Chapter 9

Synthesis & discussion

Since ancient times many etiological explanations for sciatica have been proposed. In 1934 Mixter and Barr revolutionized the understanding of sciatica when they asserted that sciatica was caused by a herniated disc pressing against a nerve root.[1, 2] Worldwide this mechanical compression theory has been accepted giving rise to a greater interest in the lumbar disc as a source of sciatica and in the surgical treatment of such a disorder, which has come to be known as the "Dynasty of the Disc".[3, 4] Surgery for back and leg pain in association with nerve root compression has become one of the most commonly performed operative procedures worldwide. The mechanical concept of root compression by a herniated disc offers a satisfying explanation for most symptomatic patients. However, the scientific confusion lies in the observation of several Magnetic resonance imaging (MRI) studies showing a high prevalence of disc herniations ranging from 20 to 76% in persons without any symptoms.[5, 6] Nevertheless, MRI is considered the imaging procedure of choice for patients suspected of lumbar disc herniation[5, 7] and is also frequently performed in patients with persistent or recurrent symptoms of sciatica.[8] As such MRI is thus widely used in diagnosis and treatment planning of patients with intervertebral disc herniations.[9] The aim of this thesis was to uncover the relationship between MRI findings and clinical outcome in patients with sciatica. In this chapter the relationship between clinical outcome on one hand and baseline and follow-up MRI findings on the other hand will be placed in a scientific context. Furthermore the limitations and future research directions will be discussed.

How is interobserver agreement among spine specialists regarding MRI findings and does it impact clinical outcome?

In patients who suffered from sciatica for 6 to 12 weeks and who were potential candidates for lumbar disc surgery based on clinical grounds interobserver agreement among two neuroradiologists and a neurosurgeon was almost perfect for the affected disc level and the nerve root that most likely caused the sciatic symptoms (chapter 2). Substantial inter- and intra-observer agreement was observed regarding the presence of disc herniation and nerve root compression when the categories were "probability above 50%" and "probability lower than 50%". However, in general moderate agreement was found regarding the more specific characteristics of the impaired disc level (like signal intensity on T2 images and absence of epidural fat) and characteristics of the disc herniation (like its location, size and whether it should be classified as a protrusion or as an extrusion), which indicate that the assessment of many variables is fairly subjective. Within the literature, values of agreement on disc degeneration show a high variation depending on the variable investigated.[10] Although a few nomenclatures for degenerative disc disease have been proposed (like The Combined Task Force nomenclature or the Nordic Modic Consensus Group classification),[11] none has been widely recognized as authoritative or has been widely used in practice. This absence of consensus is greatly related to the multiple controversial aspects of disc abnormalities.[12] However, good reliability of imaging data in degenerative disc disease is important to determine the relationship between specific

imaging characteristics and patient outcomes. To gain more insight in this relationship, those interpreting the images should reliably assess the finding. One reason that a prediction model might lose its predictive power is the incorrect assessment of MRI findings (the predictors), which causes the inputs in the prediction model to be faulty.[13] As a first step on the road to determine the relationship between specific imaging characteristics and patient outcomes, radiologists and clinicians should strive to reduce variability in interpretations and adhere to a specific nomenclature for degenerative disc disease.[14] However, despite the adherence to predefined definitions in this thesis, the MRI assessors in this thesis sill only reached moderate agreements regarding many characteristics of the disc level and the herniated disc, which indicate that definitions and the adherence to a well defined nomenclature only is not enough for reaching substantial to excellent agreements. In addition to defining the language for image interpretation for degenerative disc disease, specific training might be an important next step.[13, 14] In support are the results of two reliability studies of The Spine Patient Outcomes Research Trial.[15, 16] In one of the two studies the reported agreement on disc morphology was only fair (kappa= 0.24) between the clinicians and radiologists.[15] In another study inter-reader reliability for disc morphology was excellent (kappa= 0.81) between 3 radiologists and 1 orthopedic surgeon.[16] The observation of a much better agreement in the second study might be explained by a better training of the MRI assessors as in that study the MRI assessors, before beginning the study, first evaluated a sample set of images with use of definitions and afterwards they met in person to review each image, enabling them to better streamline the way of interpreting the images.

It has been suggested that the poor outcomes following lumbar disc surgery may be more often due to the errors in diagnosis than failure of the surgical intervention or its complications.[17, 18] After one year follow-up the most favorable clinical outcome results were reported by those patients in whom all three MRI observers independently agreed about the presence of disc herniation or nerve root compression, followed by those with inconsistent interpretation and finally by those in whom independent agreement was reached about the absence of those findings (chapter 3). Thus based on the consistency in MRI interpretation different prognostic profiles could be made in sciatica. These results enable spine physicians to better inform patients with sciatica about their prognosis. If for example a spine surgeon and a radiologist both agree about the presence of a disc herniation the patient can be informed about a likely favorable prognosis, compared to a less favorable prognosis when the spine surgeon and radiologist do disagree about the presence of a disc herniation. The mechanism behind these prognostic profiles is probably related to whether there is truly a disc herniation or nerve root compression present: if present a favorable prognosis compared with unfavorable when absent. This hypothesis is supported by an earlier study that observed that presence of nerve root compression in patients with sciatica is associated with favorable prognosis in primary care patients with sciatica.[19]

CAN MRI HELP TO PREDICT SURGERY FOR SCIATICA?

The natural history of acute sciatica is in general favorable, with spontaneous resolution of the leg pain within 8 weeks in the overwhelming majority of cases.[20, 21] When patients fail to respond to conservative care, surgery might be considered. However, the duration of conservative care is not well defined. Of the patients who were randomized to receive prolonged conservative care in the Sciatica Trial a considerable part of 39% ultimately received surgery during the first year.[22, 23] Qualitative MRI parameters and the baseline size of the disc herniation did not significantly differ between the surgical and non-surgical group (chapter 4). Patients who did undergo surgery during follow-up had at baseline higher RDQ scores, more intense leg pain and smaller dural sacs and spinal canals compared to patients who did not undergo surgery. However, additional Receiver operating characteristic curve analysis showed that the MRI variables have only a poor ability to discriminate between patients who underwent delayed surgery and patients who did not. The overall results suggest that MRI is not suitable to distinguish between patients who will and those who will not undergo surgery for sciatica.

ARE THERE PROGNOSTIC RELEVANT MRI DIFFERENCES BETWEEN SCIATICA PATIENTS WITH AND WITHOUT DISABLING BACK PAIN?

Patients with sciatica frequently complain about associated back pain.[24] Patients with both sciatica and disabling back pain at baseline (defined as a Visual Analogue Scale for back pain of at least 40mm on a 0-100mm scale[25, 26]) reported an unfavorable prognosis at one-year follow-up compared to those with predominantly sciatica (chapter 5). If additionally a clear herniated disc with nerve root compression on MRI was absent, the results were even worse (one-year satisfactory results ranged from 50 to 91%). Herniated discs and nerve root compression on MRI were more prevalent among sciatica patients with compared to those without disabling back pain. However, vertebral endplate signal changes were equally distributed between those with and without disabling back pain. Large disc herniations and extruded disc herniations were also equally distributed between the two groups.

The clinical relevance of MRI morphological variations has been ongoingly debated over the past two decades.[5, 6] MRI differences have been reported between patients with both sciatica and low back pain compared to control subjects without symptoms,[5] and between sciatica patients compared to low back pain patients.[27] However, previous studies did not compare these findings between sciatica patients with and without back pain. Disc herniations are often seen on imaging studies in patients without symptoms.[5, 6] Contrary, in chapter 5 it was shown that a substantial number of patients without disc herniation or nerve root compression suffered from sciatica. Some researchers suggested that inflammation of the nerve root may also be a major factor in sciatica.[28, 29] If this hypothesis is correct, the finding that sciatica patients with back pain less often had a herniated disc compared to patients with predominantly sciatica may be explaind by a higher inflammatory component in sciatica patients with back pain. This may also explain why sciatica patients with back pain fared worse compared to patients with

predominantly sciatica as the extent of inflammation may be a causative factor in the cases with persistent pain and functional disability.

Despite remarkable advancements in diagnostic imaging and surgical techniques the results after lumbar disc surgery do not seem to have improved during recent decades: both classical studies and recent randomized controlled trials show that during longer follow-up treatment results for sciatica are satisfactory in 60 to 85% of the patients.[18, 23, 30-33] The number of proposed interventions developed by numerous disciplines including family practice, neurosurgery, orthopedic surgery, neurology, anesthesiology, psychiatry, physical therapy, social work, chiropractics, is overwhelming. Many widely prescribed treatments have no evidence for efficacy. Other effective treatments, which may be of benefit for subsets of patients, are indiscriminately applied. The results in chapter 5 of this thesis indicate that in sciatica subgroups with different prognostic profiles can be identified. A shift from a "one-size fits all" approach, where heterogeneous groups of patients receive broadly similar treatments, towards targeted treatments according to prognostic profiles or specific characteristics, may help to improve the treatment results.[34]

DO ANATOMICAL ABNORMALITIES ON FOLLOW-UP MRIS EXPLAIN WHY PATIENTS EXPERIENCE PERSISTENT OR RECURRENT SYMPTOMS OF SCIATICA?

MRI is considered the imaging procedure of choice for patients suspected of lumbar disc herniation[5, 7] and is frequently performed in patients with persistent or recurrent symptoms of sciatica.[8] Patients with sciatica and symptomatic lumbar disc herniations at baseline who were followed for one year in the Sciatica Trial still showed abnormalities in a considerable percentage after one year: 21% of surgically treated patients still had a herniated disc on MRI at one year compared to 60% of conservatively treated patients (Chapter 6). However, the presence of disc herniation or nerve root compression on MRI at one year follow-up did not distinguish patients with favorable clinical outcomes from those with unfavorable clinical outcomes. The presence of scar tissue was also not associated with patient outcome. The results give rise to a paradox that although imaging findings are not associated with patient outcomes in patients with recurrent or persistent symptoms of sciatica still many studies have shown that 60 to 82% of patients with a recurrent disc herniation on MRI improves after repeat surgery.[35-38] Despite this paradox, the results have implications for both clinicians and patients.

Clinicians should be more cautious in ascribing persistent or recurrent symptoms of sciatica to anatomical abnormalities visible on MRI. Although many physicians are aware that anatomical abnormalities correlate poorly with low back pain, for many it seems intuitively right to repeat MRI in patients with recurrent or persistent symptoms of sciatica who in an earlier stage did show abnormalities in presence of acute sciatic symptoms. Imaging has high costs, not only because of the direct costs of the imaging itself, but also due to the downstream effects such as additional tests, follow-up, referrals and invasive procedures.[39, 40]

For many physicians it is a logical step to perform surgery or other invasive procedures such as epidural injections in case repeat MRI still shows the abnormalities. Increased frequency of lumbar MRI has been shown to be associated with higher rates of spine surgery.[40, 41] However, the real issue is that until now, no better patient outcomes have been demonstrated with this increased use of advanced imaging.[41, 42] For example, in a randomized trial of simple versus advanced imaging for patients with low back pain, patients who received an MRI were twice as often more likely to undergo surgery over the subsequent year than were those undergoing plain radiography.[42] However, clinical outcomes at 1 year were equivalent, despite the difference in surgery rates. Based on the results of this thesis, it may well be that also for patients with recurrent or persistent sciatica follow-up clinical outcomes are simillar between those who undergo and those who do not undergo repeated MRI, rendering it of no benefit in the evaluation of patients with recurrent or persistent symptoms of sciatica.

Patients asking for reimaging because of persistent or recurrent symptoms should be informed about the difficulty in MRI interpretation after a first episode of acute sciatica. Wanting diagnostic testing is a frequent reason for repeated office visits for patients suffering from chronic back pain.[43] Many patients believe that the more diagnostics tests performed, the higher and better the quality of care.[44] Many physicians admit they succumb to their patients who are asking for spine imaging, even after explaining to the patient that imaging is unnecessary.[45] However, spine imaging may have an adverse effect as telling patients that they have a back imaging abnormality could result in unintended harms related to labeling.[46] In a randomized controlled trial involving patients with acute back pain or sciatica, patients were randomly assigned to whether or not receive their imaging results. Patients who received their imaging results reported less improvements in general health than those who were blinded to their results.[47] The mindset of patients that more imaging testing means better care must be abandoned in favor of a more evidence-based approach.[39] Patient education about the limits of spine imaging may help to bring patient's expectations more in line with the evidence.

ARE VERTEBRAL ENDPLATE SIGNAL CHANGES ASSOCIATED WITH BACK PAIN IN SCIATICA?

Patients with sciatica frequently experience disabling back pain. One of the proposed causes for back pain is Vertebral Endplate Signal Changes (VESC) as visualized by MRI. VESC are even a frequent surgical indication to perform a fixation of two or more vertebrae in the lower spine or replacing the disc by a prothesis, resulting in rising back surgery rates. The results in chapter 7 showed that undergoing disc surgery for sciatica was highly associated with progression in the extent of VESC compared to non-operative care. However, both at baseline and after one year follow-up, those with and those without VESC reported disabling back pain (defined as a Visual Analogue Scale for back pain of at least 40mm on a 0-100mm scale[25, 26]) in nearly the same proportion, regardless of having undergone surgery or not. Therefore the results suggest that VESC are not responsible for disabling back pain in patients with sciatica and one should therefore be reticent to offer back surgery based on VESC.

The relevance of VESC is highly debated in current literature.[48] VESC have been reported to be associated with low back pain in the general population aged 40 years[49] and in working populations.[50, 51] Two studies did not observe more VESC among chronic low back pain patients compared to control subjects,[52] or between VESC and previous back pain in subjects without current back pain or sciatica.[53] Two earlier studies investigated the correlation between VESC and low back pain in patients treated for lumbar disc herniations, with contradictory results to the present study.[54, 55] Unfortunately in both studies the VESC were described by only one radiologist. Possibly, results in the current thesis are contradictory with these two studies due to the definition of back pain. While they used self-reported back pain as the outcome, in this thesis 'disabling back pain' was defined according to patients' reported VAS for back pain.

In this thesis VESC Type 2 was the most common VESC at baseline (when patients presented with acute sciatica), a finding in concordance with previous studies in unoperated sciatica patients.[54, 56] The most common conversion in the surgical group was progression from no VESC at any level to type 1. In the study of Rahm et al. most patients developed VESC type 2 changes after lumbar discectomy.[57] However, contrary to the 12 months time interval between initial and follow-up MRI in this thesis, their interval varied from 32 to 59 months. In general it is agreed that VESC type 1 are unstable lesions which may convert to type 2 or back to normal.[58] The high observed prevalence of type 1 lesions at 12 months may still represent the more active stage of inflammation following disc surgery and these lesions may convert to type 2 or back to normal over time. Furthermore, the observation that 81% of conservatively treated patients did not convert from one VESC type to another after one year is in concordance with longitudinal studies that investigated the natural course of VESC and have observed that 48 to 86% of people do not convert from one VESC type to another over periods of 14 to 72 months.[54, 56, 59-61]

SHOULD ONE GIVE GADOLINIUM-BASED CONTRAST WHEN IMAGING PATIENTS WITH SCIATICA?

Gadolinium (Gd)-enhanced MRI is frequently performed in patients with persistent or recurrent symptoms of sciatica after surgical treatment.[8, 38, 62-64] The MRI assessors (2 experienced neuroradiologists and one neurosurgeon) presented substantial disagreement about gadolinium enhancement in lumbar spine MRIs between observers which was in firm contrast with their excellent agreement about the disc level of the herniated disc and compressed nerve root at baseline (chapter 8). Furthermore, no relationship was observed between enhancement findings and clinical findings at one year. The overall results indicate that Gd-MRI is not more helpful than non-enhanced MRI in the post-treatment evaluation of patients with sciatica.

Since the interobserver agreement regarding the enhancement findings was rather low, one could question the added value of correlating enhancement findings with clinical findings. To truly uncover the meaning of enhancement findings those interpreting the images must reliably assess the enhancement finding as one reason that a prediction model might lose its predictive power is the incorrect assessment of MRI findings, which causes the inputs in the prediction

model to be faulty.[13] It is crucial that radiologists and clinicians strive to reduce variability in interpretations as inconsistency in interpretation may lead to alternative treatment options between clinicians and therefore may impact the outcome of patient treatment.[11 65]

This thesis did not demonstrate an added value of Gd-MRI over non-enhanced MRI, which is in contrast with the expected diagnostic value. Given the additional costs of invasive contrast infusion compared to unenhanced MRI scanning, the addition of gadolinium in the postsurgical lumbar spine leads to more confusion at a higher financial reimbursement rate. Combined with the results in chapter 6 and 7 one could question the value of obtaining follow-up MRI at all when evaluating patients with recurrent or persistent symptoms of sciatica.

STRENGTHS AND WEAKNESSES

A strength of the studies in this thesis was that all images were assessed by two experienced neuroradiologists and one neurosurgeon who independently evaluated all MR images, blinded to clinical information. None of the readers had been involved in either the selection or care of the included patients. In addition, no meeting was organized in which a sample subset of images was evaluated as the discussion during this meeting might have caused the observers to adjust their diagnostic imaging criteria. Such a meeting could have led to an overestimation in the agreement among the three readers compared to the situation as it existed before undertaking the meeting. Moreover, the presence of disc herniation and nerve root compression was assessed with a four point scale providing the MRI assessors the opportunity to express their uncertainty. Another strength was that all sciatica patients who underwent MRI at baseline were followed, regardless of participation in the randomized controlled trial. At last, the percentage of patients who underwent MRI at one year follow-up is high (94.3%), especially in light of the observation that the majority of patients was recovered and one therefore may expect less willingness of patients to undergo repeat MRI.

The current thesis has also several shortcomings. Firstly, the interobserver agreement observed may have been overestimated, since one reading pair consisted of two neuroradiologists who had nearly the same observer experience and also worked together which may have led to an informal agreement in their diagnostic criteria.[66] However, the agreement between the neuroradiologists did not substantially differ from that of the reading pairs containing one of the two neuroradiologists and the neurosurgeon. Secondly, the use of standardized reporting forms with definitions and multiple choice categories allowed the assessments to be structured far more than possible in general clinical practice which may have caused an overestimation in the interobserver agreements.[16] Thirdly, the study population consisted of sciatica patients who had severe symptoms and were referred to the neurologists. These patients were willing to undergo surgery, so patients with a clear preference for conservative treatment are underrepresented in the current thesis. Fourthly, the reported MRI findings and their relation with clinical outcome was timed only once, one year after randomization. It is uncertain if comparable results at other time points would have been observed.

The results of this thesis have placed the relevance of MRI findings in patients with sciatica in a new light and many findings are in contrast with the intuitive feelings and ideas of spinal physicians. The finding that in patients re-imaged one year after treatment for sciatica, anatomical abnormalities visible on MRI did not distinguish patients with persistent or recurrent symptoms of sciatica from asymptomatic patients was remarkable. The same holds for a lack of a correlation between vertebral endplate signal changes and back pain. Gadolinium-enhanced MRI did also not prove more helpful than non-enhanced MRI in the post-treatment evaluation of patients with sciatica.

The role of MRI in patients with sciatica should be rethought, especially in patients with recurrent or persistent symptoms of sciatica. The results of this thesis counteract the intuitive feeling of the necessity of repeating MRI in these patients. The mindset of patients that more imaging testing means better care should be reshaped in favor of a more evidence-based approach. MRI may be repeated only when repeat surgery is considered in presence of unfavorable clinical history and physicical examination. More research is needed to assess the value of MRI in clinical decision making for patients with persistent or recurrent sciatica, in particular if treatment strategies according to MRI findings lead to different clinical outcomes in patients who experience persistent or recurrent symptoms of sciatica. It also remains unclear why symptoms relate poorly to evidence of disc herniation or nerve root compression on MRI. Inflammation of the nerve root may be a more important factor than mechanical compression. It seems that we will make a paradigm shift from mechanical into inflammatory origin, which comes down to going back in time to the 18th century when Cotugnio argued that sciatic complaints are a consequence of neuritis or edema of the sciatic nerve. Insight in the balance of mechanical and inflammatory factors may enable us to solve the paradox of no relationship between presence of a disc herniation on MRI and patient outcome in patients with recurrent or persistent sciatica while surgery is often helpful for these patients.

Prognostic profiles in sciatica vary greatly (ranging from 50 to 91% in this thesis). Reasons behind the different prognostic profiles in sciatica are currently not known. It may well be that the inflammatory component, which is currently not visible or quantifiable, plays also an important role in this observation. More research is needed to identify the reasons behind the different prognostic profiles in sciatica and how to apply new or existing therapeutic strategies accordingly. A shift from a "one-size fits all" approach towards targeted treatments according to prognostic profiles or specific characteristics will probably improve the treatment results.

At last, to thoroughly gain insight in the clinical relevance of imaging findings, good interobserver agreement is a prerequisite, which for some (especially gadolinium-enhancement) findings in this thesis was very low. As earlier mentioned, no nomenclature in the literature has been widely recognized as authoritative or has been widely used in practice. It is worthwile to consider approaches how to reach more consensus and how to subsequently adhere to one

nomenclature. Specific imaging training and defining the language for image interpretation by involving the various desciplines may help to attain this goal.

CONCLUSION

In contrast with the intuitive feeling of physcians many worrisome MRI findings do not correlate with patient outcome in patients with sciatica. Physicians should not ascribe persistent or recurrent symptoms of sciatica to the presence of abnormalities visible on MRI. However, many issues remain to be solved, especially the paradox of no association between presence of a disc herniation on MRI and patient outcome in patients with recurrent or persistent sciatica while surgery is often helpful for these patients.

Physicians should inform their patients about the limits of spine imaging in sciatica. One possible strategy is to explain patients of how common worrisome MRI findings are observed in persons who do not have any symptoms. This thesis enables physicians to implement this strategy and in that way reshape the mindset of many patients thinking that knowing imaging findings can only be good.

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