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Magnetic Resonance Imaging in Early Stage Charcot Arthropathy – Correlation of Imaging Findings and Clinical Symptoms

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Abstract
Objective: To report on qualitative and quantitative MRI findings in early stage of diabetic osteoarthropathy (CA) and correlation with clinical symptoms.
Materials and Methods: Clinical data of 13 patients (mean age = 61.2 years) with Charcot arthropathy (CA, Eichenholtz 0) were compared with findings in native and contrast-enhanced MRI. 12 patients had diabetes mellitus (7 type 2, 5 type 1), one had idiopathic polyneuropathy. Evaluation was performed at acute stage of CA and at a 4 months follow-up. After baseline assessment, patients were treated with pressure-relieving means. Mean values of signal-intensity in short T1 inversion recovery (STIR) images of bones of the foot and ankle and corresponding contrast-enhancement were evaluated. Additional MRI-findings (soft tissue edema, varicosis, tenovaginitis, joint effusion) were analyzed. A correlation with symptoms (reddening, swelling, hyperthermia, pain) was performed.
Results: Bone marrow edema in affected bones significantly decreased ($p < 0.001$). Soft tissue edema and pain showed a significant correlation with intensity of bone marrow edema ($p < 0.05$). The presence of bone marrow edema in the STIR sequence was strongly associated with a corresponding contrast enhancement ($p < 0.0001$, κ-coefficients 0.976 at baseline and 0.953 at follow-up).
Conclusion: MRI in early stage of CA provides valuable diagnostic information on the activity of the disease. A significant correlation of intensity of bone marrow edema in MRI and some clinical parameters (soft tissue edema and pain) was found. Paramagnetic contrast-agent did not provide additional information. This is the first report on quantitative assessment of signal alterations in stage 0 CA before and after treatment.

Key words: Charcot arthopathy, MRI, Early stage, Diabetes

Introduction

Charcot arthropathy (CA) of the foot and ankle is one of the most common and most complex long-term complication of patients with diabetes mellitus. A prevalence of 0.8 – 7.5 % has been reported in patients with peripheral neuropathy [1]. In various studies, characteristics of CA were analyzed. For the most part, these evaluations describe clinical and imaging findings in late stage patients with periarticular fractures, joint displacement, deformations of the feet, and osteomyelitis [2, 3, 4, 5]. Based on these findings, classifications have been introduced which take predominantely late stage changes into consideration. Criteria are derived from evaluation at clinical assessment and radiography. The classification of Eichenholtz [6] (1966) describes the activity of CA (stage 1 to 3) and was extended later by an additional stage 0 (clinical stage) including early symptoms like erythema, soft tissue edema, and increased temperature to the affected foot [7]. Another classification, focussing on the localization of deformations and fractures in CA, was proposed by Sanders et al. in 1993 [8], and now is widely accepted. Tables 1 and 2 summarize the Eichenholtz and Sanders classification.

Early detection of CA and adequate treatment results in a good clinical outcome. Most cases of acute CA (stage 0) can be treated non-surgically with pressure-relieving methods, leading to a rapid reduction of soft tissue edema within one week [1]. Even patients with joint diastasis and subluxation do not develop foot deformity in 25% of cases when treated with pressure-relieving total contact casting.

Magnetic resonance imaging (MRI) proved highly useful for the early detection of a large variety of traumatic, degenerative, inflammatory, and infectious musculoskeletal diseases. Various MRI abnormalities have been describedin early stage of CA, such as bone marrow and soft tissue edema, localized soft tissue fluid collections, joint effusions, and fluid accumulations within tendon sheaths [9]. Moreover, MRI is accepted as a valuable diagnostic tool to differentiate infection from neuropathy in CA, provided adequate technique is applied and adequate interpretive skills are available [10, 11, 12]. However, to date, a quantitative analysis of bone marrow edema in early CA has not been published. Therefore we performed a prospective MRI study in patients with early stage CA including correlation with clinical findings.

Research Design and Methods

Study Population

Twelve patients with previously diagosed diabetes mellitus (type 2: n = 7, type 1: n=5) and one patients with idiopathic neuropathy and acute clinical symptoms of CA were selected for the study. All patients had signed informed consent for contrast-enhanced MRI as part

of the clinical diagnostic work-up and were enrolled in the study. The mean age of patients at initial MRI assessment was 61.2 years and the mean duration of diabetes was 20.5 years (n = 12). Symptoms included acute pain, erythema, edema, and increased temperature to the affected feet. Patients with foot ulcers, previous foot surgery or fractures, or apparent deformation, were excluded. Follow-up MRI was performed in all 13 cases after a mean interval of 4.2 months.

Therapy

Therapy of acute early stage CA included primarily pressure-relieving methods like a strict non-weight bearing in a brace or cast during the period under observation. Pressure-relieving was started shortly after MRI, and patients were instructed to follow the strict pressure-relieving assignment. No standardized changes in general diabetes care (oral medication, insulin dose, food intake) were initiated.

Imaging

Imaging for baseline and follow-up scans was performed on a 1T Magnetom Harmony scanner (Siemens Medical Solutions, Erlangen, Germany). Patients were placed in a feet first and supine position. A dedicated foot and ankle coil was used to increase the signal-to-noise ratio. The MR protocol is summarized in Table 3. T1 fat-suppressed imaging was performed after injection of gadopentetate dimeglumine (0.1 mmol/kg body weight, Magnevist®, Schering, Germany).

Clinical Parameters

Clinical information was collected during visits of patients in the outpatient department. Parameters from clinical assessment included presence or absence of pain, erythema, edema, and increased temperature to the affected foot. Changes between two visits were noted in a clinical assessment sheet (presence or absence of clinical parameters) and saved as a base for clinical correlation. Data were taken from standard clinical notes, no study spread sheets were available.

Image Evaluation

Presence or absence of bone marrow edema within different bones of the foot and ankle (distal tibia [1.5 cm above joint surface], calcaneus, talus, naviculare, cuboideum, cuneiforme mediale, intermedius, and lateral) was determined from STIR images by two experienced readers who reached a consensus. For statistical analysis, only signal intensity values of the affected bones (visible edema) were enrolled. For signal intensity measurement, a manual region of interest (ROI) around each bone surface was determined. The ROI

Table 1. Eichenholtz Classification of Charcot Arthopathy (1966). The classification includes modifications of Shibata et al. (1990). Stages are determined according to clinical evaluation and radiography.

Stage 0 (Clinical Phase)	Swelling, reddening, increased temperature of the affected foot. No radiographic findings.
Stage 1 (Development Phase)	Bone fragmentation.
Stage 2 (Coalescence Phase)	Absorption of small bone fragments, fusion of joints.
Stage 3 (Remodeling Phase)	Healing and new bone formation.

Table 2. Sanders and Frykberg. Classification of Charcot Arthropathy (1993). The classification focuses on the localizations of changes. Combinations of different types are common.

Type 1	Metatarsophalangeal joints and interphalangeal joints of the forefoot.
Type 2	Lisfranc line (tarsometatarsal joints).
Type 3	Chopart line (navicular-cuneiforme, talonavicular, and calcaneocuboid joints)
Type 4	Ankle joint
Type 5	Calcanear localization

Table 3. Scan protocol for evaluation of early stage diabetic osteoarthropathy.

	SO	**TR ***	**TE**	**FA**	**ST**
STIR	sagittal	6300	29	180	3.6 mm
T1w	sagittal	572	12	90	3.6 mm
T2w	axial	4000	90	180	3.6 mm
CE T1w fat sat	sagittal	620	17	90	3.6 mm
CE T1w fat sat	axial	620	17	90	3.6 mm

* variable according to number of slices. SO = slice orientation, TR = relaxation time, TE = echo time, FA = flip angle, ST = slice thickness.

was placed on the slice with the widest extension of bone marrow edema. In follow-up scans, readers determined the most similar slice position compared to the baseline evaluation, and re-evaluated the signal intensities of STIR images on respective images Subsequently, mean values of STIR signal intensities of the affected regions were calculated for each foot and a comparison of baseline versus follow-up studies was performed. Baseline and follow-up measurements of affected bones served as a base for longitudinal statistical analysis. Signal intensity values from the metatarsal bones were not taken into account, in order to exclude signal inhomogenities at the distal end of the field of view. Localizations of contrast enhancement and bone marrow edema were compared. Moreover, additional findings (synovialitis, tenovaginitis, varicosis, soft-tissue edema, and joint effusion) were assessed in a descriptive analysis. Signal intensities from post-contrast T1w images was not evaluated in order to avoid false results due to fat-suppression inhomogenities.

Statistical Analysis

Mean signal intensities in STIR images were correlated to each clinical symptom (pain, erythema, soft tissue edema, and increased temperature to the affected foot). Descriptive statistical analysis for presence or absence of bone marrow edema, clinical symptoms and additional imaging findings was performed. Statistical significance was tested using the Mann-Whitney test for unpaired samples. Correlation of contrast-enhancement in fat-suppressed T1 images and bone marrow edema (STIR sequence) was determined with the Cohen-Kappa-coefficient.

Results

Bone Marrow Edema and Clinical Parameters

Soft tissue edema measured in STIR images significantly decreased during the period under observation ($p < 0.001$). Frequencies of clinical symptoms at baseline and follow-up are summarized in Figure 1. In the course of pressure-relieving therapy, the number of clinical symptoms decreased. Pain and soft tissue edema were most common at baseline and follow-up examinations.

Signal intensity of bone marrow edema in STIR imaging showed a significant correlation with the presence of soft tissue edema and with the presence of pain at clinical evaluation ($p < 0.05$). Other clinical parameters (erythema, and elevated temperature to the affected foot) did not show a statistically significant association with intensity of bone marrow edema. 85% of patients (n = 11) showed uniform changes of both, mean bone marrow edema and intensity of clinical symptoms. 10 patients revealed a decrease of mean bone marrow edema under pressure-relieving therapy associated with an improvement of clinical symptoms. In one patient an increase of mean bone marrow edema was found, which as associated with an increase of clinical symptoms. In one patient with a slight decrease of mean bone marrow edema (-13% signal intensity), intensity of clinical symptoms remained unchanged. One patient with decrease in mean bone marrow edema (-74% signal intensity) presented with increasing pain and persistent soft tissue edema at follow-up assessment.

Additional Findings

Frequencies of most common additional MRI findings, excluding bone marrow edema, at baseline and follow-up are summarized in Figure 2. Among them, soft tissue edema and joint effusions in the ankle and subtalar joints were most frequent. Tenovaginitis with contrast-enhancement of the synovial membrane and fluid collections within the tendon sheaths was predominantly present in flexor tendons. Synovial enhancement was also found in the ankle and subtalar joints. There was no substantial changes of these additional findings between baseline and follow-up MRI.

Bone Marrow Edema and Contrast Enhancement

The presence or absence of bone marrow edema (STIR sequence) and contrast enhancement (fat-suppressed T1 sequence) was evaluated. Bone marrow edema and contrast enhancement showed a strong significant positive correlation ($p < 0.0001$). Correspond-

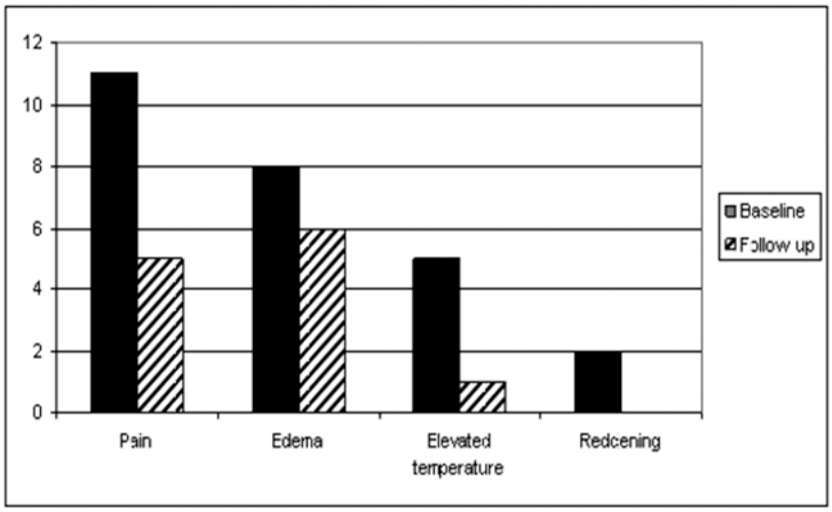

Fig. 1. Clinical symptoms (n) at baseline and follow-up assessment. Presence of clinical symptoms showed a reduction during the course of treatment.

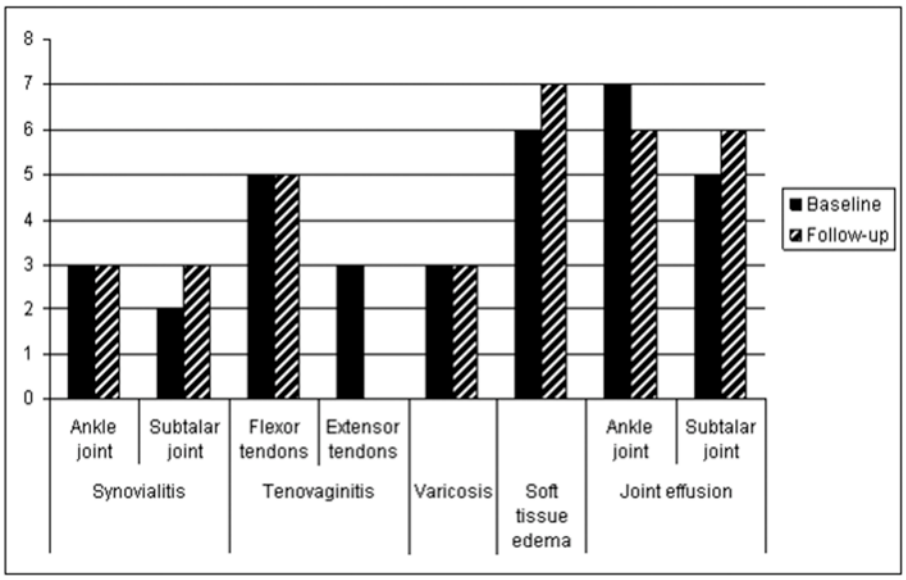

Fig. 2. Additional findings in MRI at baseline and follow-up assessment (n). Besides bone marrow edema, additional findings could be observed when reading MRI studies. No significant increase or reduction of additional findings could be observed.

ing κ-coefficients were 0.976 at baseline and 0.953 at follow-up scans.

Example

Figures 3 and 4 show MRI studies of a 76 year-old patient with known idiopathic neuropathy. He presented with symptoms of acute Charcot artropathy at baseline. Patient history and image descriptions are given in the figure legends.

Discussion

Bone Marrow Edema and Clinical Symptoms

In the course of pressure relieving therapy, bone marrow edema in MRI significantly decreased. Apart from soft tissue edema and pain, no other clinical parameters showed a significant correlation with the changes of bone marrow edema in MRI. However, pain might not represent a reliable parameter, since patients with peripheral neuropathy frequently suffer from pain sensations even without presence of CA [16]. While soft tissue edema decreased in clinical examination, MRI revealed at least a slight persistence of interstitial and subcutaneous edema and fluid collections, respectively in 6 out of 7 patients.

Imaging Findings and Pathophysiology

CA is a chronic destructive process affecting bone architecture and joint alignment. Various pathophysiologic approaches have been discussed over the last decade. An increase in the number of osteoclasts, particularly associated to the resorptive bone lacunae in CA, have been reported [13]. There is an extensive increase of osteoclast-to-osteoblast ratio in the Charcot-reactive bone. Osteoclasts demonstrate immunoreactivity for IL-1, IL-6 and TNF-α with a grade of moderate or strong activity. The extensive bone marrow edema observed in active CA, which in the current evaluation was present in all patients with clinical symptoms of CA, might be a macroscopic correlate with a localized inflammatory reaction.

Recently, micro-trauma has been reported to be the initial trigger to induce an inflammatory cascade of bone resorption through increased expression of proinflammatory cytokines, including TNF-α and IL-1β [14]. This cascade might be responsible for an increased expression of the nuclear transcription factor, NF-κB, which results in increased osteoclastogenesis [15]. In the present study, no signs of localized microfractures were detected in MRI. Reactive, inflammatory bone marrow edema might mask subtle signs of microfracture in early stage of CA.

Therapeutic approaches, including high dose systemic glucocorticoids and combinations with, or isolated use of TNF-α-antagonists, are currently under evaluation. Treatment is intended to break up the inflammatory activation cascade of bone resorption. MRI might help to identify the adequate point of time to start medication in future clinical practice.

The vasomotor regulation in early stage of CA is impaired. Increased baseline blood-flow has been reported, and may enhance dysregulation of proinflammatory cytokines. Extensive soft tissue edema which can be observed in both, clinical and MRI assessment, may also result from vasomotor dysregulation and is likely to represent an increased amount of lymphoid fluid in active stage of CA.

Bone Marrow Edema and Contrast Enhancement

All patients with contrast enhancement of bone marrow in fat-saturated T1 images showed corresponding edema in the affected bone in STIR sequences. In our patient collective (all Eichenholtz stage 0), there were no clinical signs (e.g. foot ulcers) for soft tissue infection or osteomyelitis. Contrast enhancement with gadopentetate dimeglumine did not provide any additional information on the state of activity of CA. In baseline and follow-up examinations, the active osteoarthropathic inflammation could also be detected with STIR imaging alone. Therefore, in MRI of early CA, STIR imaging might be sensitive enough for the detection of bone marrow edema and corresponding inflammatory reaction. Contrast-enhancement in fat-

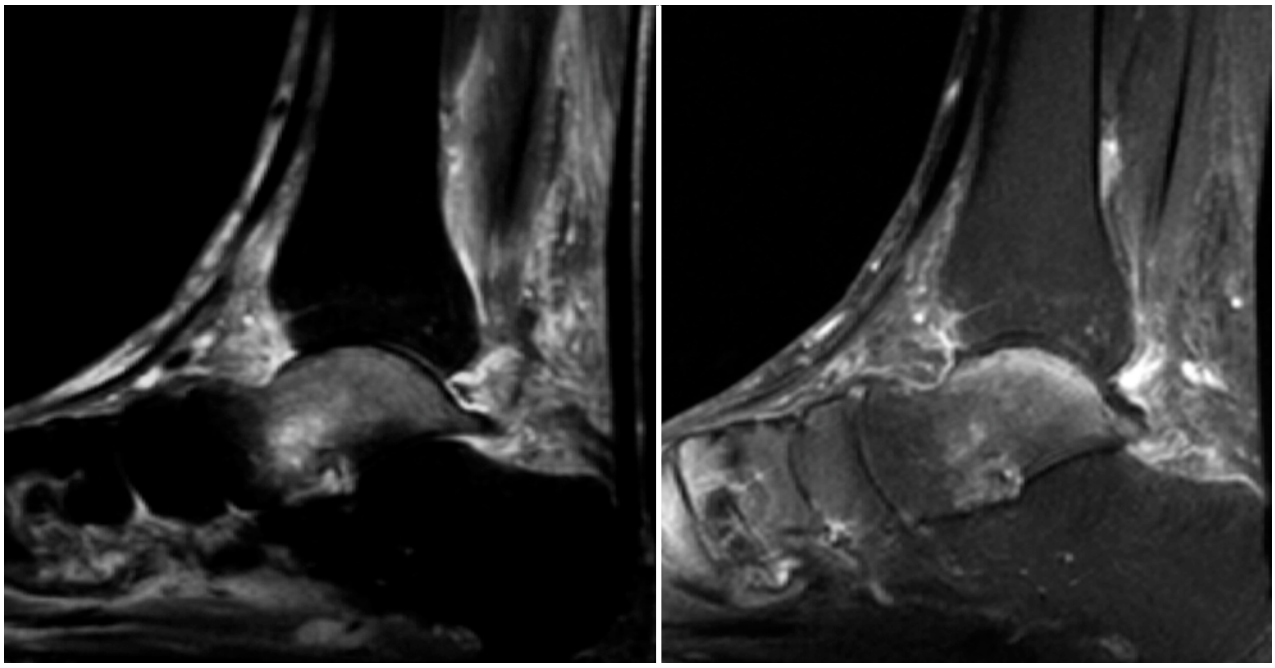

Fig. 3 a and b. Baseline MRI (left foot) of a 76 year old patient with idiopathic neuropathy who presented with symptoms of CA (soft tissue edema, pain, and elevated skin temperature of the left foot). Imaging findings include a strong edema in the trabecular bone of the talus and high signal intensity within the soft tissues around the ankle. Contrast enhancement was present in the whole talus, which was most pronounced in the subchondral area.

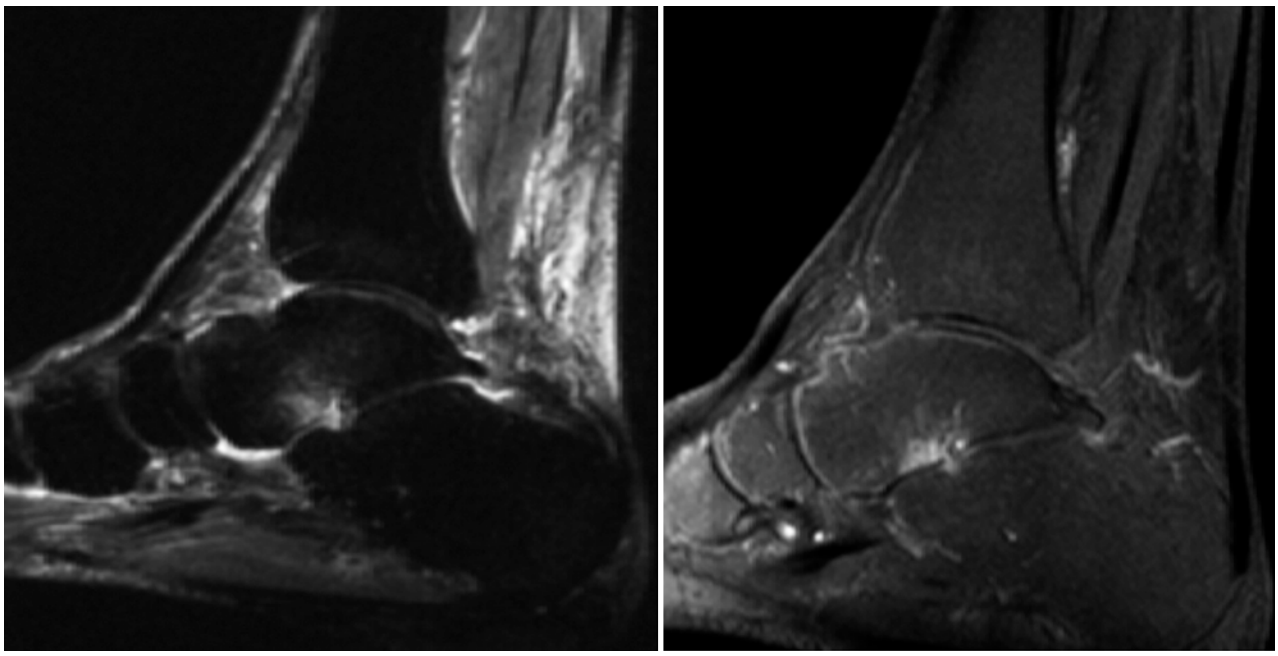

Fig. 4 a and b. 4 months after pressure relieving-therapy. Pain and elevated temperature of the right foot had disappeared. MRI shows a significant reduction of bone marrow edema and there were only slight persistent signals in STIR images adjacent to and within the sinus tarsi, and in the subchondral talar area of the ankle joint (Fig. 4a). Fat-suppressed T1 images show a minor slight enhancement within the same region (Fig. 4b).

supressed T1 images did not provide additional information on inflammatory status.

Clinical impact

It has been reported that MR imaging may enable to monitor the response to therapy. In current clinical practice, treatment response is monitored by visual assessment of reduction of foot edema and hyperthermia in relation to x-ray changes. In our patient collective, the temperature of the affected extremity was not a very sensitive parameter. Temperature changes could only be observed in 38% (n = 5) of patients during the period of observation. Chantelau et al. (2006) have

reported a total disappearance of bone and soft tissue edema in MRI, when casting of the foot was conducted for up to six months [16]. The quantitative analysis conducted in our study is consistent with these observational findings. In the present study, all patients with a reduction of clinical symptoms showed a significant decrease of bone marrow edema in MRI. MR imaging might help to determine the appropriate time to end off-loading and immobilisation, since MR might be able to disclose residual activity in a stage 0 Charcot foot. In addition, MRI might be helpful to assess the tolerance of the healed osteoarthropathic foot for load bearing during walking. Non-compliant patients who would not follow the strict pressure-relieving assignment, might be identified earlier, compared to isolated clinical evaluation. Furthermore, MRI may contribute to differentiate isolated neuropathic pain and pain induced by acute stage of CA.

Limitations of the Study

Elevated temperature in this study was assessed by clinical examination. Standardized evaluation, including measurement of skin temperature, might produce more reproducible results and should be considered in follow-up evaluations.

Only a small patient population (n = 13) has been examined in this study. However, to date, it is the first comparison of clinical findings and quantitative MRI-data published in the field of stage 0 CA. Patients with stage 0 disease are quite rare in such a clinical surrounding. However, during the course of study, both, clinicians and radiologists became more aware of stage 0 CA. While this study was undertaken as part of cooperation of departments of reconstructive foot surgery and radiology, inclusion of the department of diabetology may enable to recruit larger patient collectives.

Classification

In late stage osteoarthropathy, plain radiography provides important anatomic information on fractures and subluxations. However, in the early stages of the disease, MRI is definitely more sensitive in the detection of subtle soft tissue, bone marrow, and tendon lesions. Therefore, MRI assessment should be included in existent grading-schemes of CA. Our results and those of other authors indicate, that stage 0 of CA can be subdivided into an active and non-active stage of disease. Assignment to these groups can be accomplished based on a combination of MRI and clinical findings. Over the last years, the value of MRI in this entity is gradually more accepted by clincians [16].

Conclusion

MRI in early stage of CA provides valuable diagnostic information on the activity of the disease. There is a high correlation of intensity of bone marrow edema and clinical assessment. The effect of pressure-relieving treatment can be monitored. The role of MRI for classification of early stage CA should be further evaluated in an interdisciplinary approach in order to possibly support these preliminary results. Paramagnetic contrast agents did not provide additional diagnostic information in the early stage of CA.

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