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CHAPTER 1

Introduction
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*Neuropathic foot in leprosy
*Imaging evaluation of osteomyelitis
*MRI - the Dixon technique
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**WHAT IS LEPROSY**

Leprosy is an infectious disease that is still incompletely understood and often feared. The causative micro-organism *Mycobacterium leprae* (*M. leprae*), is an acid-fast obligate intracellular organism first described by Armauer Hansen in 1874 [1]. The most probable spread of the *M. leprae* is by respiratory route, and it preferably invades skin and peripheral nerves. The majority of people will not develop clinical symptoms, since an effective immune response is developed before clinical disease appears. When clinical signs occur, after an incubation period of several years, one may only have an often self-healing, single lesion (indeterminate leprosy) [2,3]. However, when self-healing does not happen, the disease can progress.

The classification of leprosy is based on the immunological response of the host towards *M. leprae* [4]. This is the so-called Ridley-Jopling classification with a division in tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL) and lepromatous (LL) leprosy. The World Health Organization (WHO) nowadays classifies leprosy patients according to the number of lesions. Patients with 5 or less skin lesions are classified as paucibacillary leprosy (PB); patients with six or more skin lesions are classified as multibacillary leprosy (MB). The standard treatment for leprosy is the multidrug therapy (MTD) [5]. This MTD consists of rifampicin, dapsone and clofazimine, in which PB patients are treated with a combination of rifampicin and dapsone and MB patients are treated with a combination of rifampicin, dapsone and clofazimine. The chosen combination of drugs depends on the classification [5,6,7].
LEPROSY - GLOBAL SITUATION[8]

In 1991, WHO and its Member States committed themselves to eliminate leprosy as a public health problem by the year 2000; elimination being defined as prevalence <1 case per 10,000 people. At the end of 2000, the global prevalence of leprosy was below 1 case per 10,000. At the end of the year 2000 the latest available information indicates that there were 597,232 cases registered for treatment globally, with 719,330 cases detected during the last year of reporting. Among 122 countries considered endemic in 1985, 107 countries have reached elimination at the country level. At the end of 2000, leprosy was a public health problem in only 15 countries (prevalence rate >1 per 10,000 and population above 1 million), mainly in Africa, Asia and Latin America, of which the leading six countries are India, Brazil, Myanmar (Birma), Madagascar, Nepal and Mozambique.

LEPROSY - LOCAL SITUATION

In the Netherlands leprosy occurs as an import disease since a long time. The majority of patients nowadays are from Surinam: this is related to the colonial history. In the Academic Medical Center there is a relatively large group of patients with foot pathology due to leprosy. This group consists of patients with recent as well as longstanding neuropathic foot problems. They are treated in a multidisciplinary setting with a core of a tropical dermatologist, a surgeon, and a specialist in rehabilitation medicine (physiatrist). A specialized nurse provides regular foot and ulcer care. Registration of the complications of the feet is documented on the so-called FINU (Foot Ischemia Neuropathic Ulcer) data-form, designed by the Dutch Neuropathic Foot Society [9,10].

NEUROPATHIC FOOT IN LEPROSY

The invasion of Schwann cells by _M. leprae_ with the resulting peripheral nerve damage can lead to a so-called neuropathic foot. A neuropathic foot is defined as a foot in which one or more of the neuronal functions i.e. sensory, motor function or autonomic function is disturbed (consensus Dutch Neuropathic Foot Society). In leprosy the neuropathic foot is one of the major contributors to morbidity due to peripheral nerve damage.
The total number of leprosy-patients with foot problems is estimated on 20-30% of the leprosy patients worldwide. The sensory loss means that patients may not perceive trauma, resulting in development of complications. To identify the patients that lack the preventing sensibility the Semmes Weinstein monofilament test is used [11]. The feet of patients with a sensory loss of a 10-gram force are considered neuropathic feet at risk [11].

The neuro-osteoarthropathy in leprosy is comparable to diabetes and may lead to tarsal disintegration with osteolysis, fragmentation and progressive bone resorption. In extreme cases dissolution of the mid-foot results in separation of the forefoot and the hind foot, changing all biomechanics [9,12-14]. The skeletal abnormalities are evident in 20-70 % of hospitalized patients [15]. The most important difference between leprosy and diabetes is the fact that in principle in leprosy the neurological pathology is the only pathology present ("a pure neuropathic foot"), while in diabetes there is nearly always a combination of vascular disease and neurological disease.

Ulceration and infection (cellulitis or osteomyelitis) are important complications. When a patient with a longstanding neuropathic foot presents himself with a warm foot it is a clinical challenge to discriminate neuro-osteoarthropathy from an ongoing infection. This is especially difficult in the presence of an ulcer, since an ulcer itself leads to increased local temperature [12,16]. Clinical signs are often not conclusive in discriminating between infection (cellulitis or osteomyelitis) and neuro-osteoarthropathy. The need for further evaluation with imaging is present [17].

**Imaging evaluation of osteomyelitis**

Osteomyelitis is a serious medical problem that is associated with significant morbidity. Osteomyelitis may result from hematogeneous spread, from adjacent soft tissue infection or direct inoculation. In neuropathic feet most often osteomyelitis is due to adjacent soft tissue infection. Accurate early diagnosis is necessary to optimize treatment strategies. Since clinical evaluation is not accurate, support from diagnostic imaging techniques is required.

Diagnosing osteomyelitis is a well-known challenge in diagnostic radiology. Various imaging modalities are investigated in the analysis of
osteomyelitis in neuropathic feet [15,18-28]. Plain radiography does not show abnormalities related to osteomyelitis until 10-20 days after the onset of symptoms. Acute osteomyelitis has a permeative pattern on conventional radiographs. Characteristic findings include osteopenia with small ill-defined lucencies in the medullar bone and cortex. A chronic osteomyelitis may show areas of sclerosis. However, the radiographic diagnosis of osteomyelitis in neuropathic feet is more difficult, the differentiation from neuro-osteoarthropathy is not easily done [15,18,25,26,29].

Radionuclide imaging can also be used [18,25,26]. Three-phase $^{99m}$Technetium bone scintigraphy, $^{111}$Indium white blood cells scintigraphy or $^{67}$Gallium citrate scintigraphy may be used. Interpretation of three phase $^{99m}$Technetium bone scintigraphy is difficult in neuropathic feet. A high false positive rate is due to the simultaneous presence of neuro-osteoarthropathy. Also, $^{67}$Gallium citrate scintigraphy is generally not helpful because of the high percentage of false positive scans. Of the radionuclide modalities, $^{111}$Indium white blood cells scintigraphy is thought to be the most specific for osteomyelitis and carries the highest sensitivity [18,25].

Of all available imaging modalities, Magnetic Resonance Imaging (MRI) has been described as the modality with the highest sensitivity for diagnosing osteomyelitis, and carries a high specificity for differentiating osteomyelitis from cellulitis in the neuropathic foot of diabetic patients [18-22,25,30-34]. Tissue characterisation and spatial resolution facilitate identification of associated soft tissue pathology.

Normal healthy peripheral fatty (yellow) bone marrow shows a hyperintense signal intensity (SI) both on T1-weighted spin echo (SE) images (Short Repetition Time (TR), Short Echo Time (TE)) as on dual echo Fast SE (Long TR/TE). Osteomyelitis will change the SI due to the presence of more water in the bone marrow. Since water shows high signal intensity on T2-weighted images, it is not easy to detect when using T2-weighted fast SE sequences. Fat-suppression techniques are frequently used in MR imaging of the musculoskeletal system, in order to better appreciate bone marrow abnormalities, and soft tissue pathology [23,35-37]. The suppression of the relatively high signal of fat can lead to a more efficient use of the dynamic range for the display of tissue contrast on MRI [38]. Therefore several fat-suppression techniques are used. The
most widely used technique is frequency-selective presaturation [37]. However, in areas of irregular shape and abrupt changes between soft tissue and air, such as the distal extremities (hand and foot), this technique produces uneven fat-suppression and artifacts because the required magnetic field homogeneity cannot be achieved [23,33,39]. Since much of this problem is caused by physical properties of the patient, it is largely independent of the equipment used. Another widely used technique for suppression of the fat signal is the STIR (Short Tau Inversion Recovery) sequence. STIR is based on the rapid T1 recovery of fat and is, therefore, not significantly affected by field inhomogeneities. STIR is considered the most sensitive technique for identifying subtle bone marrow pathology [23]. Unfortunately, STIR suppresses all short T1 species, including tissues that have absorbed Gadolinium (Gd). Hence, it is not possible to use STIR fat-suppression to improve the detection of contrast enhancement [35]. For the detection of osteomyelitis this is an important disadvantage, because previous studies suggested that MR imaging with both fat-suppression and Gd enhancement may be the imaging method of choice in clinically complicated situations [33,40]. For the detection of subtle bone marrow pathology, such as a low-grade chronic infection, it is mandatory to use fat-suppression sequences with the use of contrast administration in state-of-the-art musculoskeletal MRI [21,22,33]. Similarly, using fat-suppression can increase the conspicuity of enhancement after contrast administration. A homogeneous fat-suppression in the entire field of view both before and after intravenous contrast material (Gadolinium-chelate (Gd)) is necessary, to avoid misconception [23].

**MRI - the Dixon Technique**

An alternative method for fat-suppression is the phase-contrast method, first described in 1984 by Dixon, which is based on the frequency difference between fat and water [41]. It does not require a high field homogeneity in order to achieve adequate fat-suppression, thus field inhomogeneity is not a limiting factor [41,42]. This technique has been applied successfully in MR imaging of adrenal masses and bone marrow [42-46].
In the original Two-Point Dixon technique, which we use, two sets of acquisitions are performed: one in which water signal (W) and fat signal (F) are "in-phase", which means that at any moment in time, the fat and water spins point in the same direction, and their signals add up in the image (Fig 1a): \( I = W + F \).

In the second acquisition fat and water have opposed-phases: fat and water spins point in opposite directions, and the resulting image shows the magnitude of the difference of the fat and water signals (Fig 1b): \( O = |W - F| \).

In order to separate the fat and water signals we need to know in every pixel which signal is stronger. The "phase-difference" (Fig 1c, \( \Phi \)) helps us to sort out regions with water dominant signal and regions with fat dominant signal. Borders between these regions are characterized by a 180° step, i.e. half way through the grey scale, e.g. from white to grey, from light grey to dark grey, or from grey to black. Borders from white to black represent 360° transitions, which have no physical meaning.

With help of an algorithm, developed at our department [46] the Sign image is produced (Fig 1d, S) which shows water dominant regions (white, \( S = +1 \)) from fat dominant regions (fat, \( S = -1 \)). Finally we obtain the water image (Fig 1e): \( W = I + S \cdot O \), and the fat image (Fig 1f): \( F = I - S \cdot O \).
A potential problem in using this chemical shift technique is the occurrence of displacement artefacts that hamper the application of the technique [25,37]. The necessary postprocessing requires the same position with absolutely no shift of the object between the in-phase and opposed-phase sequences [46,37].

**AIM AND OUTLINE OF THE CONDUCTED STUDIES**

In summary MRI has been described, as an important modality to assess the neuropathic feet of diabetic patients, but has not been described in leprosy. For the detection of osteomyelitis previous studies suggest that intravenous Gadolinium administration is mandatory. Furthermore, the use of fat-suppression techniques will increase the detection of enhancement after contrast administration.

This thesis was conducted with the following research questions:

*Can the Two-Point Dixon Chemical shift Imaging technique serve as a clinical feasible fat-suppression technique in the extremities?*

In order to answer this question the use of Two-Point Dixon chemical shift imaging as fat-suppression technique was evaluated in 31 consecutive patients clinically suspected to have bone marrow disease. The results are reported in **Chapter 2**

*What are the MRI findings of Dixon chemical shift imaging as fat-suppression technique in patients with leprosy and clinically asymptomatic neuropathic feet?*

Since the technique was found a good technique for achieving uniform fat-suppression in the distal parts of the extremities, applicable in a routine clinical setting, it was used to study leprosy patients. Early detection of feet at risk may help to prevent complications. The question was raised whether changes prior to the appearance of clinical signs are present and detected by MRI. Are there MRI changes present in these patients? When changes are present, is there a role for MRI in relation to clinical management, in the early assessment of the asymptomatic neuropathic foot in leprosy patients? All available data in the literature address clinically complicated neuropathic feet. To our knowledge, no papers, concerning MRI in asymptomatic neuropathic feet, exist. The results of this study are presented in **Chapter 3**
Introduction

What are the MRI findings with use of Dixon chemical shift imaging as fat-suppression technique in patients with leprosy and clinically complicated neuropathic feet, suspected for osteomyelitis?

The problem that clinicians encounter when treating leprosy patients with longstanding neuropathic feet pathology is the discrimination between neuro-osteoarthropathy and ongoing infection (cellulitis, osteomyelitis) in a patient with a warm foot, not responding to therapy. The radiological literature available on MRI and osteomyelitis in neuropathic feet nearly exclusively concerns diabetic foot pathology, being the most frequent cause of neuropathic feet in the western world. As far as we know, no papers concerning the use of MRI in neuropathic leprosy feet, clinically suspected of osteomyelitis exist. Our results are described in Chapter 4.

In Chapter 5 an overview of the results of the performed studies is given and the implications are discussed. Further some areas for future research are described.

References

Chapter 1


Introduction