Clinical applications of Dixon chemical shift MR imaging: Morbus Gaucher, Morbus Hansen
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Summary, general discussion and future research
SUMMARY

In this thesis a new application based on an earlier described MRI technique is introduced. W.T. Dixon has described the basics of this technique, two-point chemical shift imaging, in 1984; a spectroscopic technique that can be used for imaging purposes (simple spectroscopic imaging) [1]. Two-point Dixon chemical shift imaging (Dixon technique) is based on the phase difference between water and fat when performing MRI. Conventional qualitative MR images are based on the sum of the signals of water and fat, while with the Dixon technique the relative contribution of water and fat to the overall MR signal are separated.

In our hospital there is a relatively large population of patients with neuropathic foot disease, usually caused by diabetes mellitus or leprosy. MRI as a diagnostic procedure is regularly performed in our institution for suspicion of osteomyelitis in in this population. A reliable homogeneous fat-suppression technique is necessary in particular in MRI investigations in case of suspected osteomyelitis [2-4]. With our MR imager, the frequency-selective presaturation fat-suppression did not provide a homogeneous fat-suppression in the distal extremities, a problem known from literature [5,6]. Since this is mainly caused by physical properties of the patient, it is largely independent of the equipment used.

In Chapter 2 a study concerning the clinical use of two-point Dixon chemical shift imaging as fat-suppression technique is described. In this study 31 consecutive patients clinically suspected of having bone marrow disease in distal parts of the extremities were evaluated with the Dixon technique. Since this technique consists of two MRI sequences, in-phase and opposed-phase series, a potential problem is displacement of the patients' hand or foot between these two series. The uniformity of fat-suppression, the frequency of occurring displacement artifacts and the applicability in routine clinical setting were investigated. A uniform fat-suppression was achieved in all 64 studies (100%). Displacement artifacts that severely hampered MRI reading were only present in one examination (2%). Two-point Dixon chemical shift imaging was concluded to be a reliable, excellent technique for achieving uniform fat-suppression in distal parts of the extremities and applicable in routine clinical setting.

Our group of patients with neuropathy and suspected osteomyelitis consist of patients suffering from diabetes mellitus or leprosy. Although there is extensive literature on MRI in patients with diabetes mellitus
suspected for osteomyelitis, no literature at all is present concerning MRI in patients with leprosy suspected for osteomyelitis [2-4, 7-13].

**Chapter 3** is, as far as we know, the first MRI paper on neuropathic feet in leprosy. We studied 10 leprosy patients with neuropathic feet, without complications, clinically not suspected of infection. The purpose was to obtain a baseline of the MRI changes, with the Dixon technique as fat-suppression technique, which could be present in leprosy. Almost all patients showed MRI changes, of which 90% were located in the region of the first metatarsophalangeal joint. An important finding was the degradation and interruption of the subcutaneous fat pad at the plantar side of the medial foot. From literature on MRI in patients with diabetes mellitus it is known that these changes may consist of hemorrhage and/or fibrosis [7,14]. It is hypothesized that these changes may precede the development of plantar ulcers in leprosy, as is suggested in diabetes mellitus. MRI could play an important role in detecting (areas of) neuropathic feet that are at risk for developing ulcers; this may influence clinical decision-making.

In **Chapter 4** the clinical problem, which initiated this research, is described. Leprosy patients with longstanding complicated neuropathy with a persistent warm foot in the presence of a non-healing ulcer, clinically suspected for osteomyelitis are described. Clinical examination lacks specificity in this patient group. A total number of 18 MRI investigations in 12 leprosy patients were analyzed. The accepted primary MRI criteria for osteomyelitis (low signal intensity on T1-weighted images, high signal intensity on T2 and (t)STIR or fat-suppression images and enhancement after intravenous contrast administration) [2-4,7-13] were positive in 17 of 18 MRI examinations. Of the secondary MRI signs earlier described for neuropathic feet of patients suffering from diabetes mellitus (ulcer, cellulitis, cortical interruption, sinus tract and abscess), an ulcer and cellulitis were present in all patients [2]. When compared to the gold standard for the diagnosis osteomyelitis (positive culture and/or histopathology taken from bone material) or clinical outcome after 6 months follow-up (when the gold standard was not available or not conclusive) there was agreement in 17 of 18 events. This study indicates that the primary MRI criteria established for diabetes can adequately be used in a population of patients with leprosy and longstanding neuropathic foot disease, for the detection of osteomyelitis.
Contrary to diabetes literature the secondary MRI signs seem of no additional value in diagnosing osteomyelitis in these leprosy patients.

**GENERAL DISCUSSION AND FUTURE RESEARCH**

The studies included in this thesis demonstrate the feasibility and clinical relevance of a new fat-suppression technique used in evaluating neuropathic feet in leprosy. This concerns patients in which MRI examinations, to our knowledge, have not yet been performed. Fat-suppression through the use of two-point Dixon chemical shift imaging provides homogeneous fat-suppression in the entire field of view. It is used in daily practice in particular when feet are imaged and fat-suppression after intravenous contrast administration is necessary. A limitation of the technique is that it is not a standard sequence on the MR machine and that post-processing is required.

Besides providing good qualitative imaging results by separating fat from water, this Dixon technique has the potential of providing quantitative data of fat and water. This is discussed in detail in the other part of this thesis, for another clinical application (Gaucher disease). This intrinsic possibility of the technique may proof to be of value in patients with neuropathic feet. The development of claw toes, a clinical problem in neuropathic feet, is thought to be caused by decrease in function of the intrinsic muscles of the forefoot. This has been analyzed by measuring the volume of these muscles with the use of MRI, hypothesizing that a decrease in volume of these muscles is related with the presence of claw toes [15]. On MRI this presents as a decrease in volume of muscle fibers, and an increase in intramuscular fat. By using the Dixon technique, the fractions of water and fat in these muscles can be analyzed. An earlier detection of loss of water might be found and feet at risk for developing claw toes might be identified. This clinical problem and the possible role for Dixon MRI is currently under investigation in a collaboration between the departments of radiology and internal medicine of our hospital.

Another intrinsic feature of the Dixon technique is the acquired out of phase (opposed-phase) sequence. In a regular in-phase MR image both fat and water contribute to the signal. In an opposed-phase signal fat and water are contributing in opposite direction to the MR signal. This means that areas in which water and fat are present in approximately equal
amount, the MRI signal is approaching zero. Therefore, areas of low signal intensity on the opposed-phase T1-weighted images in bone marrow represent areas with an equal percentage of fat and water. A sharp demarcation of areas with much water is seen. After intravenous contrast administration enhancement may be seen in these areas. The clinical relevance of these findings should be explored in another study, in which various sequences such as (t)STIR, Dixon fat-suppression, fat saturation T2-weighted TSE and Dixon opposed-phase images are compared.

Data are presented of MRI examinations in the neuropathic foot of leprosy patients in the Netherlands. We investigated neuropathic feet of patients without complications or complaints. We hypothesize that changes in the plantar fat pad at the first MTP joint in these patients may precede ulceration [7,14]. When, by intensifying physical examination these MR findings can be detected, this may lead to improvement in preventing the ulcer development. The second group of patients consisted of patients with a complicated foot with longstanding neuropathy and suspicion of osteomyelitis. MRI abnormalities compatible with osteomyelitis were detected at the medial side of the foot as well as (more frequently) at the lateral side of the foot. Patients with neuropathic feet, without longstanding disease, that have an ulcer or cellulitis, without clinical suspicion of osteomyelitis, are a group of interest. What are the MRI findings in these patients? What are the sites of involvement? It would be of interest to evaluate these patients. In this way a more complete overview of MR abnormalities in leprosy is obtained. In order to approach this target we currently work together with the Institute Oswaldo Cruz, Fiocruz, Rio de Janeiro, Brazil.

The study described in Chapter 3 revealed surprising results. In this chapter patients with leprosy and neuropathic feet without complications and clinically unsuspected of infection were studied. In these patients degradation of plantar fat pad at the medial side of the foot, in the region of the MTP 1 joint, was found. This new finding led us into a brief exploration of the biomechanics of the neuropathic foot in leprosy. Literature on this topic is sparse. Only a few authors published on the biomechanics in neuropathic feet, in a small number of patients [16-19].
It is stated that the alteration of biomechanics in neuropathic feet may influence the disturbance of plantar fat pad leading to hemorrhage and fibrosis and to fat pad degradation, which might precede ulcer development. These MRI detected findings were located primarily on the medial side of the foot, plantar to the first MTP joint. In order to conclude that in this particular patient population the medial side of the foot is at risk for developing ulceration and that this is due to changes in the biomechanics in this population needs confirmation in a larger patient population. The findings in the patients population of longstanding complicated neuropathic foot disease, described in chapter 4, differed from the previous ones since abnormalities were found in half of the patients on the lateral side of the foot. It seems that from a biomechanical point of view there is a difference between the two patient groups. There is little literature on the biomechanics in complicated neuropathic leprosy feet. Brandsma et al. hypothesized that the function of the ankle joint might be of importance in changing biomechanics from medial to lateral side of the foot in walking [20]. This might be a cause for the different distribution of MRI changes in the two groups. It would be of interest to analyze the walking cycle in different groups of leprosy patients with neuropathic feet. In this way more information is gained on the stress distribution in the foot. These findings should be correlated with the function of the ankle joint and with the MRI findings. In this way more information on the feet at risk, more precise the areas in the foot that are at risk will be obtained, thereby increasing the possibilities for prevention. In the western world neuropathic feet are far more commonly seen in patients suffering from diabetes mellitus. This most often is a combination of neural and vascular pathology; thereby differing from leprosy patients, who have, in essence a pure neuropathic foot. In our hospital there are outpatient clinics for patients with diabetes mellitus as well as leprosy. This combination is not often found. It would be of interest to start a comparative study between the two groups, focussing on the nature and the distribution of MRI changes. These findings should be correlated with biomechanical analysis and should be performed in patients with complicated longstanding neuropathic foot disease as well as patients with non-complicated neuropathic foot.
Summary, general discussion and future research

MRI examinations in leprosy patients with neuropathic feet are valuable. In non-complicated neuropathic feet, abnormalities are encountered that are hypothesized to represent areas at risk for developing ulcerations. In complicated feet suspected for osteomyelitis the extent of infection, both in soft tissue as well as bone marrow is visualized. Two-point Dixon chemical shift imaging is a good qualitative technique, producing a uniform fat-suppression in the entire field of view. The potential value of the other specific qualities of this technique, i.e. the out of phase sequence and the quantitative fat/water fraction measurement are promising and can be part of future research.

REFERENCES


