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QUESTION 4: What is the best method to differentiate acute Charcot foot from acute infection?

RECOMMENDATION: Differentiation between acute Charcot neuroarthropathy (CN) and acute infection/osteomyelitis is complex and requires multiple (>1) diagnostic criteria. These criteria include an emphasis on the presence of neuropathy, history and physical examination. The absence of skin wounds and resolution of swelling/erythema with elevation makes the likelihood of infection very low.

In unclear cases, laboratory testing, histological examination and culturing of bone specimens, scintigraphy, and imaging, especially magnetic resonance imaging (MRI), may be of benefit.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

At initial presentation, acute infection comprising of cellulitis and osteomyelitis (OM) and CN may be difficult to differentiate. However, it is important for the clinician to make an accurate diagnosis, as correct treatment largely determines outcome as both present a substantial risk of limb amputation and mortality.

Physical features can provide essential clues to the diagnosis. The "probe-to-bone" test, which tests whether the underlying bone is palpable via a probe inserted into a wound, has demonstrated sensitivity ranging from 38 to 95%, specificity ranging from 84 to 98%, and a positive predictive value ranging from 53 to 97% for the diagnosis of osteomyelitis [1–6]. In their study of 1,666 consecutive diabetic patients, Lavery et al. demonstrated that a positive probe-to-bone test increases the probability of OM greater than 50%, whereas a negative test is a strong predictor of absence of infection [3]. The test, however, has shown to have a high variability when performed by inexperienced clinicians, but this intra-observer variability was demonstrated to decline with experience [7].

In terms of other physical features, CN typically affects the midfoot and lacks associated skin breakage, whereas OM is more frequently found in the forefoot and is often accompanied by soft tissue infection or ulcer [8,9]. Additionally, while it is possible to contract OM through hematogenous spread, the vast majority of cases are spread directly via a soft tissue infection or ulcer. A wound size > 4.5 cm^2 is associated with a three times higher chance of underlying OM [10]. However, others have suggested that both ulcers of size > 2 cm^2 and depth > 3 mm are also significant [11,12]. White blood cell (WBC) counts, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are often utilized for work-up of infection. Some investigators have concluded that elevated ESR (> 70 mm/h) is strongly associated with OM [11–14].

A further benefit of ESR is that, while levels of the other inflammatory markers drop rapidly once antimicrobial treatment begins, ESR remains elevated for longer periods of time, therefore making it useful in monitoring treatment efficacy. Interleukin (IL)-6 has also been suggested as a marker for diagnosis of OM and monitoring treatment in preliminary studies [15,16]. However, these inflammatory markers are nonspecific and may be elevated by various other factors. Given that many patients with histologically proven OM may present with a normal WBC count, hematologic studies alone are not reliable for diagnosis of OM [11–14].

Bone culture alone is reported to have a sensitivity of 92% and a specificity of 60% in diagnosing OM in diabetic feet [17]. Bone samples can be obtained by percutaneous biopsy or during surgery [12,18]. However, bone specimens may often yield false-positive or false-negative results. Histologic analysis is suggested to be important in preventing these undesirable results, as several studies have shown that 40 to 60% of histologically proven cases of OM at surgery or biopsies of foot and ankle had negative cultures [19–22]. Therefore, standard criteria for the diagnosis of OM should be a positive culture with histopathologic evidence of infection in bone specimen [23].

Radiographic signs of infection, such as demineralization, periosteal reaction and cortical destruction, may not appear until two to three weeks after onset and require a loss of 40 to 50% bone mass to detect the difference [8,24]. The accuracy of plain radiography for early diagnosis is 50 to 60% with a sensitivity of 60% and a specificity of 80% [25,26]. Therefore, more advanced imaging is needed for diagnosis of acute osteomyelitis.

Magnetic resonance imaging (MRI) is suggested to be an effective modality to aid in early diagnosis [27,28]. A previous meta-analysis has shown that the sensitivity of MRI to diagnose OM in the foot and ankle is 90% sensitive and 79% specific [29]. In a meta-analysis of 16 studies, MRI performance was superior to that of technetium ^{99m}Tc bone scanning, plain radiography, and WBC studies. The sensitivity for the diagnosis of OM was found to be 90% while specificity was 85% [30]. MRI was better able to identify the extent of the involved area, whereas WBC bone scan may have better performance in differentiating OM from CN, especially in patients with metal implants [23,24].

While chronic CN shows low intensity in both T1- and T2-weighted images, both acute OM and acute CN show low signal on T1-weighted images and hyperintensity on T2-weighted images with contrast enhancement. However, these are common markers in both infective and neuropathic disease, making differentiation

of the two difficult [31]. OM almost always follows surrounding soft tissue infection, therefore identifying soft tissue edema, ulceration, or sinus tracts on imaging would suggest infection. MRI findings of diffuse bony edema in bony prominences (calcaneus, metatarsal heads, malleoli) and phalanges, with a contiguous spread would also suggest OM [32–34]. CN typically shows periarticular and subchondral changes (including fractures) as the pathology centers around the joint [35]. Disease affecting one or multiple joints, in particular of the midfoot, would also suggest CN [35].

Aside from MRI imaging, three-phase bone scintigraphy has a high sensitivity (80 to 100%) but poor specificity (25 to 60%) in diagnosing OM [36]. Labeled leukocyte scans (tagged WBC scans) are similarly sensitive, but more specific [23]. Capriotti et al. reported 86% sensitivity and 85% specificity for ^{99m}Tc-labelled leukocyte scintigraphy [37] and Dinh et al. reported that a ^{111}in-labelled leukocyte scan had a sensitivity of 74% and specificity of 68% [29]. Fluorodeoxyglucose (FDG) positron emission tomography (PET), which measures increased intracellular glucose metabolism, has demonstrated promise in diagnosing CN, particularly with regards to negative predictive value. Basu et al. found sensitivity and specificity of FDG PET in the diagnosis of CN to be 100% and 93.8%, both higher than the corresponding values of 76.9% and 75% for MRI [38]. Study results are inconclusive, however, with some authors finding that its use is limited when compared to MRI and WBC scintigraphy [39,40]. Further interesting developments in aiding in diagnosis are PET-computed tomography (CT) and PET-magnetic resonance (MR), which show promising early results [41–43]. Rastogi et al. reported the sensitivity and specificity of FDG PET-CT to be 83.3% and 100%, compared with 83.3% and 63.6% for contrast-enhanced MRI for the diagnosis of diabetic foot OM in the background of CN [41].

Previous systemic reviews of the literature (including the International Working Group on the Diabetic Foot's consensus scheme for the diagnosis of diabetic foot OM) and meta-analyses have proposed specific criteria for differentiation of CN from OM [21,23]. The proposal was based on using post-test probabilities to define broad levels of diagnostic certainty, with OM most likely being present if (1) a bone sample shows positive culture and is confirmed with histopathology, (2) intraoperative finding shows purulence in the bone, (3) intraosseous abscess is found on MRI or (4) exposed bone exists in the foot ulcer with corresponding changes in advanced imaging. However, the validity of the criteria has not been clinically tested and should, therefore, be utilized with caution.

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