Muir 1977, Hukins 1988, Buckwalter 1995.)

The AF is a lamellar structure of 10–20 concentric layers of collagen fiber bundles that are 0.14–0.52 mm thick. The total disc height contains 20 to 62 fibre bundles. The fibre bundles are perpendicular in successive layers. Average interbundle space is 0.22 mm wide and is filled with a gelatinous material. The structure of anulus is highly irregular and 40% of the layers are incomplete in any 20° circumferential segment of the disc. (Marchand & Ahmed 1990.) Tsuji *et al.* have noted irregular laminate structure in the posterior parts of the AF, with greater proportion of incomplete laminar layers, increased fiber interlacing angle and loose interlaminar connections (Tsuji *et al.* 1993). The outer lamellae of AF are attached to the ring apophysis of the lower and upper vertebrae. The inner lamellae are attached to the end-plates. Collagens of the AF are type I (~70–80%), type V (~3%), type VI (~10%), type IX (~1–2%) and type III (<1%). The collagens provide the tensile strength and proteoglycans, interacting with water molecules, are responsible for the resilience to compression (Eyre *et al.* 1989). The disc has a low cell density. The cells have a role of maintaining disc health by producing the extra cellular matrix (Maroudas *et al.* 1975). In vitro experiments have shown that mature disc cells possess

the capacity to respond to growth factors and that disc repair can be modulated by growth factors (Thompson *et al.* 1991).

2.1.2 Nerve root

At each lumbar level a pair of dorsal and a pair of ventral nerve roots leave the dural sac just above the level of each intervertebral foramen. The dorsal root transmits sensory fibres from the spinal nerve to the spinal cord, whereas the ventral root largely transmits motor fibres, along with some sensory fibres, from the cord to the spinal nerves. Dorsal and ventral nerve roots at both sides converge at the outlet of the root canal. The soma of ventral roots lies in the ventral horn of the spinal cord, whereas the soma of the afferent dorsal roots lies in the dorsal root ganglia (DRG). A DRG typically lies at the distal end of the dorsal root inside the apex of the dural sleeve, directly inferior to the pedicle and close to the nerve root axilla (Cohen *et al.* 1990). Nerve roots are surrounded by an extension of dura and arachnoid mater called the dural sleeve, which is approximately 2–3 cm long (Olmarker 1991). Nerve roots differ from peripheral nerves. Nerve roots bathe in the cerebrospinal fluid (CSF) and do not contain endoneurium or perineurium (Rydevik *et al.* 1984). The nerve root is located cephalad in the foramen (Rauschnig 1987). With straight leg raising (SLR), the lumbar nerve roots slide 0.5–5 mm and sustain 2–4% longitudinal strain (Smith *et al.* 1993). The prevalence of conjoined nerve roots is 2–4% among patients undergoing imaging studies and 14% in anatomic studies (Gomez *et al.* 1993, Piatt 1994). They may be associated with lumbosacral developmental anomalies and increased risk of disc herniation or cases of failed back surgery (Okuwaki *et al.* 1991, Gomez *et al.* 1993).

2.1.3 Anterior (ALL) and posterior longitudinal ligaments (PLL)

The vertebral column is supported anteriorly and posteriorly along its length by ALL and PLL. The PLL is described as having deep and superficial layers, though recent studies have suggested three layers. Both ligaments contribute to the stability, mobility and flexibility of the vertebral column (Loughenbury *et al.* 2005). The 8–10 mm wide central band of PLL extends over several vertebral segments and it has wider attachment to the IVD (Wiltse *et al.* 1993, Wiltse 2000). The deep and superficial layers of PLL attach to a mid-line bony septum on the posterior surface of the vertebral body. The PLL is also strongly attached to the adjacent vertebral margins together with outer AF fibers at the level of the IVD (Loughenbury *et al.* 2005). There is considerable variation even within the lumbar region, where the central fibers and “fan-like” IVD attachment portion appear to decrease in width between L1 and L5 (Wiltse *et al.* 1993).

2.2 Intervertebral disc herniation (HNP)

2.2.1 Definition and terminology of disc herniation

Herniation is defined as a localized displacement of disc material beyond the limits of the intervertebral disc space. The disc material may be nucleus, cartilage, fragmented apophyseal bone, anular tissue, or any combination thereof. The disc space is defined cranial and caudal by the vertebral body end-plates and, peripherally, by the outer edges of the vertebral ring apophyses, exclusive of osteophytic formations. The term "localized" contrasts with "generalized," the latter being arbitrarily defined as greater than 50% (180°) of the periphery of the disc. Herniated discs may take the form of a protrusion or extrusion, based on the shape of the displaced material. Protrusion is present if the greatest distance in any plane between the edges of the disc material beyond the disc space is less than the distance between the edges of the base in the same plane. The base is defined as the cross-sectional area of disc material at the outer margin of the disc space of origin, where disc material displaced beyond the disc space is continuous with disc material within the disc space. In the cranio-caudal direction, the length of the base cannot exceed, by definition, the height of the intervertebral space. Extrusion is present when, in at least one plane, any one distance between the edges of the disc material beyond the disc space is greater than the distance between the edges of the base in the same plane, or when no continuity exists between the disc material beyond the disc space and that within the disc space. Extrusion may be further specified as sequestration, if the displaced disc material has lost completely any continuity with the parent disc. The term migration may be used to signify displacement of disc material away from the site of extrusion, regardless of whether sequestered or not. Because posteriorly displaced disc material is often constrained by the posterior longitudinal ligament, images may portray a disc displacement as a protrusion on axial sections and an extrusion on sagittal sections, in which cases the displacement should be considered an extrusion. Herniated discs in the cranio-caudal (vertical) direction through a break in the vertebral body end-plate are referred to as intra-vertebral herniations.

Disc herniations may be further specifically described as contained, if the displaced portion is covered by outer anulus, or uncontained when absent of any such covering. The use of the distinction between protrusion and extrusion is optional and some observers may prefer to use, in all cases, the more general term herniation. Further distinctions can often be made regarding containment, continuity, volume, composition, and location of the displaced disc material. In the current study the term uncontained herniation was used when the herniation did not penetrate the PLL. This is due to local traditions and the fact that most of the image analyses were carried out before the international nomenclature was published.

The term "migrated" disc or fragment refers to displacement of disc material away from the opening in the anulus through which the material has extruded. Some migrated fragments will be sequestered, but the term migrated refers only to position and not to continuity. In this study the term uncontained was used if the displaced disc material penetrated the PLL because the majority of image analyses were carried out before the publication of the international recommendations.

Presence of disc tissue circumferentially (50–100%) beyond the edges of the ring apophyses may be called bulging and is not considered a form of herniation, nor are diffuse adaptive alterations of disc contour secondary to adjacent deformity, as may be present in severe scoliosis or spondylolisthesis (Fardon & Milette 2001).

Schematic presentation of normal disc and typical pathologic conditions is seen in Figure 1.

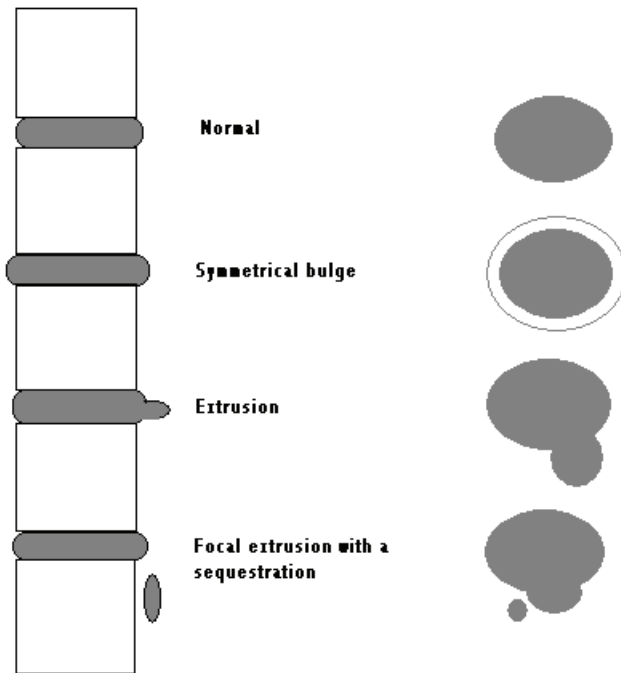


Fig. 1. Simplified illustration of normal disc, bulging disc, extrusion and sequestration.

2.2.2 Mechanism of disc herniation

Under laboratory conditions, anular protrusions and nuclear extrusions have been produced by axial loading in slightly flexed and rotated cadaveric spines. It has been suggested that disc herniation is peripheral in origin, with the AF being the site of primary pathologic change (Gordon *et al.* 1991). Posterior elements protect the disc from overstretching in normal spine (Adams *et al.* 1994). Deterioration of AF, due to anular tears and loosening of the interlamellar structures, predisposes the NP to herniate through the AF. The vast majority of the herniations occur at the posterolateral location, where anatomical irregularities in the AF are most often found (Ebeling *et al.* 1992, Tsuji *et al.*

1993). Familial predisposition and clustering of lumbar disc herniations in young patients has been reported (Varlotta *et al.* 1991, Matsui *et al.* 1992).

Although disc degeneration is often noted in association with HNP, the latter does not develop in all degenerated discs. The causal effect of annular tears on formation of HNP has not been proven directly *in vivo*, but there are observations to support the theory of annular tears being the necessary pathologic phenomenon leading to HNP (Gordon *et al.* 1991). Gradual herniations have been reported in cadaveric spines that were subjected to loading by bending and compression. Annular lamellae distortion and formation of annular fissures were followed by gradual HNP in the spinal canal (Adams & Hutton 1985). There are three types of annular tears found in post mortem studies: radial, concentric and transverse (Yu *et al.* 1988). From the anatomical point of view, a HNP cannot precede an annular tear. AF tears lead to accelerated IVD degeneration in animal models (Osti *et al.* 1990, Kääpä *et al.* 1995). Moreover, it appears that genetics has a considerable role in the development of IVD degeneration (Battie & Videman 2004) and the number of ruptures in the AF (Videman *et al.* 2001). The pressure in the NP becomes lower as the NP expands to tears in the AF, leading to increased pressure on it (Adams *et al.* 1996).

Disc herniations most often contain gelatinous NP, but there may also be components of anulus and cartilage or bone fragments present. In a review of 508 discectomy cases, 85% of the cases contained only nuclear material and the rest a combination of nuclear material and anulus fibrosus (Boutin & Hogshead 1992). Bony fragments are most often encountered in elderly patients (Harada *et al.* 1989, Tanaka *et al.* 1993). Protrusions can include either NP or AF, depending on whether the AF is totally ruptured or not (Yasuma *et al.* 1986).

In a cadaveric study by Adams and Hutton (1985) herniations of NP did not occur in the older age group following axial loading and bending despite the fact that there were fissures in the AF. Instead, herniations were noted in the younger age group. This could be due to changing composition of the NP with advancing age towards a non-gelatinous, fibrotic structure. Age-related changes in lumbar IVD are numerous and include replacement of normal NP by fibrous tissue from the fifth decade onward (Boos *et al.* 2002). The prevalence of lumbar disc syndrome is highest in the age group of 45 to 64 years. The risk of subsequent hospitalization because of back disease increases markedly with age up to 49 years, and thereafter gradually declines (Heliövaara *et al.* 1987).

2.2.3 Symptoms and signs of HNP

The classic symptoms of lumbar HNP include low back pain that worsens in the sitting position, and radiating pain to a lower extremity. The radiating pain, i.e. sciatica, is usually described as dull, burning or sharp, accompanied by intermittent sharp electric shock-type sensations. Sciatica symptoms may also include numbness or tingling, motor or sensory defects of the respective affected nerve root, or reflex abnormalities. The straight leg raising (SLR) test is used to evaluate the involvement of nerve root entrapment by provoking a radiating pain in cases of nerve root tension. The level of possible disc herniation can be evaluated according to the distribution of neurological symptoms and signs. Clinically, HNP most often occurs at L4-5 or L5-S1 levels (Kortelainen *et al.* 1985). One

must remember, however, that many cases are asymptomatic (Boden *et al.* 1990, Greenberg and Schnell 1991).

2.3 Pathogenesis of sciatic pain

2.3.1 Nerve root compression and inflammation

In 1934, Mixter and Barr reported that sciatica was associated with disc herniation (Mixter & Barr 1934). Disc-related sciatica was therefore ascribed to compression of the nerve root by a herniated intervertebral disc. Surgical removal of the herniated disc material became treatment of choice in severe forms of sciatica. Decompression of the affected nerve root was the aim of the treatment. During decompression operations performed using local anaesthesia, sciatic pain could be provoked by pressure applied to a swollen nerve root or dorsal root ganglion (DRG). Normal nerve roots or other tissue could not be provoked to produce sciatica by pressure. (Smyth & Wright 1958, Kuslich *et al.* 1991.) Chemical inflammatory factors have proven to have an important role in the pathophysiology of sciatic pain in several studies. Intervertebral disc has been shown to be immunogenic. (Gertzbein *et al.* 1975, Marshall *et al.* 1977, McCarron *et al.* 1987, Olmarker *et al.* 1993.) Inflammation mediators such as phospholipase A2, prostaglandin E2, interleukin (IL)-1, IL-1 β , IL-6, TNF α , and nitric oxide (NO) have been identified in and around the IVD in both in vitro and in vivo studies (Saal *et al.* 1990, Kang *et al.* 1996, Takahashi *et al.* 1996, Goupille *et al.* 1998, Ahn *et al.* 2002, Burke *et al.* 2002). According to earlier studies disc-related sciatica was not thought to occur in the absence of mechanical compression (Rydevik *et al.* 1989, Rydevik *et al.* 1991, Olmarker 1991, Pedowitz *et al.* 1992, Cornefjord *et al.* 1997). Olmarker *et al.* (1993), however, demonstrated in an animal study that autologous NP injected as a solute to cauda equina caused reduction of nerve root conduction velocity, and furthermore that intravenous methylprednisolone injection within 24 hours of NP injection was beneficial for the nerve function. It was later experimentally demonstrated that TNF α is expressed by herniated NP cells, and that exogenous TNF- α applied to rat nerve roots produces neuropathologic changes and behavior deficits that mimic experimental studies with herniated NP applied to nerve roots (Igarashi *et al.* 2000). Two interesting animal studies have compared the effect of NP or of compression of a nerve root and the combination of the two on nerve root histology and pain behavior (Olmarker & Myers 1998, Kawakami *et al.* 2003). In both of these studies the application of NP combined with nerve root compression had more severe histological consequences than either alone. Additionally, thermal hyperalgesia was detected only in the combination group. It seems reasonable therefore that the nerve root is sensitized by inflammatory factors, and compression applied thereafter triggers the typical radiating pain.

2.4 MRI of the intervertebral disc

2.4.1 Anatomic structures in MRI

The IVD undergoes marked anatomical changes with advancing age and the view of the spine imaged by MRI also changes (Yu *et al.* 1991). The IVD is prominent during infancy, but the volume decreases at older age (Szumowski & Simon 1991). The transition between NP and AF is relatively sharp in a young disc but becomes less distinct later in life (Yu *et al.* 1988). Normal NP has high water content and is seen as a high or medium signal intensity area surrounded by the low signal intensity AF on T2W images in healthy young adults (Yu 1989). The signal intensity of NP changes gradually with advancing age as the water content decreases and the turgid gel of proteoglycans transforms into a more desiccated fibrocartilaginous structure resembling the structure of inner AF (Buckwalter 1995, Erkintalo *et al.* 1995). It is usually seen as a horizontal central linear focus with decreased signal intensity in T2W sagittal images, and it is called the intranuclear cleft (Schiebler *et al.* 1991). Weidenbaum *et al.* (1992) have reported a linear correlation between water content and signal intensity in T2W MR images in proteoglycan solute in vitro. In a cadaver study an association was observed between low T2 signal and dehydration, decreased total protein and decreased chondroitin/keratan ratio in the NP (Tertti *et al.* 1991).

Normal outer anulus is hypointense in all pulse sequences (Morgan & Saifuddin 1999). Anular tears are thought to represent degenerative changes in IVD and they are seen as high signal intensity areas in AF in T2W images (Yu *et al.* 1989). Correlation between pain and anular tears is not very clear since they are found in asymptomatic subjects also (Stadnik *et al.* 1988). The signal intensity of endplate is normally very low, since dense calcified bone has very low hydrogen content. PLL is seen as a very thin low signal line posterior to the discs and vertebrae (Wiltse 1993). Some blood vessels can be seen as dark areas with no signal in T1W and T2W images because of the flow void phenomenon caused by moving blood. The segmental arteries can be seen using time of flight sequences and with phase contrast sequence venous structures can be visualized even without contrast material.

The usual sequences in degenerative lumbar spine MRI in clinical use are T1W sagittal spin echo (SE) and T2W sagittal fast spin echo (FSE) (Morgan & Saifuddin 1999) supplemented with T1W SE and T2W FSE axial images (Gundry & Fritts 1997). Slice thickness is usually 4 mm and interslice gap 1 mm. By changing field of view and using thinner slice thickness it is possible to achieve even submillimeter pixel size.

The sensitivity of T2W MRI in detecting annular tears varies between 31% (Saifuddin *et al.* 1998) and 43% (Carragee *et al.* 2000). Combined radial and circumferential tears are seen as a high intensity zones (HIZ) on T2W, whereas concentric tears are not usually detected (Aprill & Bogduk 1992).

2.4.2 Gadolinium enhanced MRI

Gadolinium is a lantaside metal with a paramagnetic property. When a patient is in an MRI scanner and thus in a strong homogenic magnetic field, the accumulation of intravenously administered gadolinium creates a small local “disturbance” on the magnetic field. T1 relaxation times of surrounding protons shorten at the site of gadolinium. Gadolinium is toxic in its free state, but when bound to e.g. DTPA (diethylenetriaminepentaacetic acid) it can be safely used in clinical imaging (Runge 1989). Several commercial products with slight chemical differences are available.

The enhancement is based on the accumulation of contrast material at the site where normal blood vessel integrity has been disturbed or abnormal vascularity is present. Gd-based contrast materials do not normally penetrate the blood-brain barrier. Enhancement of a tissue is nonspecific, since many pathologic conditions such as tumours, inflammation and trauma can cause enhancement (Pels *et al.* 1994). In lumbar spine, the Gd-visualized rim enhancement around the HNP varies usually from 1 to 3 mm, and consists of neovascularized granulation tissue with inflammatory cells (Ross *et al.* 1990, Yamashita *et al.* 1994). The enhancement is best seen with fat-saturated T1W imaging sequences (Georgy *et al.* 1995), although an opposing opinion has been presented (Bradley 1999). Gd-DTPA is useful e.g. for detecting anular tears (Ross *et al.* 1990), because AF tears are often accompanied by invading fibrovascular tissue (Peng *et al.* 2005), which can be detected as an enhancing area in the otherwise avascular AF (Ross *et al.* 1990).

2.4.3 The role of MRI in HNP diagnosis

There is no need to perform an imaging study on every patient presenting with symptoms of HNP. Imaging is recommended only for patients who are candidates for disc surgery, or if the symptoms do not resolve within four to six weeks as expected (Kotilainen 1995). In a benign condition with a rather good prognosis imaging has to be safe and reliable. The most informative imaging modality in lumbar spine pathology is MRI (Modic *et al.* 1986, Modic & Ross 1991). It is non-invasive and there is no radiation involved in the examination. However, the limited availability at some institutions and the higher cost of MRI compared to computed tomography (CT) favor the use of CT in daily praxis. Nevertheless, MRI may be the optimal modality if it can reveal prognostic findings related to good or poor clinical outcome.

Disc ruptures can also be imaged with discography and CT discography, which can reveal AF ruptures even better than MRI. The use of discography is primarily indicated in cases of suspected painful disc without a neural compromise or a clear HNP. Myelography is no longer used due to its many limitations. Ultrasound is not used in HNP diagnostics because of its limited capacity to visualize the contents of the spinal canal and nerve root canals. Epidural venography is not used in HNP diagnostics nowadays.

2.4.4 Asymptomatic HNP

Boden *et al.* studied 67 subjects with MRI who had no previous history of back pain, sciatica or neurogenic claudication. They reported that 20% of subjects under 60 and 36% of those over 60 years had at least one HNP in MRI. Other abnormal imaging findings were also surprisingly common. (Boden *et al.* 1990). Greenberg and Schnell performed MRI on 66 asymptomatic patients and found that 18% had either disc protrusion or herniation, and an additional 39% had a bulging disc (Greenberg & Schnell 1991). Jensen *et al.* performed MRI examination on 98 asymptomatic people and noted that 36% of the individuals had normal discs at all levels, 52% had a bulge on at least one level, 27% had a protrusion and 1% an extrusion. The prevalence of bulges increased with age (Jensen *et al.* 1994), which indicates that not all herniations are symptomatic. The reasons for asymptomaticity are not clear, although the presence of nerve root compression has been suggested as the most important MRI finding related to symptoms (Boos *et al.* 1997). The involvement of nerve root may also explain the association between the severity of sciatica and the size of lumbar disc herniation adjusted for the size of the spinal canal in computed tomography (Thelander *et al.* 1994).

2.4.5 Accuracy of MRI

MRI can be considered a well established and the most sensitive method for evaluating the intervertebral disc (Modic *et al.* 1984). MRI has superior contrast discrimination in evaluating soft tissue structures compared to other imaging modalities, and it also has multiplanar imaging capability, which makes it the modality of choice in IVD imaging (Gibson *et al.* 1986, Gundry & Fritts 1998). Pevsner *et al.* studied 250 patients referred for MRI of the lumbar spine. CT and MRI were performed on 50 patients and MRI, CT and myelography on 20 patients. Twenty patients had surgical confirmation of the imaging findings. MRI was best for demonstrating degenerated discs, better than CT for demonstrating disc bulge without herniation, and slightly better for herniated disc demonstration than CT. Myelography did not demonstrate degenerated discs. (Pevsner *et al.* 1986.) Bischoff *et al.* used CT-myelography, MRI and standard myelography for examining 57 patients for a disc herniation or spinal stenosis. Compared with surgical findings, CT-myelography was the most accurate test (76%), and plain myelography the most specific (89%) for diagnosing a disc herniation (Bischoff *et al.* 1993). This study, however, had several methodological limitations. The patients were a subset of 475 surgical candidates, who had all three imaging tests performed, and they represented patients who did not have a clear-cut diagnosis. The study protocol included contrast studies (CT-myelography and myelography) only if MRI was inconclusive, and the decision to operate was based on these contrast studies. This could have artificially decreased the accuracy of MRI and increased the accuracy of contrast studies. Myelography is also often performed in a half-standing position, which can give a disc a different form than in supine MRI. Comparing supine MRI and sitting MRI has demonstrated that the disc can take a very different shape depending on the position of the patient (Choy 1997). In another study of 95 patients with acute low back and radicular pain, all underwent MRI and 32 of

them underwent CT and 63 CT-myelography. Fifty-six patients underwent surgery, and 39 received conservative treatment. Receiver operating characteristic (ROC) analysis was performed to correlate the results of blinded image reading with "true" diagnoses determined by an expert panel. There was no statistically significant difference in the diagnostic accuracy of HNP-caused nerve compression among the three modalities (Thornbury *et al.* 1993). Observer reliability is a commonly encountered issue when evaluating the results of a test. Brant-Zawadzki *et al.* assessed inter- and intra-observer variability in interpretation of lumbar disc abnormalities detected with MRI. Using the nomenclatures "normal, bulging or herniated disc" vs. "normal, bulge, protrusion, herniation", the inter-observer agreement between the two expert neuroradiologists was 80% (kappa value 0.58) and the intra-observer agreement 86% for each reader (kappa values 0.71 and 0.69, respectively) (Brant-Zadawadzki *et al.* 1995).

Silverman *et al.* have reported that MRI had only 29% sensitivity, 65% specificity and 42% accuracy in evaluating the PLL penetration of a HNP, whereas Grenier *et al.* reported 100% sensitivity and 78% specificity (Grenier *et al.* 1989, Silverman *et al.* 1995).

2.4.6 MRI and nerve root compression and inflammation

Nerve root compression can be evaluated with MRI, since it detects nerve roots easily. Nerve roots are surrounded by fat tissue in the neural foramina, and diminishing or absent perineural fat can help to evaluate the neural compromise by HNP or foraminal stenosis. The nerve root can be dislocated and squeezed by a HNP, often leading to swelling of the nerve root. The swelling is caused by microcirculation disturbances in the nerve root. Thrombus formations occur in blood vessels of the nerve root, inducing ischemia. Furthermore, increased permeability of the vessels results in edema of the nerve root (Rydevik *et al.* 1977, Rydevik *et al.* 1984). Nerve root enhancement has been observed in several MR studies after Gd injection (Toyone *et al.* 1993, Itoh *et al.* 1996, Tyrrell *et al.* 1998, Vroomen *et al.* 1998). It has been found after lumbar disc surgery (Boden *et al.* 1992) and in the presence of HNP (Toyone *et al.* 1993, Itoh *et al.* 1996, Vroomen *et al.* 1998). Nerve root enhancement is thought to occur after blood brain barrier disruption and permeability changes in the nerve root (Jenkins 1993, Crisi *et al.* 1993, Lane *et al.* 1994).

Correlation of nerve root enhancement with sciatic symptoms was observed in subjects with severe sciatica preoperatively, whereas postoperative nerve root enhancement did not correlate with symptoms (Taneichi *et al.* 1994). Among HNP patients, correlation of enhancement of the symptomatic nerve roots with severity of sciatica has been found (Toyone *et al.* 1993). Moreover, Vroomen *et al.* reported nerve root enhancement to correlate with neurological deficits in general and sensory impairment in particular in preoperative HNP patients (Vroomen *et al.* 1998). On the other hand, Crisi *et al.* (1993) could not correlate nerve root enhancement with symptoms in 26 patients with symptomatic HNP. Interestingly, 60% of asymptomatic persons have been reported to have nerve root enhancement. The authors assumed this phenomenon to be due to enhancing lumbosacral radicular veins (Lane *et al.* 1995).

The dorsal root ganglion (DRG) is considered to have an important role in the pain mechanism (Weinstein 1986), especially since application of soluble NP induces edema in the DRG (Olmarker & Myers 1998) and DRG is also sensitive to compression (Rydevik *et al.* 1989). DRG edema has been reported in the affected nerve root in sciatic patients with a HNP (Aota *et al.* 1997). The edema can be evaluated in T2W images (Aota *et al.* 1997), but also using MR myelography (Aota *et al.* 2001). It has been argued that disturbance of the blood nerve barrier and edema are the causes of enhancement of nerve root and DRG (Toyone *et al.* 1993, Kobayashi *et al.* 1993).

2.5 Natural history of HNP

2.5.1 Spontaneous HNP resorption

Spontaneous regression of a HNP occurs where intervertebral disc herniation loses its volume partly or totally without surgical interventions. The first case report of intervertebral disc herniation regression using repeated CT exams was published in 1984 (Guinto *et al.* 1984). The first case-controlled study describing spontaneous regression of HNP using sequential CT examinations was published in 1985 (Teplick & Haskin 1985). The follow-up time was from five months to three years and 11 patients were enrolled in the study. Two of the patients were asymptomatic and nine had HNP-related radicular symptoms, which disappeared during follow-up. The mechanism responsible for regression is not totally known but histological studies have shown an inflammatory reaction around the herniated NP. Local production of TNF α by Schwann cells, endothelial cells, fibroblasts and mast cells attracts macrophages to the site of injury (Gadient *et al.* 1990, Stoll *et al.* 1993, Chao *et al.* 1995, Olmarker & Larsson 1998, McHale *et al.* 1999). Neovascularisation has also been reported at the edge of HNP (Ozaki *et al.* 1999). Both inflammation and neovascularization, i.e. new angiogenesis, are thought to be required for phagocytosis (Yasuma *et al.* 1993, Arai *et al.* 2000, Haro *et al.* 2002). Interaction between activated macrophages and disc tissue leads to generation of inflammatory cytokines (Kato *et al.* 2004). These cytokines and catabolic enzymes are then involved in the induction of angiogenesis (Haro *et al.* 2002, Koike *et al.* 2003, Kato *et al.* 2004), and the new blood vessels formed conduct new molecules into degrading HNP tissue. Many studies have demonstrated that a neovascularized zone infiltrated with macrophages develops in the outermost layer of herniated disc tissue (Yasuma *et al.* 1993, Ikeda *et al.* 1996). Macrophage infiltration seem to be more prominent in large HNPs, as sequestrations have 2–3 times more inflammatory cells than extrusion-type herniations (Virri *et al.* 2001). Neovascularization is also most abundant in extrusions and sequestrations, and is hindered by ligaments and/or annulus fibrosus (Ozaki *et al.* 1999). Several molecules have been suggested to be involved in the neovascularization of herniations. These include tumor necrosis factor alpha (TNF α), matrix degrading enzymes (matrix metalloproteinase (MMP)-3 and -7 and plasmin) (Kato *et al.* 2004), and growth factors (Tolonen *et al.* 1997, Minamide *et al.* 1999, Haro *et al.* 2002).

In older age groups the immunological response, and thus angiogenesis, may be weaker. Herniations in older age groups are also harder, fibrotic and desiccated in the cervical spine (Mochida *et al.* 1998). Moreover, they also tend to have less nucleus pulposus and more annulus fibrosus and cartilaginous endplate material (Harada *et al.* 1989, Tanaka *et al.* 1993), the latter being able to inhibit neovascularization of the herniated disc (Carreon *et al.* 1997). On the other hand, in an experimental canine model the younger animals had absent neovascularization and inflammatory cell accumulation in the sequestered disc fragment (Hasegawa *et al.* 2000). HNP is a rare disease under the age of 15 years and no follow-up or histological studies have been published on this matter to the author's knowledge. Therefore it would be unwise to generalize this finding in a canine model to children.

It seems that both generalized and localized bulges have the poorest potential to regress. There are some logical explanations for this when considering the relatively well-preserved nutritional status of the bulge and also the weaker inflammatory reaction caused by bulges and by contained herniations. There might also be disparities between different degrees of disc displacement in terms of inflammatory mediator production and the degree of neoinnervation. In vitro studies have shown differences in inflammatory cell populations between bulges, and contained and uncontained herniations, but it is very difficult to measure cytokines and other small molecules in vivo (Ahn *et al.* 2000). A simplified schematic presentation of the inflammatory reaction caused by HNP is seen in Figure 2.

Apoptosis plays a central role in the homeostasis of all organisms in normal development and tissue turnover (Horvitz 1999). The TNF-receptor super family can activate caspase-8 mediated mitochondria-dependent cell apoptosis (Nicholson *et al.* 2000). The role of apoptosis in HNP resorption is unclear, but it is reasonable to suspect that it might have an active role.

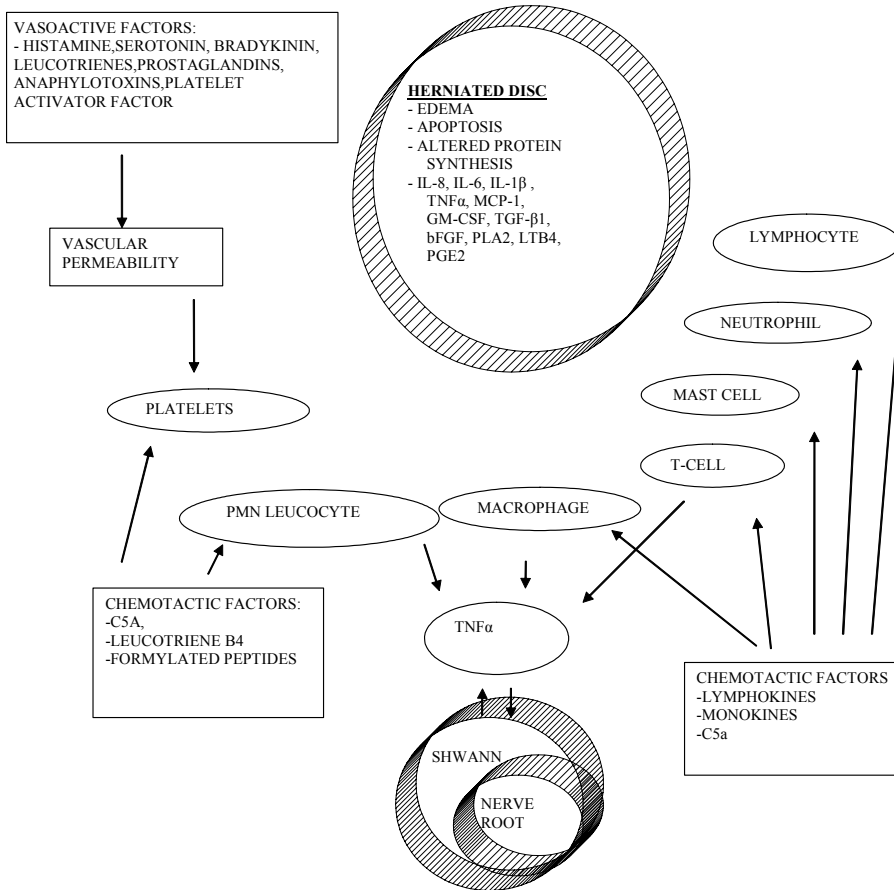


Fig. 2. A simplified schematic presentation of the inflammatory reaction caused by HNP. On the left side are acute or subacute type of reactions, mediators and cells. On the right side are depicted cells that appear later.

2.5.2 MRI and spontaneous HNP resorption

Progressive recovery from sciatic symptoms has been described in early clinical reports (Lindblom & Hultquist 1950, Hakelius 1970). Since the invention of computed tomography (CT) and MRI, spontaneous regression of lumbar HNP has been described in many studies (Teplick *et al.* 1985, Guinto *et al.* 1984, Saal & Saal 1990, Dullerud & Nakstad 1994, Ito *et al.* 2001). Thoracic and cervical herniations are known to regress in the same way as lumbar herniations (Wood *et al.* 1997, Reddy *et al.* 2003).

Komori *et al.* studied retrospectively 77 patients with radiculopathy caused by a lumbar disc herniation. All patients were studied more than twice using MRI during conservative treatment, with a mean interval of 150 days. The further the herniated nucleus pulposus had migrated the more it decreased in size during the follow-up. Small herniations and protrusions showed little or no change (Komori *et al.* 1996). Yukawa *et al.* reported on 30 sciatic patients treated conservatively and repeatedly followed with MRI for more than two years. Reduction of the size of herniation was found in 57% of patients compared to no change in 40%. The improvement in clinical course correlated with the reduction in herniation size. Larger herniations regressed more than smaller ones in this study. Patients with progression of disc degeneration showed more marked HNP regression than those in whom progression was not observed. (Yukawa *et al.* 1996.) Bone fragments and cartilage in a HNP could particularly have a negative effect on the resorption rate, which has been shown experimentally in rabbits (Carreon *et al.* 1997).

Henmi *et al.* reported that higher signal intensity of HNP on T2W images corresponded to a more favorable HNP resorption. They described a signal intensity ratio (SIR) (signal intensity of the HNP divided by signal of the parent disc) exceeding 1.2 as a good prognostic sign in HNP regression. However, the number of patients was small, with five herniations in the low-SIR (≤ 0.8) and four in the high-SIR (≥ 1.2) group. A significant correlation was found between SIR value and duration of the symptoms, indicating that herniations have a higher signal in the early phase of the disease. Hydration of the herniation was suggested as a causative factor for the increased signal. (Henmi *et al.* 2002.) Masaryk *et al.* have also noted that extruded or sequestered disc fragments may demonstrate higher signal intensity than the parent disc (Masaryk *et al.* 1988). In addition to hydration there are other possible explanations for the higher signal in a HNP. In theory, as a result of herniation a sudden decrease in compressive and tensile forces acting on the disc could result in a change in the equilibrium between the swelling pressure of the herniated fragment and the external forces (Urban & McMullin 1988, Saal *et al.* 1990). Low signal of a HNP on T2W is a sign of lower water content and is considered one of the signs of NP degeneration (Modic *et al.* 1988, Weidenbaum *et al.* 1992, Boos *et al.* 1995). The significance of containment of a HNP is based on studies suggesting that uncontained herniations have a better regression potential (Saal & Saal 1990, Ahn *et al.* 2000). Ahn *et al.* studied 36 patients with symptomatic lumbar disc herniations treated conservatively: they divided them into three groups; subligamentous HNP, transligamentous HNP, and sequestrations. At the follow-up 56% of the subligamentous, 79% of the transligamentous and 100% of the sequestrations were reduced. The reduction of HNP volume was 17%, 48% and 82%, respectively. The tendency to regress was related clearly more to the presence of transligamentous extension of the HNP than to the initial size of the herniation. (Ahn *et al.* 2000.)

According to histological studies the regression potential seems to be related to a more abundant inflammatory cell accumulation and neovascularization. In a study on operated HNPs, inflammatory findings such as cell infiltration, neovascularization and granulation were observed in 17% of the protruded discs, 82% of the subligamentous HNPs, 100% of the transligamentously extruded HNPs, and 80% of the sequestrations. The infiltrated cells were composed mostly of macrophages and a small number of T-lymphocytes. Cell infiltration was more prominent in the NP than in the AF (Ikeda *et al.* 1996).

A neovascularized zone at the periphery of a herniation can be depicted in Gd-DTPA enhanced T1W fat saturated images (Yamasita *et al.* 1994, Modic *et al.* 1995). In a study on 48 patients with lumbar radiculopathy who underwent a contrast enhanced MRI twice or more during the follow-up, those patients with an increase in rim enhancement thickness had better clinical course than those with no change in enhancement thickness. Furthermore, the regression of HNP was poorer in the five cases with no change in enhancement. (Komori *et al.* 1998.)

2.6 Treatment of HNP

It has been estimated that 5 to 20% of patients with symptomatic HNP require surgery (Heliövaara *et al.* 1987, Seyo *et al.* 1990, Frymoyer 1992). In 1995, the overall rate of lumbar disc surgery in Finland was nearly 78 per 100 000 (Keskimäki *et al.* 2000). However, the great majority of sciatic patients do not require operative treatment since there is a strong tendency to spontaneous resorption of HNP and resolution of the symptoms. Satisfactory clinical outcome of patients treated conservatively has been documented in several studies (Hakelius 1970, Weber 1983, Saal & Saal 1989). In a follow-up of 82 hospitalized sciatica patients, one third had been operated on, half of the conservatively treated patients had residual symptoms, and half were symptom free (Balague *et al.* 1999). Recommendations about conservative treatment of sciatica have been issued, although only a limited number of randomized controlled trials exist. According to Vroomen *et al.*, only 19 RCTs (randomized controlled trial) were found, of which eight met the three major requirements (comparability of the groups, observer blinding, and intention-to-treat analysis). On the basis of this systematic review of non-operative treatment, no significant effect was demonstrated for NSAIDs (nonsteroid anti-inflammatory drugs), traction, or intramuscular steroids. It was concluded that only epidural steroids may have some transitional benefit for a patient with sciatica (Vroomen *et al.* 2000).

2.6.1 Epidural and periradicular steroid injection

Lumbar spine injection procedures have been employed in the management of patients with radicular pain syndromes for almost a century (Cannon & Aprill 2000). The first epidural steroid injection was reported in 1952 (Robecchi & Capra 1952). Locally corticosteroids are thought to inhibit the inflammatory response by interfering with specific leukocyte functions, including leukocyte aggregation at the inflammatory site, prevention of degranulation of granulocytes, mast cells and macrophages, and stabilization of lysosomal and other membranes (Di Rosa *et al.* 1986). Corticosteroids also inhibit phospholipase-2 (PLA2) activity, thus interrupting the arachidonic acid cascade (Hayashi *et al.* 1998). It has also been reported that dexamethasone may have at least three actions which interfere with the pathogenesis of IgE-, mast-cell-, and cytokine-dependent inflammatory reactions in mice: suppression of the IgE-dependent increase in TNF α mRNA by mast cells, inhibition of the IgE-dependent production of TNF α protein by mast cells, and

diminution of the responsiveness of target cells to TNF α . (Wershil *et al.* 1995). Figure 3 presents a simplified version of the effects of methylprednisolone and anti-TNF α treatments in the inflammatory and resorption process in HNP.

Transforaminal epidural steroid injections or selective nerve root blocks to treat lumbosacral radiculopathy were evaluated in a recent review of five articles (DePalma *et al.* 2005). The evidence supporting the favorable effect of these invasive methods was considered moderate. Slipman and Chow (2002), however, have pointed out that the effect of transforaminal epidural steroid injections is better in herniation-induced radiculopathy than in radiculopathy due to trauma, scar or foraminal stenosis.

2.6.2 Anti-TNF α treatment

The TNF α molecule was found to mediate pain in an animal study (Igarashi *et al.* 2000). In the following year Olmarker and Rydevik were the first authors to report that selective inhibition of TNF α could have clinical value in the treatment of sciatica. TNF α inhibition prevented NP-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity in pigs (Olmarker & Rydevik 2001). Treatment with intravenous infusion of infliximab, a monoclonal antibody against TNF α , is indicated for the management of rheumatoid arthritis, plaque-type psoriasis, active ankylosing spondylitis and Crohn's disease. Infliximab seemed to be effective for HNP-induced sciatica in a small open-label study (Karpinen *et al.* 2003), but the results could not be replicated in a randomized controlled trial (Korhonen *et al.* 2005).

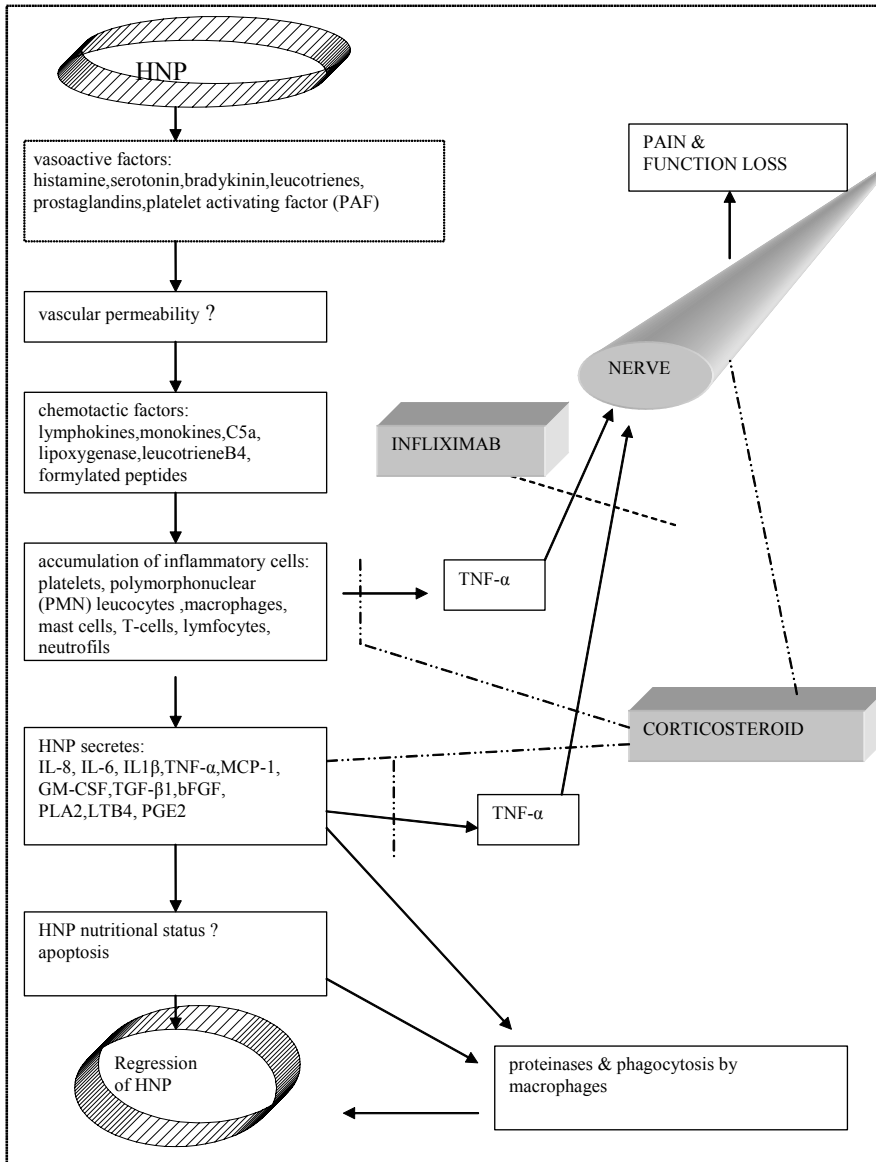


Fig. 3. Theoretical schematic presentation of the effects of infliximab infusion and periradicular methylprednisolone injection on the components of HNP-induced inflammatory reaction. The more targeted effect of infliximab compared to methylprednisolone is presented in the figure.

3 Purpose of the study

The purpose of the present study was:

1. To analyse magnetic resonance imaging findings in relation to symptoms and signs among sciatic patients.
2. To investigate determinants of spontaneous resorption of intervertebral disc herniation
3. To examine the effect of periradicular methylprednisolone injection on spontaneous resorption of intervertebral disc herniation.
4. To study the effect of intravenous infliximab infusion on resorption of intervertebral disc herniation.

4 Subjects and methods

4.1 Study population (I–IV)

The study population in Studies I, II and III consisted of consecutive patients with unilateral sciatica referred by general practitioners to the Department of Physical Medicine and Rehabilitation in Oulu University Hospital. Duration of sciatica was from three to 28 weeks. Patients with earlier back surgery, an application for early retirement, clinical depression, anticoagulation treatment, unstable diabetes, epidural injection during the preceding three months, pregnancy, claustrophobia, and with rare causes of sciatica such as synovial cysts and non-degenerative spondylolisthesis, were excluded from the studies. Studies I, II and III were substudies of a randomized controlled trial for periradicular infiltration of sciatic patients, approved by the ethical committee of Oulu University Hospital (Karpinen *et al.* 2001).

Periradicular injections were performed between January 1997 and May 1998. Every randomized patient (N=160) was MRI-scanned at baseline. The study population for the rescanning study arm consisted of 74 patients, of whom 39 received periradicular methylprednisolone and 35 saline. Of these 74 patients, 53 were rescanned at 1 year. The reasons for exclusion from the two-month and one-year rescannings are presented in Figure 4. The gender distribution, age, and baseline parameters of interest (volume of herniation, extent of rim enhancement, thickness of rim enhancement) did not differ between the two treatment groups of rescanned patients.

The study population in Study IV consisted of patients with severe HNP-induced sciatica, who were candidates for discectomy based on evaluation of an independent orthopedic surgeon. The exclusion criteria were: history of back surgery, serious infection in the preceding three months, active or latent tuberculosis, documented human immunodeficiency virus (HIV) infection, and malignancy within the past five years. The study protocol was approved by the ethical committee of Oulu University Hospital. All 21 patients who were enrolled in the MRI substudy were included in the data analysis. The treatment groups were comparable with regard to baseline demographic and disease characteristics.

4.2 Evaluation of patients

4.2.1 Clinical symptoms (I–IV)

The patients answered a self-administered questionnaire with items about medical history including sciatica and back pain, history of current back pain, and sick leaves. Back pain and leg pain were recorded by each patient on a 100-mm VAS scale, and disability using the Oswestry Low Back Disability Questionnaire (Fairbank *et al.* 1980, Grönblad *et al.* 1993).

4.2.2 Diagnostic evaluation (I–IV)

4.2.2.1 Clinical examination (I–IV)

The clinical examinations were performed within one week prior to MRI. The straight leg raising test (SLR) was performed on both legs. The result was measured using a goniometer and recorded to the nearest 5°. Sensory and motor defects, and tendon reflexes were examined.

4.2.2.2 MRI (I–IV)

MRI examinations were performed with an 1.5 T imaging system (Signa, General Electric, Milwaukee, Wisconsin). Imaging sequences in Studies I–III were T2W sagittal (time of repetition (TR)/echo time (TE) 4000/95 ms), T1W transaxial (TR/TE 640/14) and T1W transaxial fast spin echo (FSE) fat saturated sequence (TR/TE 540/10.3). The matrix in sagittal images was 512x224 and number of excitations (NEX) 3, and in transaxial images 256x192 and 2 NEX. A field of view (FOV) of 20x20 cm was used in axial- and 30x30 cm in sagittal images. Slice thickness was 4 mm and interslice gap 1 mm in T2W sagittal sequence and 0.5 mm in all other sequences. Gadolinium (Magnevist, Schering, Berlin, Germany) 15 ml was administered intravenously prior to the T1W fat saturated sequence.

The imaging sequences in Study IV were T2W sagittal FSE (TR/TE 4/106.8, NEX 4, FOV 28x28, matrix 256x256), T1W sagittal spin echo (SE)(TR/TE 400/14, NEX 2, FOV 28x21, matrix 256x224), T2W axial fast recovery FSE (TR/TE 3800/106.0, NEX 3, FOV 20x20, matrix 256x224), T1W axial SE (TR/TE 500/9.0, NEX 3, FOV 20x20, matrix 256x192), and T1W axial FSE fat saturated sequence (TR/TE 540/10.3, NEX 2, FOV 20x20, matrix 256x192) with contrast enhancement. Slice thickness was 4 mm in all sequences and interslice gap was 1 mm. Gadolinium (Magnevist, Schering, Berlin, Germany) 0.2 ml/kg was administered intravenously prior to the T1W fat saturated sequence.

4.2.2.3 MRI measurements and interpretation (I–IV)

In all studies (I–IV) disc displacement was graded as normal, bulge (a symmetrical extension of the peripheral annulus beyond the margins of the vertebral endplates), contained herniation (a focal extrusion of disc material not penetrating the PLL), uncontained herniation (an extrusion of disc material through the PLL), and sequestration (a herniated disc fragment not in contact with the parent disc). Volume was calculated only from the herniations by measuring the area of herniation in axial slices in T1W fat saturated sequence after gadolinium injection. The sum of areas was multiplied by slice thickness including interslice gap to obtain the volume of herniations. All the enhancing disc tissue in the herniation was included in the volume. The thickness of the rim enhancement was measured in the posterior parts of the herniation to avoid enhancing vascular structures. Thickness of enhancement was measured from a point representing mean thickness. The extent of the rim enhancement was measured as the percentage (0–100%) of the circumference in axial images. A mean value for the extent of enhancement was calculated if enhancement was seen in more than one image. Neural compromise was classified as: no compromise, minor compromise (minor dislocation or minor nerve root compression), or major compromise (moderate or major dislocation and/or nerve root compression). Nerve roots were classified as normal or edematous within the first two centimeters from their origin. The location of herniation in the epidural space was graded as central, medial, lateral or ultralateral. In Study III herniations were also classified into four types according to Komori *et al.* (1996). Type 0 represents normal or bulging disc, type 1 herniation extends one-third or less of the vertebral body height in cranial or caudal direction from the IVD level, type 2 herniation extends from one-third up to two-thirds of the vertebral body height in cranial or caudal direction from the IVD level, and type 3 herniation extends from two-thirds up to the entire vertebral body height in cranial or caudal direction. Sequestrations were included in type 3 herniations. In Study I, signal intensity of the rim enhancement was also measured, and compared to the intensity of enhancement in the psoas muscle.

Some herniation volume or enhancement parameter data could not be obtained in Studies I–III (e.g., baseline volume unmeasurable for three patients), and therefore the calculated changes from baseline to two months, and from two months to one year are less than the initial number of patients (74 and 53 respectively, for the two time periods).

In Study IV all 21 patients had imaging performed at baseline, week 2 (mean 18 days, range 14 to 27 days), and week 12 (mean 87 days, range 68 to 96 days). At week 26 (mean 186 days, range 173 to 196 days), 17 patients had repeat MRIs and four patients had undergone surgery (two patients in each treatment group). Because of a surgical consideration, one patient had the week-26 follow-up scan performed early.

4.3 Patient information and randomization (I–IV)

4.3.1 Studies (I–III)

Patients meeting the criteria for inclusion were requested to read through preliminary information about the infiltration procedure and the trial. They were informed of the trial option both orally and with a written description of its content and purpose. Where written consent was obtained, patients underwent the investigations and completed the questionnaires. The randomization took place immediately before the intervention, and was based on a published list of random permutations (Cohran & Cox 1957) with a block size of 16. A person uninvolved in the study placed the assignments in sealed envelopes with running numbers. The envelopes were used in the order provided. On their way to the injection procedure, each patient took an envelope to the Department of Radiology, where an authorized nurse filled a tape-covered syringe with the treatment agent indicated therein. The assignments were thus masked to the patients, the physicians and the radiologist giving the injection.

4.3.2 Study (IV)

After confirmation of eligibility and signed informed consent, patients were allocated to treatment groups using random number tables with a random variation of block sizes of four and six.

4.4 Clinical follow-ups (II–IV)

4.4.1 Studies II and III

Immediately after the injection, each patient recorded his/her back and leg pain on a paper questionnaire, which was filed separately from the other data. At the follow-up checks (2 weeks, 1 month, 3 months, and 1 year after the intervention) the same questionnaires as those at the baseline were completed. Usually, the same physician performed the patient's clinical examinations throughout the follow-up assessments. The physician decided on any future interventions and documented the clinical status on separate forms filed with the rest of the patient data.

4.4.2 Study IV

Leg and back pain were assessed three hours after the initiation of the infusion and by phone on day one after the infusion. The clinical examination was repeated after the cessation of the infusion. Follow-up assessments (including clinical examinations and subjective symptom assessments) were performed at one week, two weeks, one month, three months, six months and one year after the infusion. Additionally, the occurrence of side effects and the number of discectomies were monitored and recorded. In case of persistent symptoms during the follow-up the independent orthopedic surgeon decided on whether to refer the patient to surgery or not.

4.5 MRI follow-ups (II–IV)

Follow-up MRI was performed two months, six months and 12 months after baseline in Studies II and III. In Study IV the follow-up MRI was performed two weeks, three months and six months after the infusion. After discectomy, no follow-up imaging was performed.

Imaging data was stored on digital archives and cd-rom discs in Study IV and on films and optical discs in Studies I,II and III.

4.6 Statistical analysis (I–IV)

4.6.1 Reliability of MRI findings (I–IV)

In Study I all the images were analyzed by a radiologist (RA), and a random subgroup of 19 patients was analyzed by two radiologists (M.K. and R.A.) to obtain intra- and inter-observer agreement for HNP volume and extent of enhancement. Intra-observer and inter-observer agreement values for HNP volume and the extent of enhancement were moderate (Table 1).

In Study IV all baseline and follow-up images were read independently twice by two readers (R.A. and R.O.). Patient identification data and the time of imaging were removed from the studies when saved on cd-rom. Examinations were coded by a four-digit number. Intra-class correlation coefficients (HNP volume, extent and thickness of rim enhancement) and kappa statistics (nerve root swelling) were calculated to determine inter-reader agreement of MRI readings. As patients were scanned at two weeks, and three and six months, a total of 80 MRI scans were read blinded without any patient identifier and independently by the same reader (intra-observer) or both readers (inter-observer). Intra-class correlation analysis indicated that HNP volume and rim enhancement extent measurements were reliable (Table 1). The intra-observer score for enhancement thickness was 0.93, whereas the inter-observer value was only 0.46. The reliability of the estimates of

nerve root swelling had the poorest reliability (Table 1). Furthermore, the validity of Komori classification, and penetration through the PLL were poor, too (Table 1).

Table 1. Reliability of MRI findings. Reliability is presented as κ -values.

Variable	N	Interobserver	Intraobserver
Study population I (RA and MK)			
HNP volume	19	0.659	0.469
Enhancement extent	19	0.399	0.689
Study population IV (RA and RO)			
HNP volume	21	0.90	0.98
Enhancement extent	21	0.70	0.95
Enhancement thickness	21	0.46	0.93
Nerve root edema	21	0.26	0.73
Komori classification	21	0.31	0.95
Anulus penetration	21	0.24	0.81

4.6.2 MRI findings in relation to symptoms and signs (I)

Mean values and standard deviations were calculated for the measurements. The associations between continuous and categorical variables were calculated by the Kruskal-Wallis test. Correlations between continuous variables were evaluated by Pearson correlation analysis. The presence of abnormal Achilles reflex was analyzed by categorical variables: gender (female vs. male), age (≤ 38 , 39–49, and ≥ 50 years), duration of symptoms (≤ 1 month, 1.5–2.5 months, and ≥ 3 months), neural compromise (no compromise or minor compromise vs. major compromise), nerve root edema of the symptomatic root (no vs. yes), type of disc displacement of the symptomatic disc (bulge or contained herniation vs. extrusion), herniation volume ($< 750 \text{ mm}^3$ and $\geq 750 \text{ mm}^3$), thickness of rim enhancement ($< 1 \text{ mm}$ and $\geq 1 \text{ mm}$), and extent of rim enhancement ($< 75\%$ and $\geq 75\%$). Statistical significances were evaluated with the χ^2 or Fisher's exact test (for 2x2 tables). Stepwise logistic regression analysis was performed to clarify the determinants of abnormal Achilles reflex. Statistical analyses were performed with SPSS (Chicago, IL, USA) software.

4.6.3 Determinants of spontaneous HNP resorption (II)

Repeated-measures analysis of covariance (ANCOVA) models were used with volume of HNP at baseline and at either two or 12 months (time periods 1 and 2) as dependent variables, imaging (baseline and follow-up) as a within-subject factor, and gender, age and rim enhancement thickness as between-subject factors. Duration of radicular symptoms was used as a covariate. Significances of Komori classification, disc displacement classification, localization of HNP in the epidural space, degree of disc degeneration at symp-

tomatic level, body mass index (BMI) and smoking were assessed both one at a time and with all determinants included in the model. All the determinants were categorical or categorized except for the duration of radicular symptoms. Correlation of HNP resorption with clinical symptoms was evaluated with the t-test. Significant resorption was defined as at least 40% of volume reduction from the baseline value at two months. P values less than 0.05 were considered statistically significant. SPSS 11.0 software was used to conduct the analyses.

4.6.4 Effect of periradicular cortisone injection on herniation resorption (III)

Median values were used in the study because of the skewed distribution of the measured enhancement parameters. The Mann-Whitney U test was therefore used to compare the actual changes of the variables of interest from baseline to two months, and from two months to 12 months between the saline and methylprednisolone groups, and to analyze resorption according to location of herniation in the epidural space. The nonparametric Friedman test was used to evaluate the significance of resorption separately in both groups. P values less than 0.05 were considered significant. SPSS 11.0 software was used in the statistical analysis.

4.6.5 The effect of infliximab on spontaneous HNP resorption (IV)

The objectives of the MRI substudy of the Finnish Infliximab Related Study II (FIRST II) were to evaluate the effect of infliximab versus placebo on the change in herniation volume, thickness of rim enhancement, rim enhancement extent and nerve root edema over the six-month follow-up period. The differences between treatment groups for continuous variables, i.e. baseline status and changes in MRI variables at each time point, were assessed with the Mann-Whitney U test or Student's t-test for normally distributed variables (age, height, weight and duration of current sciatic episode). Fisher's exact test or the Chi-square test was used for categorical variables. A p-value less than 0.05 (two-sided) indicated statistical significance.

The overall changes in herniation volume, thickness of rim enhancement and extent of rim enhancement were evaluated using repeated measures analysis with a general, linear, mixed model with fixed times and covariates, including the baseline value of the variable of interest, duration of current sciatic episode and age. For the change in nerve root edema, analysis of repeated measures for categorical data was used. In discectomy cases, the last-observation-carried-forward technique was used for the post-surgical MRI data. Results for patients not undergoing a surgical procedure were shown separately. All analyses were performed on an intention-to-treat basis.

5 Results

5.1 Correlation of symptoms and signs with MRI findings (I)

5.1.1 Patient disposition and characteristics

MRI was performed on 160 patients. The symptomatic level was L3–L4 in six cases, L4–L5 in 75 cases and L5–S1 in 67 patients. Six patients had a normal disc at the symptomatic level and 21 had a bulging disc. Forty-five of the herniations were classified as contained, 65 as uncontained, and 12 as sequestrations. Figure 3 describes the flow-chart of the study.

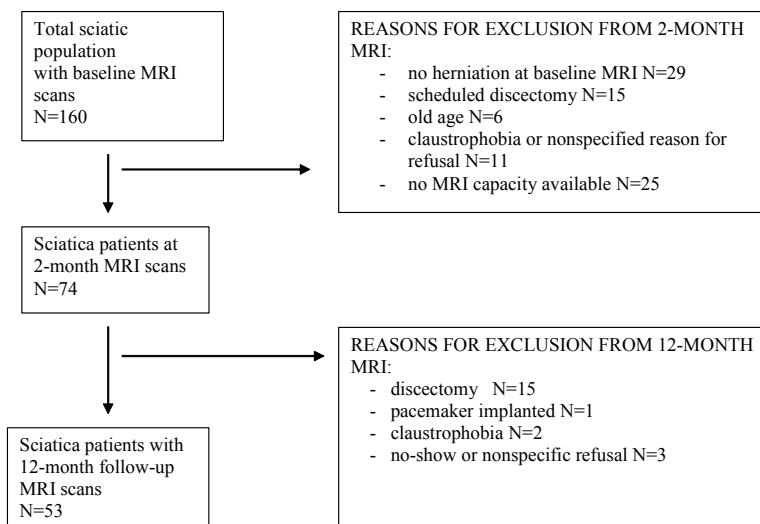


Fig. 4. Flow-chart of patients in the follow-up MRI process. Exclusion criteria are described on the right.

5.1.2 Herniation volume

The mean volume \pm standard deviations (SD) of all disc displacements was 830 ± 663 mm³; for those classified as bulges at most 149 ± 224 mm³; for contained herniations 665 ± 409 mm³; for uncontained herniations 1063 ± 643 mm³; and for sequestrations 1360 ± 987 mm³. The association between disc displacement volume and type of disc displacement was highly significant ($P<0.001$). Great values of SD, however, can cause unreliable results in group comparisons.

5.1.3 Symptoms and signs

In the whole study population neither leg pain, back pain, nor disability correlated significantly with the enhancement parameters or with the herniation volume. The result of SLR was found to correlate only slightly with the extent of rim enhancement ($r^2=-0.19$, $P=0.04$), when only herniations were included. The Achilles reflex was abnormal in 48 patients and normal in 100 patients with HNP. Abnormality of Achilles reflex correlated significantly ($P<0.001$) with disc level. Of the 67 patients with HNP at L5–S1 level, 39 (58%) had an abnormal Achilles reflex in contrast to 9 of 81 (11%) patients with HNP at the two upper levels. Four of 67 patients with a HNP at L5–S1 level had an extra-foraminal herniation. Abnormal Achilles reflex caused by disturbance of the S1 nerve root correlated significantly with volume of HNP ($P=0.003$), neural compromise ($P=0.002$), type of HNP ($P<0.001$), thickness of rim enhancement ($P=0.021$), and extent of rim enhancement ($P<0.001$). The mean extent of rim enhancement in patients with normal and abnormal Achilles reflex is presented in Figure 5.

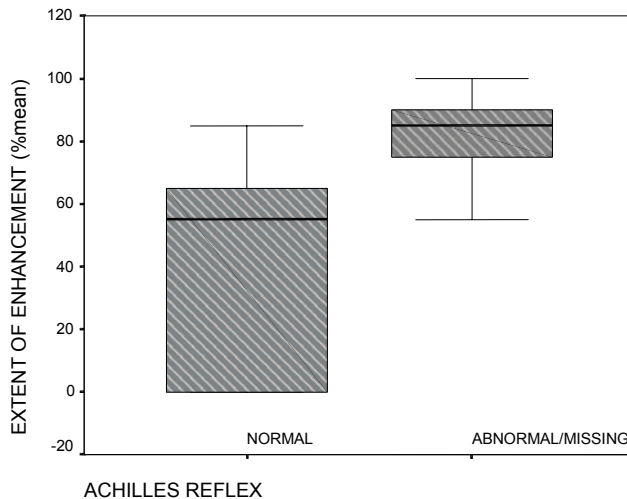


Fig. 5. Box plots representing extent of rim enhancement according to Achilles reflex. The mean extent of rim enhancement was much greater in patients with abnormal Achilles reflex. The box plots show the median (50th) percentile and the interquartile (25–75th) range. Vertical bars are minimum and maximum scores.

5.1.4 Rim enhancement

The extent of rim enhancement \pm SD averaged $16\pm 32\%$ for bulges, $65\pm 30\%$ for contained herniations, $77\pm 22\%$ for noncontained herniations, and $93\pm 7\%$ for sequestrations. The thickness of enhancement was 0.2 ± 0.5 mm for the combination of normal and bulges, 1.1 ± 0.5 mm for contained herniations, 1.3 ± 0.4 mm for uncontained herniations, and 1.6 ± 0.5 mm for sequestrations (Figure 6). No enhancement was observed when the symptomatic disc was classified as normal. The degree of disc displacement in MRI correlated strongly with all enhancement parameters ($P<0.001$ for all). However, as the associations of enhancement signal intensity with symptoms and signs were weaker, only the intercorrelations of enhancement thickness and extent were evaluated.

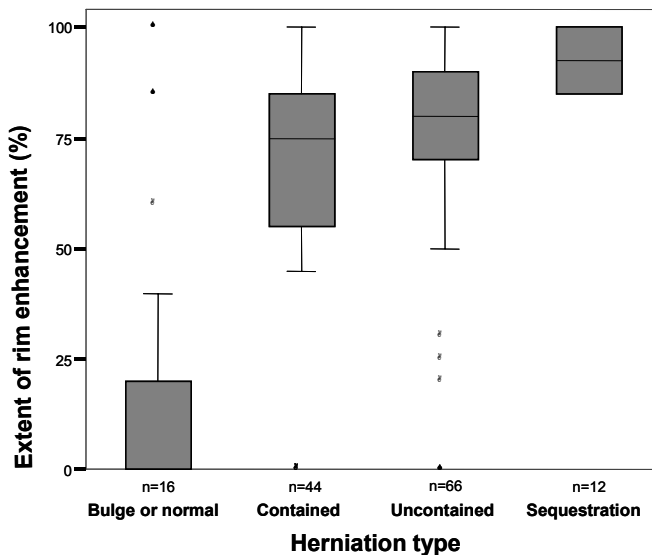


Fig. 6. Extent of rim enhancement in relation to herniation type. Uncontained herniations and sequestrations were more extensively enhanced than contained herniations and bulges.

The duration of sciatic symptoms correlated significantly with the extent of enhancement ($r^2=-0.24$, $P=0.008$) and thickness of enhancement ($r^2=-0.34$, $P<0.001$). When duration of symptoms was classified as a categorical variable, it still correlated significantly with the thickness of enhancement ($P=0.015$), but not with the extent of enhancement. The age of patients did not correlate with the enhancement parameters. The final model included only the extent of enhancement and neural compromise. A rim enhancement extent greater than or equal to 75% increased the odds for abnormal Achilles reflex 12-fold ($P=0.0002$), and for major neural compromise almost five-fold ($P=0.025$).

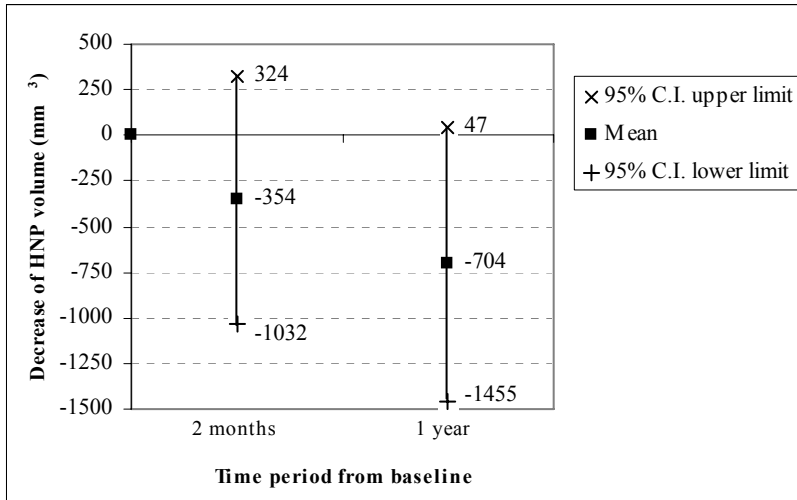


Fig. 7. Mean values of HNP volume reduction at two-month and one-year follow-up MRI. Mean value for HNP volume reduction 354 mm³ at the two-month and 704 mm³ at the one-year follow-up MRI.

5.2 Determinants of herniation resorption (II)

5.2.1 Herniation volume

Significant volume reduction of disc herniation occurred already from baseline to two months (period 1: mean change -354 mm³, N=68, p=0.004), although it was more pronounced at the final one-year follow-up (period 2: mean change -704 mm³, N=51, p<0.001) (Figure 7). The extent of enhancement did not decrease significantly over time (data not shown).

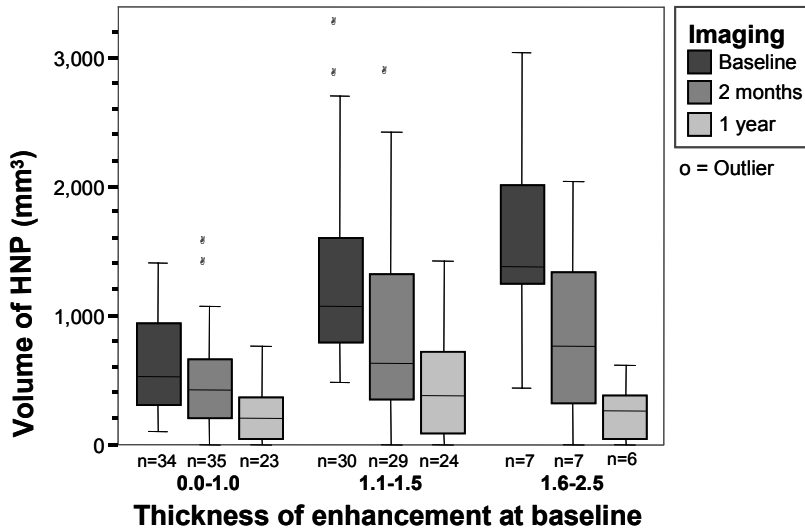


Fig. 8. Reduction of HNP volume as a function of time and thickness of rim enhancement at baseline. Regression of HNP volume is more pronounced in larger herniation, which also have thicker rim enhancement.

With all the determinants for HNP volumes regression included in the model, the most significant were time of imaging, thickness of enhancement, age at baseline, and Komori classification, all of which were selected for the final analysis with adjustment for duration of radicular symptoms. Extent of rim enhancement was also a significant determinant, but because its significance was less than that of thickness of enhancement it was not selected in the final model. In the final model, shown in Table 2, the only significant determinants for both time-periods (period 1: baseline to two months and period 2: baseline to one year) were thickness of enhancement ($p=0.003$ and 0.009 , respectively) and Komori classification ($p=0.019$ and 0.002 , respectively). Age was significant only for period 1 ($p=0.034$). Higher baseline scores of rim enhancement thickness, higher degree of HNP displacement in the Komori classification, and the age category 41–50 years were associated with higher resorption rate.

Table 2. Volume of herniated nucleus pulposus (HNP) at baseline (mean \pm SD) and volume reduction rate (%) within the follow-up periods for the most significant determinants. Repeated-measures analysis of covariance (ANCOVA) was used in the statistical analysis from baseline to two months (Δ_{0-2}), and from baseline to 12 months (Δ_{0-12}).

	N ¹	Volume at baseline (mm ³)	ANOVA tables					
			Δ_{0-2}			Δ_{0-12}		
			N ¹	$\Delta(\%)^2$	Sig.	N ¹	$\Delta(\%)^2$	Sig.
All	71	1010 \pm 710	68	-35		51	-68	
Within-subject factor: Imaging time					0.002			<0.001
Thickness of rim enhancement					0.003			0.009
0.0–0.5 mm	3	361 \pm 228	3	20		3	-42	
0.5–1.0 mm	31	642 \pm 366	29	-30		18	-55	
1.0–1.5 mm	30	1312 \pm 737	29	-35		24	-69	
1.5–2.5 mm	7	1623 \pm 874	7	-46		6	-84	
Age					0.034			0.075
19–40 years	30	1095 \pm 716	30	-20		16	-66	
41–50 years	25	1164 \pm 760	22	-57		21	-71	
51–78 years	16	609 \pm 460	16	-24		14	-65	
Komori classification ³					0.019			0.002
Normal/mild abnormality	61	892 \pm 596	59	-33		44	-63	
Migrating	10	1727 \pm 943	9	-39		7	-82	
Duration of radicular symptoms					0.924			0.849

¹ Listwise handling of missing data in repeated-measures ANCOVA.

² $\Delta = (\text{Volume at follow-up} / \text{Volume at baseline}) * 100$.

³ Komori classification: normal/mild abnormality (Komori grades 0–1) if HNP extends less than 33% above or below the height of adjacent vertebrae, and migrating if HNP extends 33% or more above or below the height of adjacent vertebrae (Komori grades 2–3).

Both Komori classification and thickness of enhancement had significant associations with time in the one-year follow-up (period 2). The interaction seems to be because herniations with higher Komori classification or with greater baseline enhancement thickness (Figure 8) have a more rapid resorption rate.

5.3 Effect of periradicular steroid injection (III)

5.3.1 Changes in herniation volume

Change in herniation volume from baseline to two months was measurable in 34 patients of both groups, and from two to 12 months in 26 patients of the steroid group and 24 patients of the saline group. There was no significant difference in the volume of herniations between the two groups at baseline. The median change of volume for the whole analyzed group from baseline to two months was -94 mm^3 in the saline group and -216 mm^3 in the steroid group ($P=0.18$). The corresponding values from two months to 12 months were -172 mm^3 and -140 mm^3 , respectively ($P=0.27$) (Figures 9 A&B). For contained herniations, the median change in herniation volume was -106 mm^3 in the saline

group and -128 mm^3 in the steroid group ($P=0.99$). However, from two to 12 months a trend in favour of the steroid option was evident (-108 mm^3 for saline and -420 mm^3 for steroid; $P=0.13$). For extrusions, the median change in volume from baseline to two months was -32 mm^3 in the saline group and -304 in the steroid group ($P=0.16$), and the change from two months to 12 months was -172 mm^3 and -116 mm^3 , respectively ($P=0.12$). The change in herniation volume was similar in the two treatment groups when analyzed according to herniation location in the epidural space.

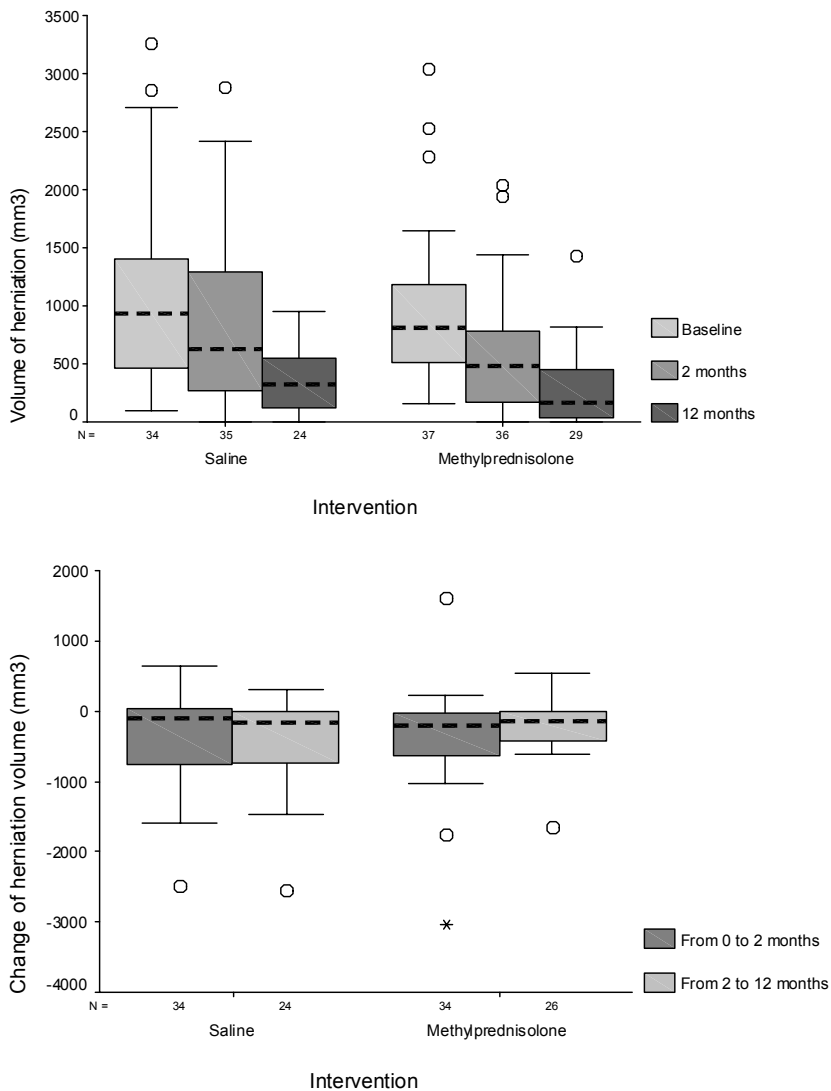


Fig. 9. A. HNP volume at different time points during the follow-up. HNP-volume decreased in both treatment groups significantly. B. Change of HNP volume for the follow-up periods in both treatment groups presented as a boxplot. There is no significant difference in the change of HNP volume.

5.3.2 Changes in enhancement parameters

Change in the extent of rim enhancement from baseline to two months was measurable in 36 patients of the steroid group and 33 patients of the saline group, and from two months to 12 months in 26 patients of the steroid group and 24 of the saline group, respectively. The median extent of rim enhancement in the saline group decreased from 80% at baseline to 75% at both two and 12 months. In the methylprednisolone group, the median extent of enhancement decreased from 80% at baseline to 75% at two months and to 55% at twelve months. There were no significant differences between the groups for either follow-up period. The median change in the extent of rim enhancement between the treatment allocations was similar in the subgroup of contained herniations and extrusions. However, for contained herniations the extent of enhancement remained high until the two-month follow-up but thereafter decreased considerably. In the case of extrusions it remained high throughout the follow-up period. The changes in the thickness of rim enhancement were minimal in both treatment groups and also in both subgroups during the follow-up period. Fifteen patients rescanned at two months underwent surgery after the two-month assessment. They were not scheduled for the one-year follow-up imaging. In the subgroup of contained herniations, seven of the operated patients had received saline and one patient steroid injections, whereas in the subgroup of extrusions, six of the operated patients had received steroid and one saline injection. No significant differences were observed in the change of enhancement parameters from baseline to two months.

5.4 Effect of infliximab on HNP resorption (IV)

5.4.1 HNP volume

At baseline, mean HNP volume was 846 mm³ in the infliximab group and 972 mm³ in the placebo group ($p=0.13$). The average HNP volume decreased from baseline to six months by 431 (± 516) mm³ in the infliximab group ($n=11$) and by 381 (± 410) mm³ in the placebo group ($n=10$). The difference in volume decrease between the infliximab and placebo groups was 50 mm³ (95% confidence interval [CI] of -379 to 478). When excluding the patients with a discectomy, the average decreases from baseline to six months were 539 (± 508) mm³ in the infliximab group ($n=9$) and 441 (± 436) mm³ in the placebo group ($n=8$). The difference between groups in this case was 98 mm³, with a CI of -395 to 591. No significant difference between the treatment groups existed in the repeated measures analysis ($p=0.81$ for all patients and $p=0.99$ when excluding discectomy patients), whereas a significant time effect ($p<0.01$; both analyses) was observed, indicating a significant HNP volume decrease in both groups over the six-month follow-up period (Figure 10).

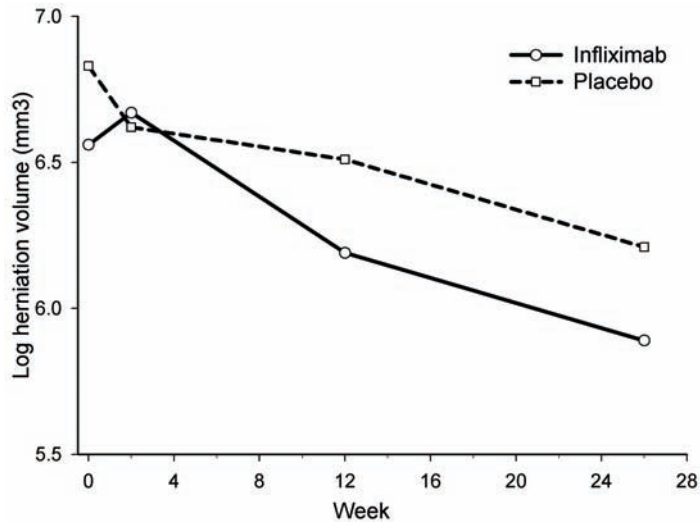


Fig. 10. HNP volume as a function of time in the infiximab and control groups. The regression of HNP is slightly more pronounced in the infiximab group after the first two weeks.

5.4.2 Rim enhancement

The treatment groups were similar with regard to baseline rim enhancement thickness. On average, rim enhancement thickness increased by 0.3 mm from baseline to two weeks in the infiximab group, compared to a slight decrease of 0.2 mm in the placebo group ($p=0.003$). After two weeks, the thickness of rim enhancement decreased similarly in both groups (Figure 11). After two weeks neither group had a significant change in rim enhancement thickness over the six-month follow-up period ($p=0.46$ for all patients and $p=0.81$ when excluding discectomy patients). Similar results were obtained in the repeated measures analysis ($p=0.10$ and $p=0.14$, respectively).

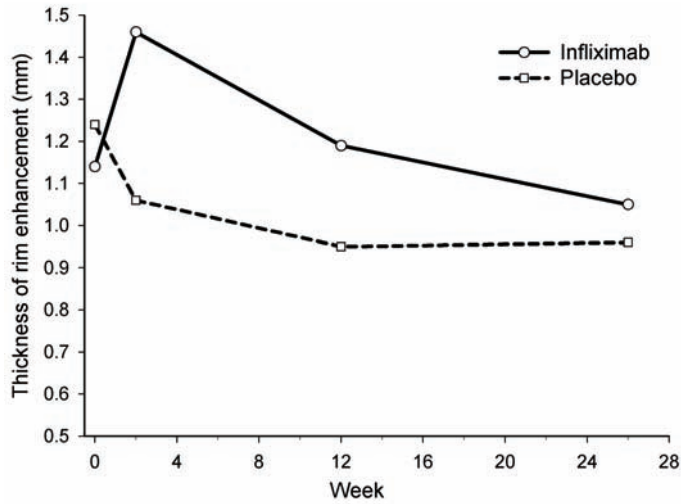


Fig. 11. Thickness of rim enhancement as a function of time in the infliximab and control groups. Thickness of rim enhancement was elevated in the infliximab group at two weeks compared to a sustained decrease in the control group.

Changes in extent of rim enhancement from baseline to six months were not significantly different between the groups ($p=0.19$) for all patients and when excluding discectomy patients. Although the extent of rim enhancement thickness decreased continuously from two weeks to six months in the infliximab group, compared to being more stable over this period in the placebo group, formal testing for interaction showed no statistically significant difference between the treatment groups ($p=0.10$ for all patients and $p=0.12$ when excluding discectomy patients).

5.4.3 Nerve root edema

At baseline, nerve root edema was observed in 91% of patients in the infliximab group and 60% of patients in the placebo group ($p=0.15$). At each time point following infusion of the study agent, as well as overall, the presence of nerve root edema was similar between the treatment groups ($p=0.47$ in repeated measures analysis, $p=0.45$ when excluding discectomy patients).

6 Discussion

6.1 Study populations

Two different study populations were gathered for this study. The first study population (I, II and III) consisted originally of 160 sciatic patients with dermatomal unilateral pain below knee level. The duration of symptoms was between one and three months. Patients who had applied for early retirement or who had previous surgery were excluded in order to achieve a more homogenous population without conflicting secondary benefits and to avoid postsurgical non-herniation-induced sciatica or complications. This selection bias was considered to be nonsignificant, because consecutive eligible patients were recruited and only eight refused to participate in the study. Of the final population only 29 had sciatica without herniated disc. Study populations in Studies II and III consisted of rescanned patients of Study I. Seventy-three patients were scanned at two months and 55 at 12 months. All patients had at least one HNP at baseline. Reasons for exclusion are tabulated in Figure 3.

The second study population consisted of 21 patients with unilateral moderate to severe sciatic pain with a MRI confirmed disc herniation concordant with the symptoms and signs of radicular pain. The duration of symptoms was similar to that in Studies I–III. Exclusion criteria included application for early retirement and previous back surgery. The small number of patients lowered the statistical power of this study. Patients in Study IV were also recruited from the catchment area of Oulu University Hospital.

6.2 Validity of the methods

In these studies, validated questionnaires and clinical examinations were used to assess sciatic patients. Periradicular injections were performed by an experienced radiologist using a conventional technique (Derby *et al.* 1992). Intravenous infliximab and saline infusions were performed after the baseline imaging in Oulu University Hospital. Thus both interventions (periradicular injection and I.V. infusion) had optimal adherence.

Computed tomography is widely used for spine imaging, mainly because of its ability to distinguish soft tissues from bony structures (Modic *et al.* 1988a). CT is also easier to obtain than MRI at short notice in many institutions. The accuracy of CT in HNP imaging is nearly as good as that of MRI (Jackson *et al.* 1989). Radiation dose reduction policies, however, favor the use of non-ionizing study methods whenever possible. MRI is the method of choice at the moment, especially in follow-up studies. Myelography does not have a significant role in modern IVD imaging, unless there are contraindications for MRI and CT or there is fixation material that causes strong artefacts in MRI and CT (Herzog 1996). Therefore, MRI was the obvious choice as the imaging modality, since it does not involve radiation, has superior anatomic resolution and allows fat suppression and free slice orientation selection (Czervionke & Berquist 1997). Moreover, Gd-DTPA has far less side-effects than iodine-based contrast materials used in computed tomography (De Ridder *et al.* 2001, Cochran 2005).

The MRI examinations were obtained with 1.5T imaging system. The images in Studies I, II and III were interpreted by one reader blinded to clinical data or whether images were from baseline or follow-up examinations. The intra- and inter-observer reliabilities for HNP volume and extent of enhancement were calculated from a subgroup of 19 patients. The agreement was moderate for both of these parameters, which were used in the data analyses. In Study IV all the examinations were read by two radiologists. Intra- and inter-observer agreements were again good or moderate for HNP volume and extent of enhancement. Intra-observer agreement for enhancement thickness was good, whereas inter-observer agreement was moderate. Nerve root swelling was found to have moderate intra-observer agreement but poor inter-observer agreement.

MRI sequences were selected in order to visualize HNP, including rim enhancement, and the whole lumbar spine, because some rare causes of sciatica (tumours, epidural hematomas, synovial cysts, spinal canal stenosis etc). were to be ruled out. Thinner slices (3 mm) in axial and sagittal planes with greater matrix could have given even more detailed images and more precise measurements, but the extra time needed for higher resolution imaging was not feasible in this study. The great number of examinations and the limited MRI capacity resulted in some compromises in the imaging protocols. All the images were analyzed on a diagnostic workstation which enabled the use of magnification and measuring of the volume and other parameters with considerable accuracy.

The Gd-DTPA injection was given just prior to the T1 fat saturated sequences to keep the time interval within two to four minutes.

This time frame usually allows Gd-DTPA to concentrate in the vascularised tissue found in the HNP, but is not too prolonged for the contrast material to “wash-out” from the tissue.

There is usually a dose-dependent curve in the enhancement of pathologic tissue (Hylton 1999), although it has not been studied in HNP tissue. The intensity of enhancement in the HNP was not, however, considered as important a factor as rim enhancement thickness and continuity. Thus increasing the Gd-DTPA dose was not considered to have any significant effect on the enhancement parameters.

6.3 Gd-DTPA enhancement in MRI versus symptoms and signs of sciatica

In the current study, disc herniation-induced neuronal function abnormality (characterized by abnormal Achilles reflex) was found to correlate strongly with the extent of rim enhancement at L5/S1 level. This finding is in accordance with earlier observations, because rim enhancement is thought to represent an inflammatory reaction around disc herniation (Ikeda *et al.* 1996). The neurotoxic nature of nucleus pulposus-induced inflammation has been demonstrated in animal models (McCarron *et al.* 1987, Olmarker *et al.* 1993). The current study showed that the process of herniation regression can involve neurotoxic elements, since the abnormal Achilles reflex correlated strongly with the extent of rim enhancement. Moreover, abnormality of the Achilles reflex was more prominent in the acute phase of the disease, consistent with the earlier observations (Olmarker *et al.* 1993).

Although peripheral disc enhancement has been studied previously, correlations between contrast enhancement and clinical signs and symptoms, as evaluated in the current study, have not been done previously. Rim-like contrast enhancement with Gd-DTPA at the periphery of a herniated disc has been reported in earlier studies (Galluzzi *et al.* 1995, Modic *et al.* 1995, Komori *et al.* 1998). Histologic studies have shown that HNPs have a zone of neovascularization at the outermost edge, which is thought to cause the accumulation of contrast material in the disc tissue. In addition to small vessels, inflammatory cell infiltrations have been discovered in herniations (Yasuma *et al.* 1993, Ikeda *et al.* 1996). Macrophages are thought to play a major role in the resorption of herniations (Haro *et al.* 1997) and they are more prominent in extrusions than in non-extruded HNPs (Grönblad *et al.* 1994, Arai *et al.* 2000). Contrast enhancement in disc periphery has usually been evaluated in follow-up studies to understand its significance in spontaneous disc herniation regression (Bozzao *et al.* 1992, Galluzzi *et al.* 1995, Modic *et al.* 1995). Contrast enhancement around disc herniations in our patients was most prominent in extrusions, which is in accordance with earlier observations (Ikeda *et al.* 1996).

Enhancement parameters, other than duration of symptoms, were not associated with clinical symptoms, whereas the extent of rim enhancement slightly correlated with SLR restriction. Modic *et al.* (1995) reported on 25 patients with acute lumbar radiculopathy, of whom 18 had disc herniation on MRI. Excellent correlation was noted between side and level of HNP and clinical radicular symptoms, but the degree of disability, pain, or frequency of neurologic symptoms did not correlate with HNP size or type. These results are in accordance with a recent study where type of disc displacement was not associated with clinical symptoms (Karppinen *et al.* 2001). SLR is a nerve root tension sign, which seems to correlate more strongly with HNP size (Thelander *et al.* 1994, Bradley 1999, Karppinen *et al.* 2001). Lack of correlation between enhancement and clinical signs in our study accords with earlier studies, because HNP enhancement merely represents a phagocytotic inflammatory reaction, and in histologic studies the amount of inflammatory cells in disc samples does not correlate with symptoms and signs of sciatica (Grönblad *et al.* 1994, Rothoerl *et al.* 1998).

Interestingly, at L5/S1 the extent of rim enhancement was a strong determinant of abnormal Achilles reflex. Enhancement extent over 75% increased the odds for abnormal

reflex 12-fold, when compared to enhancement extent less than 75%. Achilles reflex disturbance is pathognomic for irritation of the S1 nerve root (Knuttsen 1961), which is the reason abnormal Achilles reflex is a good in vivo model to study the clinical manifestations of rim enhancement. Because similar single nerve root-derived signs cannot be found at L3-L4 or L4-L5, only lesions at L5-S1 were analyzed. In the final logistic regression analysis, only the degree of neural compromise, in addition to the extent or rim enhancement, was a significant determinant of defective Achilles reflex. Furthermore, neural compromise was not nearly such a powerful determinant as extent of enhancement. This was somewhat unexpected, because neural compromise has been shown essential for symptomacy (Boos *et al.* 1995b). Many recent studies have focused on inflammatory mediators at the site of herniation. TNF α is crucial in NP-induced nerve root injury (Olmarker *et al.* 1998). This cytokine is also essential in the phagocytosis process (Haro *et al.* 2000), and can be found in granulation tissue (Takahashi *et al.* 1996). Therefore, it seems most likely that TNF α (and possibly other inflammatory mediators) have a dual action: it is beneficial for phagocytosis of the HNP, but may also have a harmful effect on the adjacent nerve root.

6.4 Determinants of spontaneous HNP resorption

Although most intervertebral disc herniations resolve spontaneously (completely or partly), the predictive factors for a benign disease course remain obscure to clinicians. Tools, such as MRI findings, prognostic of a benign disease course could thus have an important role in the physician-patient relationship. Thickness of enhancement at baseline was the strongest determinant of HNP regression in the current study population. The greater the enhancement thickness, the greater was the positive association with the HNP resorption rate. This result is in accordance with the study of Komori *et al.* (1998). Measuring the thickness of rim enhancement in disc herniation could thus become a new prognostic tool. However, if thickness of enhancement cannot be assessed, Komori classification is a useful predictive sign in MRI. Herniations extending at least 67% above or below the adjacent vertebrae have a greater resorption rate. Clinical symptom alleviation occurs concordantly with faster resorption rate. These results are in accordance with earlier pathologic studies correlating more neovascularization with faster resorption rate (Saal *et al.* 1990, Ahn *et al.* 2000) in large and uncontained herniations. The time of imaging correlated positively with HNP resorption, as predicted. This finding verifies the regression tendency of HNP in the current study population, where the symptoms of HNP were acute or subacute.

In most cases the natural course of a HNP involves its reduction in size over time (Saal *et al.* 1990, Bozzao *et al.* 1992, Komori *et al.* 1996). Larger migrating type herniations are likely to regress more readily than smaller ones (Teplick & Haskin 1985, Saal *et al.* 1990, Maigne *et al.* 1992, Komori *et al.* 1996), probably because of their tendency to penetrate the AF and PLL, thereby being exposed to the systemic circulation in the epidural space. However, in the current study penetration through the AF or PLL did not have a significant effect on resorption rate when measured by degree of HNP migration according to the Komori classification (Komori *et al.* 1996). Migrating type HNP was a significant

independent determinant of the phagocytotic process. This may be because either the evaluation of the penetration through the AF and PLL is not reliable (see Table 1) or higher degrees of migration, as evaluated with Komori classification, reflect larger HNP size as well as greater penetration through the PLL. It may also reflect a greater NP content in the migrating herniations, as higher signal intensity in disc herniations in T2W images compared to original nucleus pulposus reportedly correlates with favorable HNP regression (Henmi *et al.* 2002). This resorption mechanism is explained by swelling of the proteoglycan molecules when they are “released” from the collagen matrix. Later degradation of proteoglycans causes dehydration of the herniated disc material, thereby reducing the swelling pressure of the herniated material.

Based on the current view both inflammation and neovascularization, i.e. new angiogenesis, are required for phagocytosis (Yasuma *et al.* 1993, Arai *et al.* 2000, Haro *et al.* 2002). Interaction between activated macrophages and disc tissue leads to generation of inflammatory cytokines (Kato *et al.* 2004). These cytokines and catabolic enzymes are then involved in the induction of angiogenesis (Haro *et al.* 2002, Koike *et al.* 2003, Kato *et al.* 2004). The new blood vessels conduct new molecules into degrading HNP tissue. Many studies have demonstrated that a neovascularized zone infiltrated with macrophages develops in the outermost layer of herniated disc tissue (Yasuma *et al.* 1993, Ikeda *et al.* 1996). Macrophage infiltrations seem to be more prominent in large HNPs. Sequestrations have 2–3 times more inflammatory cells than extrusion type herniations (Virri *et al.* 2001). Neovascularization is also most abundant in extrusions and sequestrations, and is hindered by ligaments and/or annulus fibrosus (Ozaki *et al.* 1999). Several molecules have been suggested to be involved in the neovascularization of herniations. These include TNF α , matrix degrading enzymes (matrix metalloproteinase (MMP)-3 and -7 and plasmin) (Kato *et al.* 2004), basic fibroblast growth factor (Minamide *et al.* 1999), and vascular endothelial growth factor (VEGF) (Haro *et al.* 2002).

The immunological response, and thus angiogenesis, may be weaker in older age groups. Herniations are also harder, fibrotic, and desiccated, as observed in the cervical spine (Mochida *et al.* 1998). Moreover, herniations in the elderly also tend to have less nucleus pulposus and more annulus fibrosus and cartilaginous endplate material (Harada *et al.* 1989, Tanaka *et al.* 1993), which may be able to inhibit neovascularization of the HNP (Carreon *et al.* 1997). Unfortunately, MRI is not useful in differentiating the relative contributions of cartilage endplate, AF and NP.

At younger ages the inflammatory response needed for HNP resorption may be lower. Indeed, in an experimental canine model the younger animals had absent neovascularization and inflammatory cell accumulation in the sequestered disc fragment (Hasegawa *et al.* 2000). The results of the current study also support the age-dependence of HNP resorption, as the 41–50-year age group associated with an increased resorption rate.

In summary, it is proposed that when a patient has severe HNP-related symptoms MRI examination with gadolinium enhancement should be considered in order to assist clinical decision making, allowing the prognosis of spontaneous HNP regression to be taken into account along with other factors.

6.5 Effect of methylprednisolone on HNP resorption

Macrophage phagocytosis and inflammation are thought to be basic phenomena involved in the resorption of HNPs (Doita *et al.* 1996, Ikeda *et al.* 1996, Ito *et al.* 1996, Doita *et al.* 2001). Glucocorticoids suppress the immunologic response and exert numerous nonselective inhibitory effects on the synthesis of different proinflammatory mediators (Brattsand & Linden 1996, Takahashi *et al.* 1996). As the inflammatory zone, i.e., rim enhancement, around the HNP is essential for the resorption process, periradicularly injected corticosteroid may theoretically interfere with the resorption of disc herniation. The results of the current study indicate, however, that periradicular corticosteroid does not have a negative effect on the spontaneous resorption of the HNP. Instead, there tended to be even faster resorption of herniations in the steroid group from baseline to two months in the subgroup of extrusions, and from two to 12 months for contained herniations. To the author's knowledge there are no previous studies on the effect of periradicular corticosteroid on the HNP resorption process.

The number of patients in the study was limited and the variation of the measured enhancement parameters high. Furthermore, some of the patients with severe symptoms were operated early on and therefore were excluded from the one-year rescans. Although the measurements failed to show any significant differences between the non-operated and operated patients, the resorption process may have been different in those who underwent surgery. These considerations justify some caution when interpreting the results.

The hypothesis of steroid exerting a negative effect on the resorption process had to be abandoned, as no significant differences were found between the two treatments in terms of changes in HNP volume, enhancement continuity, or enhancement thickness. Minamide *et al.* (1998) described a negative effect of epidural betamethasone on the resorption of autologous intervertebral disc graft in rabbits, but the amount of corticosteroid was massive compared with the amount used in this study for periradicular infiltrations. Interestingly, for contained herniations methylprednisolone seemed even to enhance HNP regression after two months, concordant with its effect on clinical symptoms in this subgroup (Karppinen *et al.* 2001). In the current study, no marked change in the median extent of rim enhancement was observed for extrusions, whereas for contained herniations a marked drop in the extent of edge neovascularisation was detectable from two months onwards in both treatment groups. Several authors have observed a greater degree of neovascularization for extrusions than for subligamentous herniations (Doita *et al.* 1996, Ozaki *et al.* 1999), probably leading to a higher resorption rate of the extrusion type of herniations (Ahn *et al.* 2000). To the author's knowledge the current study is, however, the first to evaluate prospectively the dynamics of neovascularisation. Neovascularization probably remains high in extrusions, as these have ruptured the posterior longitudinal ligament and entered the epidural space. It may allow small vessels to penetrate the disc tissue more easily, whereas subligamentous HNPs are more or less immunoprivileged (Ozaki *et al.* 1999).

The results in this study indicate that a single injection of methylprednisolone does not disturb the process of HNP resorption. In addition, the study describes for the first time the dynamics of neovascularisation, visible in MRI, around the HNP during the healing process. Further studies are needed to clarify the mechanisms of spontaneous resorption of the HNP and the effect of different treatments on this process, because for example

multiple periradicular corticosteroid injections are being used with success in clinical practice to prevent discectomies (Riew *et al.* 2000). The dynamics of enhancement in this situation are not known.

6.6 Effect of infliximab on spontaneous HNP resorption

TNF α antagonists are very potent anti-inflammatory agents, which have been introduced for the treatment of severe sciatica (Karppinen *et al.* 2003, Korhonen *et al.* 2004, Korhonen *et al.* 2005). Due to the essential role of TNF α in the resorption process it is of utmost importance to evaluate also the effect of TNF α antagonists on the resorption of the HNP and on the rim enhancement in MRI (Haro *et al.* 2000, Haro *et al.* 2002). However, the findings in this randomized controlled trial showed that a single intravenous infusion of 5 mg/kg infliximab, a monoclonal antibody against TNF α , does not interfere with intervertebral disc herniation resorption. It confirms the earlier open-label study observation with a single infusion of 3 mg/kg of infliximab (Korhonen *et al.* 2004).

VEGF-upregulation is mediated via TNF α (Haro *et al.* 2002, Kato *et al.* 2004), and thereby anti-TNF α treatment could theoretically be deleterious, causing retardation of HNP resorption. It was therefore expected that infliximab infusion might inhibit the inflammatory reaction, depicted by rim enhancement around the HNP in contrast-enhanced MRI.

In fact, the volume of HNPs increased minimally during the first two-week observation period in the infliximab group. This coincides with the 10-day serum half-life of infliximab. It is speculated that macrophage phagocytosis compensates for this after the disappearance of infliximab from blood circulation. The mechanisms of the acceleration of resorption are unknown, but possibly the significant increase in enhancement thickness observed in the current study over the first two weeks is somehow related to this.

An interesting finding is that rim enhancement thickness remained persistently higher in the infliximab group at all assessment points. This may be linked to the slightly, but not significantly, lower herniation volume at the respective time points. The extent of rim enhancement remained at the same level in the placebo group, whereas it slightly decreased in the infliximab group. These changes were, however, quite small compared to the changes in enhancement thickness.

The observations of changes in nerve root swelling also favor infliximab over saline in the HNP resorption. However, the poor inter-observer reliability of nerve root swelling estimation makes this observation slightly doubtful. Nevertheless, the effect of infliximab on nerve root swelling correlates with the other observations, suggesting together that infliximab is not deleterious for HNP resorption. Histological samples of operated patients treated with infliximab could not be harvested in the current trial. Additional information on the effect of infliximab on the cell population and neovascularization in HNP could be gathered with histological studies. Such data would also be very interesting for assessing the expression of VEGF and TNF- α in the tissue samples. Haro *et al.* have shown that HNP tissue causes an increase in macrophage VEGF protein and mRNA expression upon exposure to disc tissue (Haro *et al.* 2002). They also showed that TNF α was required for the induction of VEGF and subsequent vascular tubule formation. Chro-

nologically, upregulation of both TNF α mRNA and protein expressions occurs first on exposure to herniated disc tissue, followed by VEGF upregulation in response to the increased level of TNF α expression. Proteolytic enzymes, needed for HNP degradation, are upregulated or activated later (Kato *et al.* 2004).

The current study is the first randomized trial to evaluate the sequential dynamics of natural HNP regression in a control group receiving only I.V. saline. The small number of patients (n=10) limits far-fetched conclusions, but full data were obtained on all patients until three months and on eight patients over the whole six-month follow-up. It is interesting to note the beneficial natural course of HNP in patients who received I.V. isotonic saline, which can hardly have any biological effect on resorption. The current observations need to be confirmed with a larger number of patients.

In conclusion, I.V. infliximab 5 mg/kg has no harmful effect on HNP resorption. Over the first two-week observation period it may slightly retard the resorption process, but after two weeks resorption is accelerated. It is an interesting observation that in patients who were candidates for discectomy, a significant HNP resorption occurred after a single I.V. infusion of isotonic saline.

7 Conclusions

1. Disc herniation-induced neuronal damage, characterized by abnormal Achilles reflex, correlates more strongly with the extent of rim enhancement than with neural compromise. Enhancement parameters were not associated with clinical symptoms, whereas the extent of rim enhancement slightly correlated with SLR restriction. According to these results the use of Gd-DTPA might be indicated in case of a symptomatic L5-S1 herniation with no clear nerve root compression.
2. Higher baseline scores of rim enhancement thickness, higher degree of HNP displacement in the Komori classification, and age category of 41 to 50 years were associated with a higher resorption rate of intervertebral disc herniation. Measuring the thickness of rim enhancement in disc herniation could thus become a new prognostic tool. However, if thickness of enhancement cannot be assessed, Komori classification is a useful predictive sign in MRI as herniations extending at least 67% above or below the adjacent vertebrae have a greater resorption rate. There are thus two objective variables that can be used in the radiologic evaluation of regression potential of a HNP.
3. As the inflammatory zone, i.e., rim enhancement, around the HNP is essential for the resorption process, periradicularly injected corticosteroid may theoretically interfere with the resorption of disc herniation. The results indicated, however, that a single injection of periradicular corticosteroid does not have a negative effect on the spontaneous resorption of the HNP. Instead, there tended to be even faster resorption of herniations in the steroid group from baseline to two months in the subgroup of extrusions, and from two months to 12 months for contained herniations.
4. Anti-TNF treatment was not noted to inhibit neovascularization, depicted by rim enhancement around the HNP in contrast-enhanced MRI. Herniation resorption was not negatively affected by anti-TNF treatment. These results imply that clinicians need not be concerned about the potential harmful effect of anti-TNF treatment on herniation resorption.

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Original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Autio RA, Karppinen J, Kurunlahti M, Kyllönen E, Vanharanta H, Tervonen O (2002): Gadolinium Diethylenetriaminepentaacetic Acid Enhancement in Magnetic Resonance Imaging in Relation to Symptoms and Signs among Sciatic Patients. *Spine* 27:1433–1337.
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