The role of radiology in nerve function impairment and its musculoskeletal complications in leprosy

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Summary Conventional techniques, such as plain radiography and bone-scintigraphy, were used in the past to evaluate skeletal changes in patients with leprosy. More recent publications focus on radiological imaging of affected nerves, and involve advanced modalities such as Computed Tomography (CT-scan), Ultrasonography (US), and Magnetic Resonance Imaging (MRI). US and MRI can play an especially important role in the evaluation of nerve involvement in newly diagnosed patients, and also during leprosy reactions. This is important, because when nerve involvement is diagnosed in time, it may be reversible with adequate treatment. Radiological modalities can also play an important role during the follow-up of patients with leprosy with nerve function impairment. Skeletal and soft-tissue abnormalities occur, even after treatment. The so-called neuropathic foot is a well known consequence. Because of nerve function impairment, there is a constant risk of developing ulcers and subsequent osteomyelitis, or neuro-osteoarthropathy (Charcot foot or tarsal disintegration), which can lead to the amputation of the affected limb. Different radiological modalities can be used during the evaluation and follow-up of patients with leprosy with a neuropathic foot. With this up-to-date review, we highlight the importance and potential role of radiological imaging techniques in leprosy.

Introduction

Nerve function impairment (NFI) is the main cause of morbidity in leprosy and is responsible for most patients’ disabilities.1 The peripheral nerve becomes infected with Mycobacterium leprae, infiltrating the nerve causing acute or chronic inflammation that leads to progressive loss of nerve function (= primary nerve impairments).2 Type 1 and Type 2 reactions in
leprosy (episodes of delayed hypersensitivity and TNFα – immune complex mediated reactions, respectively) can cause neuritis, leading to further deterioration of the (primary) nerve function impairment, even after treatment. Early detection of nerve involvement at the time of diagnosis or during a leprosy reaction is important so that adequate treatment can be started, and to prevent further nerve function impairment.

The motor, sensory, and autonomic function losses cause pareses, loss of sensitivity, and autonomic alterations of the skin (dryness) and bone (bone absorption). This can lead to so-called secondary impairments, such as hand and foot deformities and ulcers, with the risk of developing complications like infection, which can lead to amputation.

Nerve function impairment (NFI) varies from 6–56% in newly diagnosed patients with leprosy and can even deteriorate after treatment as a result of leprosy reactions but sometimes deterioration of NFI can also occurs delayed and unexplained.

Regular follow-up of patients is necessary for primary nerve function impairment and to prevent its subsequent secondary impairments.

Radiological modalities have been used in the past to study the musculoskeletal system in patients with leprosy. Plain radiography and bone-scintigraphy were used to evaluate bone changes in hand and foot deformities. More recent publications focus on radiological imaging of affected nerves and on neuropathic foot complications, and involve more advanced modalities such as Computed Tomography (CT-scan), Ultrasonography (US), and Magnetic Resonance Imaging (MRI).

The aim of this paper is to provide an up-to-date overview of the role of radiological modalities in the study of nerve function impairment and its musculoskeletal complications in patients with leprosy.

### Magnetic Resonance Imaging:

The protons (mainly water molecules) within the body placed in the MRI, align with the direction of a magnetic field. Turning a radio frequency electromagnetic field on and off causes the protons to absorb or release energy which can be detected by a scanner. Different tissues of the body can be detected because the protons in different tissues return to their equilibrium state at different rates. The relaxation time describes the rate that protons spins return to equilibrium (T1 relaxation time) and time constants describes the rate of signal decay (T2 relaxation time). T1 weighted images nicely delineate the (normal) anatomical structures. Fluid is shown as a dark signal and fat is shown as bright. T1 after contrast administration combines a clear anatomic delineation and shows enhancement of the pathology after contrast administration. T2 weighted images are useful in detecting pathology which contains a large amount of water (such as infection or inflammation) and is seen as bright areas on MRI. T1 and T2 is often combined with fat saturation technique (FAT-SAT, STIR), which means that fat is dark, and only fluid (= pathology) is bright. By decreasing the signal intensity of fat, high signal intensity objects adjacent to or within primarily fatty areas (such as subcutaneous tissue or bone marrow) are more easily seen.
Methods

An Internet-based literature search of abstracts of English-language studies in human subjects was performed to identify relevant studies on diagnostic modalities. Using the terms ‘leprosy’, ‘neuropathic foot’, ‘polyneuropathy’, ‘neuropathy’, ‘Magnetic Resonance Imaging’, ‘Computed Tomography, X-Ray’, ‘Ultrasoundography’, ‘diagnostic imaging’, ‘Radionuclide imaging’, ‘abscess’, ‘bone diseases, infectious’, and ‘osteoporosis’ as single terms or in combinations, titles, abstracts, and references were systematically scanned by one reviewer (FJS) for relevant articles on the topic of leprosy and diagnostic modalities. Articles published between 1960 and August 2009 were included. The EMBASE and Cochrane databases were also checked for relevant articles. With the electronic search, approximately 300 articles were found. Case reports, letters, comments, and abstracts were excluded. Finally, a list of 60 articles remained and was included in this study.

Soft-tissue Abnormalities

NEURITIS

Leprosy-related neuritis presents as a tender enlargement of the peripheral nerves at sites of predilection. It can be caused by acute or sub-acute neuritis that occurs as part of the leprosy infection, and also as a result of Type 1 (reversal reaction) and Type 2 (erythema nodosum leprosum) reactions. The ulnar, radial, median, posterior tibial, and peroneal nerves are commonly involved in the extremities, but the facial nerves can also become affected. Early detection of neuritis (at diagnosis or during a leprosy reaction) is important so that adequate treatment can be started to prevent further nerve function impairment.

In 11% of Tuberculoid type (TT) /Borderline Tuberculoid type (BT) patients with a long history of leprosy (before treatment) and enlarged nerves, calcifications are found, especially those of the ulnar nerve and peroneal nerve. Plain radiography shows calcification that may be linear, along the nerve, sometimes in flakes, or show oval calcifications which may be the end-result of a perineural abscess. Contrast injection along the nerve sheath is suggested to localise the calcification.

MRI, US, and CT-scan can be used to examine peripheral nerves in patients with leprosy. Martinoli et al. classified patients with leprosy into three groups based on ultrasonographic and MRI findings. Group I consisted of normal-appearing nerves, group II included enlarged nerves with fascicular abnormalities, and group III included nerves with an absence of fascicular structures.

MRI assessment can be based on a qualitative analysis of endoneural intensities on T1 and T2 weighted images, identification of nerve compression within osteofibrous tunnels, and the assessment of normal or increased contrast enhancement (Figure 1a, 1b, and 1c). Active Type 1 reaction shows a mild to moderate hyperintensity on T2, with a hypervascular pattern on contrast-enhanced MRI. Enhancement of the MRI signal after contrast administration can involve the fascicles of the nerve and the surrounding epineurium. The overall sensitivity of MRI to detect clinically recognised active Type 1 reaction is 92% (no specificity was given).

High-frequency Doppler US can be used to study nerves in leprosy. The cross-sectional area of the nerve can be measured, nerve compression within osteofibrous tunnels can be identified, and the endoneural colour flow signals can be detected. The affected nerve...
can become fusiform-enlarged (including the individual fascicles) and in patients with Type 1 reaction also hypo-echoic changes of the epineurium are found upon US.\textsuperscript{19,26,33} Jain \textit{et al.} studied the peripheral nerves in a group of leprosy patients and healthy controls and compared the use of US to clinical palpation. They concluded that enlarged peripheral nerves could be

\begin{figure}[h]
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\caption{(a) and (b) MRI axial T1 weighted images of the upper arm before (left) and after (right) contrast administration. T1 weighted images shows fluid as a dark signal and fat as a bright signal. The ulnar nerve before contrast administration (black arrow) and after contrast administration is shown. Figure 1b (figure right): there is enhancement and enlargement of the ulnar nerve (black arrow) indicating neuritis. Graphic illustration of the MRI of the left arm: 1, Humerus; 2, Biceps brachii; 3, Triceps brachii; Black arrow, ulnar nerve. (c) MRI: Sagittal T1-weighted image of the lower leg shows enlargement of the sural nerve (white arrow) indicating neuritis. Graphic illustration of the MRI of the ankle: 1, Tibia; 2, Talus; 3, Calcaneus; 4, Triceps surae; Black arrow, Sural nerve.}
\end{figure}
assessed more accurately with US than with clinical examination. Colour Doppler US showed increased vascularity (blood flow signals in the perineural plexus or intrafascicular vessels) in most patients with leprosy reactions (Type 1 and 2).\textsuperscript{19,26} The overall sensitivity of Doppler US to detect clinically recognised active RR phases is 74\% (no specificity was mentioned).\textsuperscript{19} Ultrasonography and MRI during Type 2 reaction show lesser enlargement of nerves, but also show structural abnormalities with an absence of discernible fascicular structure.\textsuperscript{19} Follow-up examinations show improvement of the US colour flow signal and of the MRI with contrast enhancement.\textsuperscript{19} CT-scans can also be used to diagnose enlarged nerves in patients with leprosy.\textsuperscript{20,21} The neighbouring structure of the peripheral nerve usually has a different fat density and tendonous density upon CT-scan, and can be a reliable method for studying peripheral nerve lesions.\textsuperscript{21} Ultrasonography and MRI are also reported in several cases of patients with leprosy as a sensitive modality to study nerve abscess.\textsuperscript{37–40}

**SOFT-TISSUE INFLAMMATION**

Loss of sensation can cause ulcers, which may lead to a secondary infection.\textsuperscript{1,4,5} The superficial soft-tissue adjacent to an ulcer can become infected as result of a contiguous spread of micro-organisms into the surrounding subcutaneous fat. Soft-tissue inflammation with localised swelling of the skin, redness, and increased temperature is clinically diagnosed as cellulitis and is regularly seen in neurologically impaired hands and feet of patients with leprosy.\textsuperscript{5,6} The infection can spread along the compartments or tendon sheaths, with abscesses developing far away from the entry site. Communication of an ulcer through a sinus tract to the underlying bones and joints constitutes a risk for osteomyelitis.

Major indications for radiological imaging of cellulitis include a suspicion of osteomyelitis or an abscess. Plain radiography can show soft-tissue swelling, but is unable to differentiate between cellulitis and osteomyelitis, or to investigate the extent of the soft-tissue infection (i.e. abscess). MRI can be used to differentiate cellulitis from osteomyelitis in patients with leprosy who have a neuropathic foot.\textsuperscript{25,27} It can detect inflammation (and the extent of inflammation) in combination with fine anatomic details. On MRI, cellulitis is seen as a loss of the fat signal in subcutaneous tissues, with a high signal, although less than that of fluid, and diffuse enhancement but poorly defined margins (Figure 2a, 2b).

An abscess is seen as a focal collection of signal that approximates fluid. After contrast administration, a thick rim enhancement can be seen. Rim enhancement is not seen in areas of necrosis. The focal fluid signal is then seen on T2 weighted images in a broader area with absence of enhancement compared with the surrounding tissue. A sinus tract is sometimes seen as parallel lines of enhancement in a tram-track pattern on post-contrast fat-suppressed T1 weighted images.\textsuperscript{25}

**SKELETAL ABNORMALITIES**

*Periostitis and osteitis*

Primary infiltration of *M. leprae*, spreading from overlying dermal or mucosal areas, initially affects the periosteum (leprous periostitis) and subsequently the adjacent cortex and spongiosa (leprous osteitis).\textsuperscript{11,41–43} Haematogenous spread to bone is found less frequently, but can lead to intramedullar foci.\textsuperscript{41} Secondary osteitis and periostitis can result from vascular changes, trauma, and secondary infections due to leprosy-related nerve function impairment.
and correlates with increasing duration of disease, a lack of or partial treatment, and a
increasing disability index.\footnote{11}

Periostitis and osteitis in patients with leprosy is mostly confined to the small bones of the
face, hands, and feet.\footnote{11} Periostitis and osteitis is found in 3–45\% of leprosy patients with
deformities, of which almost 50\% are found in the feet only.\footnote{11,18,42–44} Osteitis in the hands
commonly involves the distal ends of the proximal and middle phalanges. The metatarsal
heads are usually affected in the feet. Characteristic radiographic findings are evident in the
epiphysis and metaphysis of the tubercular bones, but direct involvement of the medullar
canal can also sometimes be visualised. Thinning of the endosteum with corresponding
widening of the medullary canal can be found in the area of the metaphysis bone.\footnote{14,18,43} More
common is a fusiform swelling of the soft-tissue overlying the corresponding part of the
affected digit, which is sometimes associated with enlargement of nutrient foramina.\footnote{6,18,43}
Progression of bone lesions is seen with ageing and is generally slow, although the cortex and
the periosteum can be affected. Osteoporosis, endosteal thinning, enlargement of the nutrient
foramina, and osseous destruction with a cystic or honeycombed appearance can become
more evident.\footnote{14,15,43} Because of weight-bearing forces, this may lead to pathological
fractures of the metatarsal heads, for instance, in the neuropathic foot.\footnote{5,15,17}

Arthritis

Clinical symptoms of arthritis are pain and swelling with joint effusion, and are usually
attributed to Type 2 leprosy reactions.\footnote{45,46} The arthritis associated with Type 1 reactions is

Figure 2. (a) and (b) Axial MRI of the metatarsal region of the midfoot. Figure on the left is T1 and figure on the right
is T1 after contrast administration with fat saturation technique (FAT-SAT). T1 combined with FAT-SAT means that
fat is dark and enhancement of fatty tissue is bright. There is an area of low signal intensity in the subcutaneous fat
(figure left; white arrow) but there is marked enhancement after contrast administration (figure on the left; white
arrow). There is no enhancement of the metatarsal (MTT) bone meaning there is no osteomyelitis; thus meaning
cellulitis. Graphical illustration of the MRI of the midfoot. I–V, Metatarsal (MTT) bones; Black arrow, cellulitis at
lateral part of the midfoot.
ascribed to a cell-mediated immune response involving sensitised macrophages and T cells that act within joints via cytokines.\textsuperscript{45,46} Direct infiltration of \textit{M. leprae} into a joint causing primary arthritis is uncommon in leprosy.\textsuperscript{47} Arthritis located in the ankle can also mimic neuro-osteo-arthropathy (Charcot foot) in a neuropathic foot or neuritis, although pain is a less profound symptom.\textsuperscript{48}

Arthritis is studied in leprosy patients using X-rays and CT-scans.\textsuperscript{49–51} There may be a symmetrical polyarthritis that does not differ in any leprosy subgroup, which can follow a chronic course. It is seen in both treated and untreated patients, involving mostly the larger joints such as the knees, ankles, and sacroiliac joints.\textsuperscript{50–52} In a case report by Helling \textit{et al.}, MRI was used in a patient with BT leprosy with arthritis of the hands and feet, and showed a symmetrical synovitis.\textsuperscript{53}

Technetium-99 scintigraphy shows an abnormal uptake in the bones and joints of patients with leprosy corresponding with cutaneous lesions/nerve thickening and anaesthetic areas, probably representing inflammation in same area.\textsuperscript{12,13,54} Therefore, Braga \textit{et al.} suggested that scintigraphy is superior to plain radiography because it can differentiate between active and inactive disease and may be used to analyse the activity of the \textit{M. leprae} infections and to evaluate treatment results.\textsuperscript{55}

Osteoporosis

Infiltration of the bone with a high number of \textit{M. leprae}, and the subsequent inflammatory response, can lead to primary osteopenic bone changes (loss of bone density). Secondary osteopenic changes can result from Type 1 leprosy reactions, treatment of reactions with corticosteroids, or increased blood supply to the region with inflammation caused by an active ulcer or bone infection.\textsuperscript{56} Prolonged immobilisation during plaster treatment in cases of a neuropathic foot with an ulcer or a neuro-osteo-arthropathy (Charcot foot) can also result in osteopenic changes.\textsuperscript{56} Hormonal dysfunction, including osteocalcin, parathyroid hormone, and hypogonadism, is also found in patients with leprosy who have osteopenic changes.\textsuperscript{57,58} Osteoporosis is diagnosed by measuring the bone mineral density (BMD) in the lumbar vertebrae and the diaphysis of the radius and femur neck, and is expressed by the bone mineral content (BMC)/W [g/cm\textsuperscript{2}] using plain radiography. Regional osteopenia of the foot has been found in cases of neuro-osteo-arthropathy in diabetic patients using quantitative ultrasound estimates of BMD measured in the foot.\textsuperscript{60} With both techniques, the BMD is expressed as Z- and T-scores.\textsuperscript{59,60} The loss of BMD can be identified as an early event in patients with leprosy and is already present at diagnosis.\textsuperscript{57,58} Measuring the BMD in male patients shows 30\% osteoporosis with each decade of life.\textsuperscript{59} Plain radiography shows osteopenic bone changes in patients with leprosy which can be diffuse, localised, or periarticular.\textsuperscript{42} Osteopenic bone changes can be found in up to 38\% of patients with physical deformities, and correlates with increasing age and a rising disability index.\textsuperscript{11,44} Recent studies by Kanaji \textit{et al.} show that patients with long-standing diagnoses of leprosy present with not only osteoporosis when evaluated by densitometry, but also with a predisposition for fracture.\textsuperscript{61,62}

\textbf{Neuro-osteo-arthropathy}

Nerve function impairment in combination with alterations in biomechanical forces and osteoporosis can cause damage to the skeleton and eventually result in
neuro-osteo-arthropathy (Charcot foot). These are called non-specific bone changes secondary to the (often longstanding) impaired nerve function. Harris et al. introduced the term tarsal disintegration because the radiological image of neuro-osteo-arthropathy of the foot in leprosy patients was predominantly represented as destruction of the tarsus. Clinical symptoms of a neuro-osteo-arthropathy are a painless swelling with increased temperature and redness, and deformation of a joint, sometimes in combination with a (minor) trauma. The navicular bone in the foot is often involved, usually in combination with the talus. The calcaneus is less frequently affected, and cuboid and cuneiform bones are seldom involved. The carpus and radiocarpal joint of the wrist have also been described in the literature. Neuro-osteo-arthropathy was found in 18% of patients with leprosy who have neuropathy of the foot, mostly located in the ankle joint (50%), in the mid-tarsal region (30%), the TMT region (14%), and subtalar (6%). The mid-tarsal lesion may be due to pareses of the peroneal and tibialis anterior muscle.

Early radiographic features are cartilage fragmentation and destruction of both cartilage and bone (Figure 3).

There can be a rapid progression towards advanced disintegration with depression, absorption, and destruction of the subchondral bone. Joint luxation, enlargement, and effusion of the soft tissue and fractures can be found (Figure 4).

The last radiographic stage shows a disorganised joint with simultaneous resorption and bone formation, usually seen in the phalanges, metatarsals, and metacarpals (Figure 5).

Five radiological patterns of tarsal disintegration have been described; a posterior pillar, central pillar, anterior pillar medial arch, anterior pillar lateral arch, and...
Radiographic alterations in the toes were introduced by Horribe et al. because most of these alterations are secondary to foot ulceration.\textsuperscript{64}

MRI examinations of the neuropathic feet of patients with leprosy, but who are without any clinical symptoms of neuro-osteo-arthropathy and who have a normal or nearly-normal foot shape, sometimes show neuro-osteo-arthropathic changes located in the midfoot.\textsuperscript{23,24}
Bone resorption

Acral bone resorption is a progressive loss of anatomic structures resulting in progressive hand and foot deformities and shortening of the digits or toes in patients with leprosy who have a neuropathy.\textsuperscript{41–44} During bone resorption, osteoclasts break down bone, release minerals, and transfer calcium from bone fluid to the blood. Absorption of the trabecular (or spongy) bone and the development of bone atrophy (loss of bone density) are associated with impaired nerve function, male sex, grade of disability at diagnosis, and the occurrence of four or more leprosy reactions (Figure 5).\textsuperscript{11,43,44,69,72,73} A relationship was found with physical activity, trauma, foot deformities, and the appearance of plantar ulcers.\textsuperscript{43,44,64,68,70}

Conventional radiology shows bone resorption as a partial or total loss of one or several phalanges (both proximal and distal) or the metatarsal bones, eventually resulting in the gradual disappearance of many bones. Chronic osteomyelitis and pathological fractures can further increase the absorption and gradual disappearance of bone.\textsuperscript{41,42} Progression of bone resorption can be found in neuropathic hands and feet, even after patients with leprosy have been adequately treated.

Osteomyelitis

Infection of the bone marrow can be caused by the mycobacterium itself, but is more often caused by haematological spread of bacteria from another part of the body.\textsuperscript{18,41} The affected bone may have been predisposed to infection because of a recent trauma. In leprosy, osteomyelitis is mostly seen as a complication of a neuropathic hand or foot with an ulcer, and can lead to amputation of the affected limb.\textsuperscript{6,7,14,56} Diagnosing osteomyelitis is a well known challenge in diagnostic radiology.\textsuperscript{41,74} It is mandatory to have sufficient clinical information, and information on the location of the ulcer to adequately read the radiographs.\textsuperscript{75}

Figure 6. Conventional radiology with neuro-osteo-arthropathy (Charcot foot) of the foot and radiological signs of osteomyelitis in the lateral part of the midfoot region. There is cortical destruction with coalescent lesions of the cuboid bone (black arrow) and metatarsal (MTT) V bone (white arrow).
Early radiological features of osteomyelitis can be soft tissue swelling, periosteal thickening and osteopenia. Cortical destruction appears later as small holes which become larger coalescent lesions, and finally progress to completely involve a region of cortex (Figure 6).

When clinical symptoms of an infections are present, radiological changes suspected of osteomyelitis can remain absent until 7–10 days. 76

Osteomyelitis is usually diagnosed on clinical, laboratory, and radiological examinations.74,75 MRI has been described as a powerful tool for diagnosing osteomyelitis in patients with leprosy with neuropathic feet and clinical signs of inflammation.25 Clinically unsuspected osteomyelitis was found in leprosy patients with neuropathic feet with minor clinical signs of inflammation and/or superficial ulcers. This indicates that compared to clinical evaluation MRI may be a sensitive method for the detection of osteomyelitis.27

The primary signs are decreased signal intensity on T1, increased signal intensity on fat-suppressed T2, and/or fast STIR and focal marrow enhancement on contrast enhancement (fat suppressed T1). Bone marrow pathology can be identified as areas with high signal intensity in otherwise low signal intensity (black) bone marrow (Figure 7a, 7b).

Osteomyelitis is often found at the distal part of the neuropathic foot and is most often related to the presence of an ulcer.27

Conclusions

This review describes how different radiological modalities have been applied to patients with leprosy, focusing on neuropathy and its related musculoskeletal pathology. In the past, plain radiography has been used mainly to determine skeletal pathology, focusing on specific
and non-specific bone changes such as neuro-osteo-arthropathy (Charcot foot or tarsal desintegration), bone infection, and bone resorption.

Recent studies used more advanced radiological techniques to study soft tissue involvement, and focused specifically on the imaging of peripheral nerves during leprosy reactions. MRI and US can play an especially important role in the evaluation of nerve function impairment in newly diagnosed patients or during leprosy reactions. This is important, because these impairments may be reversible with adequate treatment.

However, until recently, only a limited number of radiological studies have been performed. Further investigation, especially into the potential role of US and MRI in the diagnosis of early (and often clinically asymptomatic) nerve function impairment, is therefore, necessary.

Recent predictions show that a substantial number of patients will still live with nerve impairment in the coming decades. When nerve function impairment is already present, radiological modalities play an important role during the follow-up of patients with leprosy. The skeletal and soft-tissue abnormalities mentioned in this review can occur in leprosy patients after multidrug treatment.

The so-called neuropathic foot is a well-known consequence of nerve function impairment in patients with leprosy. Because of the nerve function impairment, patients are at constant risk of developing ulcers and subsequent osteomyelitis, or neuro-osteo-arthropathy, which can lead to amputation. The first modality of choice during the follow-up of patients with a neuropathic foot is often plain radiology. However, diagnostic problems start when a patient with a neuropathic foot and an ulcer begins to develop clinical signs of inflammation. It is often difficult to distinguish between cellulitis, osteomyelitis, and neuro-osteo-arthropathy, both clinically and on plain radiography. MRI has been shown to be the modality of choice to differentiate between soft-tissue infection and osteomyelitis in a neuropathic foot with clinical signs of inflammation.

The accessibility of the less expensive extremity US and MRI will allow more advanced techniques to become available in countries where leprosy is endemic, and to play an increasingly important role in the evaluation and follow-up of patients with leprosy.

References


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