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The Charcot Foot-An Indian Experience

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Contents

Abstract

Charcot neuroarthropathy is a limb-threatening, destructive process that occurs in patients who suffer from neuropathy associated with medical diseases such as diabetes mellitus. Clinicians' treating diabetic patients should be vigilant in recognizing the early signs of acute Charcot, such as pain, warmth, edema, or pathologic fracture in a neuropathic foot. Early detection and prompt treatment can prevent joint and bone destruction, which if untreated can lead to morbidity and high level amputation. High degree of suspicion is necessary. Once early signs are detected, prompt immobilization and offloading are important. Treatment should be determined on an individual basis in which it must be determined whether or not a patient can be treated conservatively or will require surgical intervention when entering the chronic phase. If diagnosed early, medical and conservative measures will only be required. Surgery is indicated for patients with severe or unstable deformities, which if untreated will end up in major amputations. A team approach including the foot and ankle surgeon, the diabetologist, physiotherapist, medical social councilor, and most important, the patient and the immediate family members, is vital for successful management of this serious condition.

Keywords: Rocker-bottom; Charcot arthropathy; Peripheral neuropathies; Redness; Swelling; Pain or Soreness; Warmth within the foot; Strong pedal pulse; Instability in the joints; Loss of sensation in the foot; Fragmentation; Bone resorption; Dislocations; Fractures; Coalescence; Sclerosis; Fracture healing; Debris resorption

Abbreviation

TNF : Tumor Necrosis Factor

OPG: Osteoprotegrin

CGRP: Calcitonin Gene Related Peptide

MRI: Magnetic Resonance Imaging

Introduction

Since its first description by Sir William Musgrave in 1703, the pathogenesis of Charcot neuroarthropathy (CN) has bewildered even the most astute physicians and scientists. In 1883, Jean-Martin Charcot described the 'tabetic foot,' as tabes dorsalis was the most common cause of neuroarthropathy at the time [1]. Diabetes mellitus has long surpassed syphilis as the leading cause of CN and the prevalence of diagnosed CN in patients with diabetes is reported to be 0.08% to 7.5% [2]. Armstrong et al has reported the prevalence of Charcot foot to be approximately 0.16% in general population and about 13% in the high risk diabetic patients presenting to a foot clinic [3]. Although not very common, CN a chronic and progressive disease of bone and joints, is one of the most destructive complications of diabetes, leading to subluxation, dislocation, deformity, and ulceration of the foot and ankle joints. It is characterized by painful or painless bone and joint destruction in limbs that have lost sensory innervations.

The prevalence of diabetes is increasing rapidly and is likely to reach epidemic proportion in the next decade. There are over 371 million diabetic patients in the world today. It is estimated that India had about 31.7 million adult diabetic patients (age group of 20 to 79 years) in the year 2000, and the number is expected to increase to 73 million by 2025 [4]. As of now, India with 61.3 million diabetic patients has the second largest number of diabetic patients in the world, after China [5].

The Charcot foot, is a condition affecting the bones, joints, and soft tissues of the foot and ankle, characterized by inflammation in the earliest phase. The Charcot foot has been documented to occur as a consequence of various peripheral neuropathies; however, diabetic neuropathy has become the most common etiology. The interaction of several component factors (diabetes, sensory-motor neuropathy, autonomic neuropathy, trauma, and metabolic abnormalities of bone) results in an acute localized inflammatory condition that may lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity (Figure 1). The hallmark deformity associated with this condition is midfoot collapse, described as a "rocker-bottom" foot, although the condition appears in other joints and with other presentations. Pain or discomfort may be a feature of this disorder at the active (acute) stage, but the level of pain may be significantly diminished when compared with individuals with normal sensation and equivalent degrees of injury [6].

'Amrita Institute of Medical Sciences and research centre' is a large tertiary, 1400 bed, super-speciality hospital at Kochi, Kerala, India. The division of diabetic lower-limb and Podiatric surgery mainly deals with diabetic lower limb surgical problems. The division is amalgamated to the department of Endocrinology. This integrated team approach, so important in the proper management of the diabetic foot and lower limb problems, is available in only few centres worldwide. This is the best of its kind in the country, and probably in Asia. We have an inpatient load of about 50 diabetic foot patients at any time. Our outpatient load is about 60 patients, each out-patient day, which is thrice a week. We see about three new Acute Charcot cases each week, and operate on about one to two severely destroyed foot and ankle Charcot cases each week, in high risk diabetic patients. Remarkably, a large percentage of these patients have destroyed hind foot Charcot. This is other than large number of forefoot corrective surgeries done every month.

Figure 1: Destroyed Mid and Hind Foot Charcot.

Pathophysiology

The exact nature of Charcot arthropathy remains unknown, but the following major theories existed regarding the pathophysiology of this condition [7].

Neurotraumatic theory

This theory states that Charcot arthropathy is caused by an unperceived trauma or injury to an insensate foot. The sensory neuropathy renders the patient unaware of the osseous destruction that occurs with ambulation. This microtrauma leads to progressive destruction and damage to bone and joints.

Neurovascular theory

This theory suggests that the underlying condition leads to the development of autonomic neuropathy, mainly sympathetic denervation, causing the arterio-venous shunts to open into the volkmann and haversian channels (Figure 2). This causes about 30% to 60% increased blood flow into the bone. This causes the minerals to be washed off and also stimulates the osteoclasts, which in their turn causes increased bone destruction, leading to osteopenia.
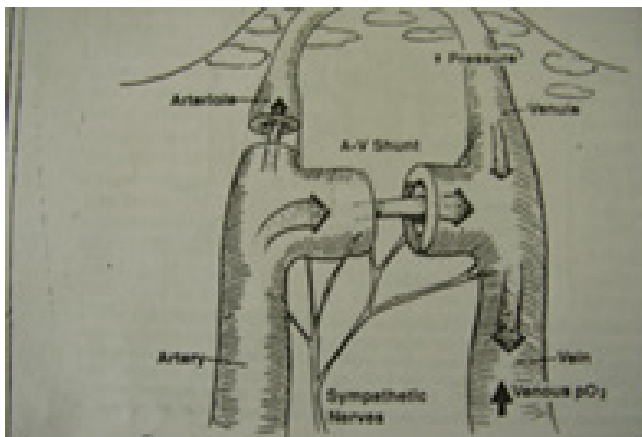
Figure 2: Arterio-Venious Shunts.

Combination theory

Charcot arthropathy most likely results from a combination of the processes described in the above theories. The autonomic neuropathy leads to abnormal bone formation, and the sensory neuropathy leads to an insensate joint that is susceptible to trauma. The development of abnormal bone with no ability to protect the joint results in gradual bone fracture and in the subluxation of the joint.

Charcot recognized the role of acute inflammation: 'the joints were inflamed, red and rather painful, similar to exacerbations of subacute rheumatoid arthritis' (translation) [8]. Indeed, it is the uncontrolled inflammation that results in the final common pathway for decreased bone density in CN with osteoclast & osteoblast imbalance. Gough et al. [9] proved that excessive osteoclastic activity occurs in patients with acute CN [9].

The role of inflammation in upsetting osteoclast-osteoblast homeostasis was investigated by Baumhauer et al. [10]. The investigators stained 20 surgical bone specimens of Charcot patients with hematoxylin and eosin (H&E), interleukin-1 (IL-1) antibody, tumor necrosis factor (TNF) alpha antibody, and interleukin-6 (IL-6) antibody. These inflammatory cytokines lead to bone resorption by promoting osteoclast recruitment, proliferation, and differentiation. Osteoclasts demonstrated a moderate pattern of staining for TNF-alpha and IL-1, and a diffuse pattern of staining for IL-6. These results suggest that osteoclasts express inflammatory cytokines during the acute and reparative phases of CN. H&E staining also showed the presence of excessive numbers of multinucleated osteoclasts in lacunae surrounded by lamellar bone. Uccioli et al. [11] further elucidated the role of inflammation in the Charcot process as they characterized the cytokine phenotype of monocytes in patients with acute CN [11].

The Role of Receptor Activator of Nuclear Factor kappa B Ligand (RANKL)

The presence of proinflammatory cytokines alone does not account for the entire influx of osteoclasts in CN. Receptor activator of nuclear factor-kappa B ligand (RANKL) has been studied extensively for its role in activating osteoclasts in diabetic CN. RANKL is an important mediator of osteoclastogenesis and is essential in osteoclast formation and modulation (Figure 3). The antagonist of the RANKL pathway is osteoprotegrin (OPG). Jeffcoate suggested that disruption of the RANKL/OPG pathway is responsible for both vascular smooth muscle calcification and the osteopenia seen in CN [12].
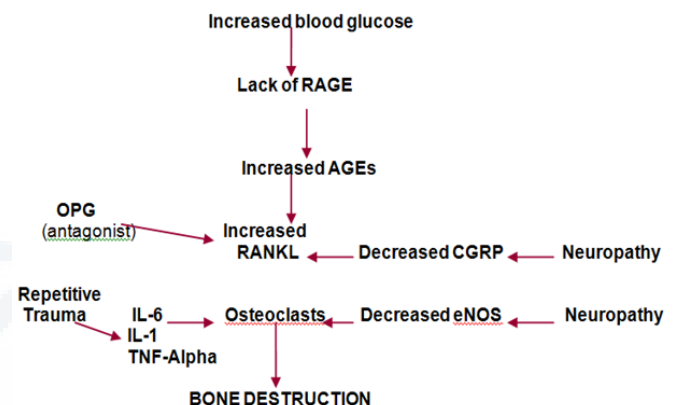
Figure 3: The antagonist of the RANKL pathway is osteoprotegrin (OPG).

Three years later, Mabilleau et al. [13] demonstrated the role of RANKL in CN and also suggested that there may be a RANKL-independent pathway [13]. The addition of OPG caused a greater decrease in resorption in the diabetic and healthy control groups than in the Charcot group, implicating that there is a RANKL-independent pathway of bony destruction in CN. This study demonstrated unequivocally that osteoclast precursor cells in acute Charcot patients are 'primed' to become osteoclasts with aggressive behavior. The authors of this study suggest that the increased levels of circulating proinflammatory cytokines, TNF-alpha, IL-6, and IL-8 induce osteoclast formation independent of RANKL. Indeed, inflammation is the final common pathway in the pathogenesis of CN.

To attempt to address the osteoclast-osteoblast imbalance, there has been research to evaluate the use of bisphosphonates in CN. Pitocco et al. [14] performed a Level 1 study of 20 patients in which the treatment group received 70 mg of alendronate once weekly, and the control group received placebo [14]. Both groups were prescribed standard off-loading methods. While these researchers found significant reductions in hydroxyproline and serum C-terminal telopeptide of type 1 collagen (ICTP), markers of bone turnover, they did not report differences in the resolution of clinical symptoms. They did, however, demonstrate a reduction in the serum levels of insulin-like growth factor 1 (IGF-1) in the treatment group. IGF-1 causes vasodilatation, adding to the hyperemia that already exists in CN. This finding prompted the same group of researchers to study the relationship between IGF-1,

neuropathy, inflammation, and the RANKL system [15]. Bisphosphonates may decrease IGF-1 and help regulate RANKL, but their clinical efficacy remains to be proven.

The Influence of Calcitonin Gene-Related Peptide (CGRP) and Nitric Oxide

Peripheral and autonomic neuropathy can minimize the release of the neuropeptide calcitonin gene related peptide (CGRP), which antagonizes the expression of RANKL. CGRP inhibits osteoclast motility, recruitment, and differentiation [16]. Associated with blood vessels, CGRP is produced in the hypothalamus and found in the periosteum and bone marrow. Experiments utilizing fractures in rat femora demonstrated that CGRP increases at the site of the fracture gap, suggesting that neuropeptides play an active role in bone remodeling [17]. With a lack of CGRP, osteoclasts are recruited by RANKL in an unchecked fashion. La Fontaine et al. [18] substantiated the CGRP hypothesis with their study in 2008 [18].

They performed immunohistological studies in bone samples of three groups: diabetic patients without neuropathy, diabetic patients with neuropathy, and diabetic patients with stage 2 or 3 CN. Samples of bone were collected during reconstructive operations, and patients with history of ulceration, osteomyelitis, or end stage renal disease were excluded. They found a trend toward significance in comparing CGRP expression, with the Charcot group having the least amount of CGRP. Additionally, these researchers looked at the relative amounts of endothelial nitric oxide synthase (eNOS), an isoenzyme that regulates nitric oxide production. Nitric oxide is a free radical that suppresses osteoclasts. Immunohistochemical studies found a statistically significant decrease in eNOS in the Charcot bone compared with the other two groups.

Advanced Glycation End Product (AGE) Accumulation

Another mechanism by which RANKL, and thus osteoclast function, is increased is by accumulation of advanced glycation end products (AGEs). The formation of AGEs is driven by hyperglycemia and primarily affects collagen in tissues with the slowest turnover, such as cortical bone [19]. AGEs have been found to increase RANKL activation as well as induce osteoblast apoptosis [20]. In patients with diabetes, there is increased formation of AGEs but a lack of a receptor for AGEs (RAGE). Witzke et al. [19] designed a cross-sectional study in which they enrolled 80 male subjects: 30 healthy controls, 30 diabetic patients without Charcot, and 20 diabetic patients with stage-2 CN [19].

They found a significant reduction in calcaneal stiffness in the patients with CN. In all subjects, there was a positive correlation between calcaneal bone stiffness and RAGE concentration, indicating that RAGE is protective against osteoclastic resorption. CN patients had RAGE values that were 86% lower than control subjects and 50% lower than diabetics without CN. In addition, these researchers found

an elevated level of osteocalcin, a marker of bone turnover, in CN patients. In summary, there was a linear relationship between impaired AGE defense (lack of RAGE), increased bone turnover, and reduced bone stiffness. This study suggests evidence that drugs that increase RAGE levels, such as ACE-inhibitors, statins, and glitazones, may be useful in preventing or suppressing CN.

Natural History

Large percentages of the patients who develop Charcot neuroarthropathy have a known duration of diabetes of over 10 years. The long duration of diabetes prior to the initiation of the Charcot process reflects the degree of neuropathy that is invariably present in these patients. The blood supply to the Charcot foot is always good. The initiating event of Charcot neuroarthropathy is often a seemingly trivial injury, which may result in a minor periarticular fracture or in a major fracture despite the inability of the patient to recall the injury in many cases. The patient may notice a change in the shape of the foot and others describe the sensation, or the sound, of the bones crunching as they walk. Following this there is a rapid onset of swelling, an increase in temperature in the foot and often an ache or discomfort.

It is these processes which, if left untreated, lead to the characteristic patterns of deformity in the Charcot foot, including the collapse of the longitudinal and transverse arches resulting in the rocker bottom foot seen in cuneiform metatarsal Charcot neuroarthropathy or collapsed and distorted ankle joints in rear foot Charcot (Figure 4). The natural history of Charcot neuroarthropathy passes from this acute phase of development through a stage of coalescence, in which the bone fragments are reabsorbed, the oedema lessens and the foot cools, into the stage of reconstruction, in which the final repair and regenerative modelling of bone takes place to leave a stable, chronic Charcot foot. The time course of these events is variable but intervention must be made in the earliest phase to prevent subsequent deformity, disability, ulceration and amputation [21].
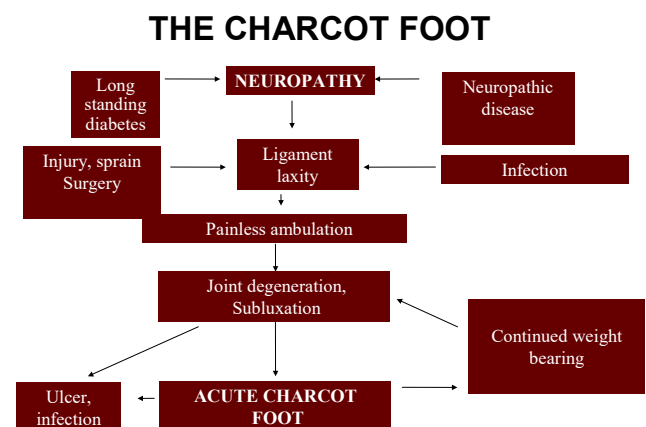

Figure 4: Natural History.

Classifications

Numerous classification systems exist for the categorization of the Charcot foot according to the severity/location and complexity of the condition. The earlier classification systems were based on the radiographic findings or anatomic location [22].

Eichenholz classification: Disease progress

The Eichenholz classification describes the evolution of the condition through time [23]. A "stage 0" has come into use to describe the swollen, hot, usually somewhat painful foot in which plain X-rays are normal. MR, however, shows bone oedema and stress fractures.

i. Stage 0: Hot foot, normal X-rays. MR shows bone oedema and fractures

ii. Stage 1: Fragmentation, bone resorption, dislocations, fractures

iii. Stage 2: Coalescence, sclerosis, fracture healing, debris resorption

iv. Stage 3: Remodelling

Brodsky classification: Disease distribution

Charcot arthropathy usually begins in the tarsometatarsal region, but sometimes it is seen in the midtarsal or ankle joints, or as pathological calcaneal fractures. The distribution is expressed by the Brodsky classification [24].

a. **Type 1:** Involves tarsometatarsal and naviculocuneiform joints, most common location (60% of cases), and collapse leads to fixed rocker-bottom foot with valgus angulation.

b. **Type 2:** Involves subtalar, talonavicular or calcaneocuboid joints, (10% of cases), unstable, requires long periods of immobilization (up to 2 years).

c. **Type 3A:** Involves tibiotalar joint, (20% of cases), late varus or valgus deformity produces ulceration and osteomyelitis of malleoli.

d. **Type 3B:** Follows fracture of calcaneal tuberosity, late deformity results in distal foot changes or proximal migration of the tuberosity.

e. **Type 4:** Involves a combination of areas.

f. **Type 5:** Occurs solely within forefoot.

Sanders and frykberg classification (Figure 5)

Sanders & Frykberg [25] classified Charcot arthropathy anatomically into patterns of joint involvement [25]. The authors divided the foot and ankle into five patterns of destruction.

a. **Pattern I:** Involves the forefoot joints and common radiographic changes include osteopenia, osteolysis, juxta-articular cortical bone defects, subluxation and destruction.

b. **Pattern II:** Involves the tarsometatarsal joints including the metatarsal bases, cuneiforms and cuboid. Involvement at this location may present as subluxation or fracture/ dislocation, and it frequently results in the classic rocker bottom foot deformity.

c. **Pattern III:** Involves Chopart's joint or the naviculocuneiform joints. Radiographic changes typically show osteolysis of naviculocuneiform joints with fragmentation and osseous debris dorsally and plantarly.

d. **Pattern IV:** Involves the ankle with or without subtalar joint involvement. Radiographs reveal erosion of bone and cartilage with extensive destructive of the joint, which may result in complete collapse of the joint and dislocation. Typically, this pattern of involvement results in a severe unstable deformity.

e. **Pattern V:** Is isolated to the calcaneus and usually results from an avulsion of the Achilles tendon off the posterior tubercle. The authors reported the midfoot (patterns II and III) to be the most common area of involvement and these patterns are often associated with plantar ulceration at the apex of the deformity.
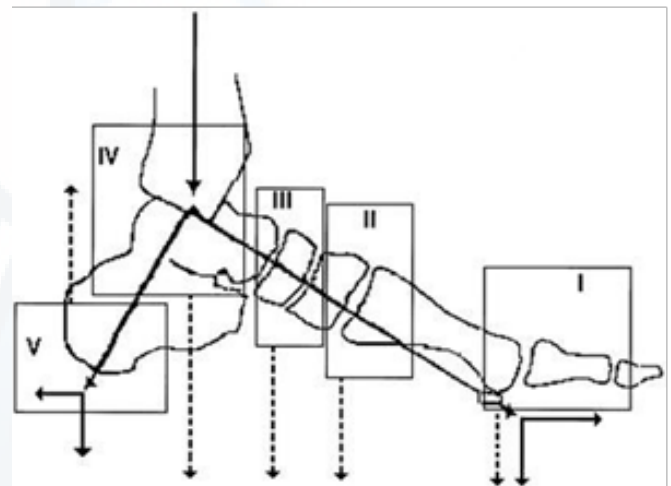

Figure 5: Sanders and Frykberg classification.

The Roger's classification of charcot foot (Figure 6)

Rogers & Bevilacqua [26] proposed a new classification scheme, which accounts for the degree of complications in the Charcot joint [26]. This new system considers deformity, ulceration and osteomyelitis, and may be helpful in predicting amputation.

This is a two-axis system (XY) and combines the features of the clinical exam, radiography and anatomy. The X-axis marks the anatomic location of involvement and the foot and ankle are divided into three regions: forefoot, mid foot and rear foot/ankle. The Y-axis describes the degree of complication in the Charcot joint. A is acute Charcot with no deformity, B is Charcot foot with deformity, C is Charcot foot with deformity and ulceration, and D includes osteomyelitis.

Therefore, one moves across the X-axis (anatomic involvement) and/or down the Y-axis (complicating factors) as the Charcot foot becomes "more complicated" and is accordingly at greater risk for amputation [22,26].
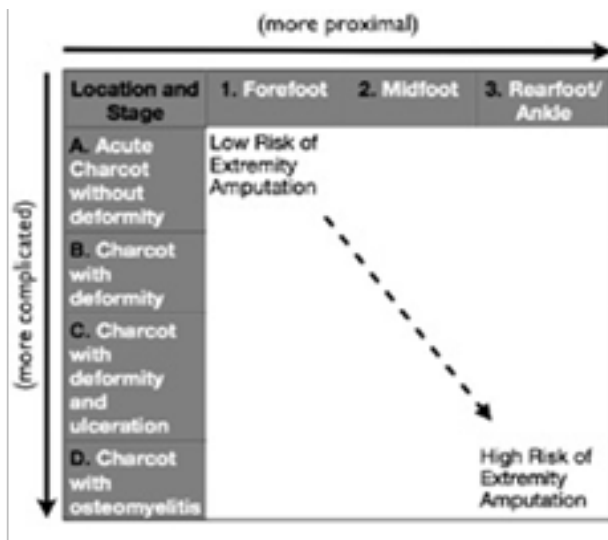

Figure 6: The Roger's classification.

Diagnosis

Diagnostic clinical findings include components of neurological, vascular, musculoskeletal, and radiographic abnormalities. There have been no reported cases of CN developing in the absence of neuropathy. Accordingly, peripheral sensory neuropathy associated with reduced sensation of pain is the essential predisposing condition that permits the development of the arthropathy [27]. Because of the very presence of insensitivity, a personal history concerning antecedent trauma is often unreliable [28]. Typical clinical findings include a markedly swollen, warm, and often erythematous foot with only mild to modest pain or discomfort [27].

Acute local inflammation is often the earliest sign of underlying bone and joint injury [29]. This initial clinical picture resembles cellulites, deep vein thrombosis, or acute gout and can be misdiagnosed as such. There is most often a temperature differential between the two feet of several degrees. The affected population typically has well preserved or even exaggerated arterial blood flow in the foot. Pedal pulses are characteristically bounding unless obscured by concurrent edema. Patients with chronic deformities, however, can develop subsequent limb-threatening ischemia. Musculoskeletal deformity can be very slight or grossly evident most often due to the chronicity of the problem and the anatomical site of involvement [30]. The classic rocker-bottom foot, with or without plantar ulceration, represents a severe chronic deformity typical for this condition. Radiographic and other imaging modalities can detect subtle changes consistent with active CN [31].

Clinical Features

High degree of suspicion is necessary. CN must be suspected in any diabetic patient coming with swelling, redness and sometimes pain of the foot and ankle, of short duration, of within four to six weeks. Usually there is no history of any known trauma. Clinical picture would resemble cellulites. However systemic features of infection may be absent. The peripheral pulses, the dorsalis pedis and the posterior tibial usually would be well palpable in CN. The erythrocyte sedimentation rate and C-reactive protein values would be normal in CN.

Symptoms of Charcot Foot May Include the Following

a) Redness.

b) Swelling.

c) Pain or soreness.

d) Warmth within the foot.

e) Strong pedal pulse.

f) Instability in the joints.

g) Loss of sensation in the foot.

h) Subluxation (misalignment of the bones that form a joint).

i) Deformity of the foot (which can be severe).

Approximately 50 percent of patients with Charcot foot remember a precipitating, minor traumatic event, and about 25 percent of patients ultimately develop similar changes on the contralateral foot. In patients with diabetes and neuropathy, Charcot joint can develop very rapidly after a minor trauma. Because trauma is not a prerequisite for Charcot foot, a patient with diabetes and neuropathy, erythema, edema, increased temperature of the foot and normal radiographs most likely has an acute Charcot process [25]. These patients are afebrile, have stable insulin requirements and normal white blood cell counts, and often have no break in skin integrity. These are all conditions that make infection unlikely. *The existence of little or no pain can often mislead the patient and the physician [26].*

Brodsky described a test to distinguish a Charcot process from infection in patients with associated plantar ulcers. With the patient supine, the involved lower extremity is elevated for five to 10 minutes. If swelling and rubor dissipate, the diagnosis of a Charcot process is supported. If the swelling and rubor persist, an infectious process is likely [24].*The acute Charcot foot can mimic cellulites. It is* strongly recommend that the diagnosis of acute Charcot foot be considered in any patient with diabetes and unilateral swelling of the lower extremity and/or foot [30]. Our experience to corroborate with these findings.

Imaging of the charcot foot

Radiographs are the primary initial imaging method for evaluation of the foot in diabetic patients. Easily available and inexpensive, especially in a country like India, where cost of medical management is an important factor, they provide information on bone structure, alignment, and

mineralization. X-rays may be normal or show subtle fractures and dislocations or later show more overt fractures and subluxations. In later stages, the calcaneal inclination angle is reduced and the talo-first metatarsal angle is broken (Figure 7).
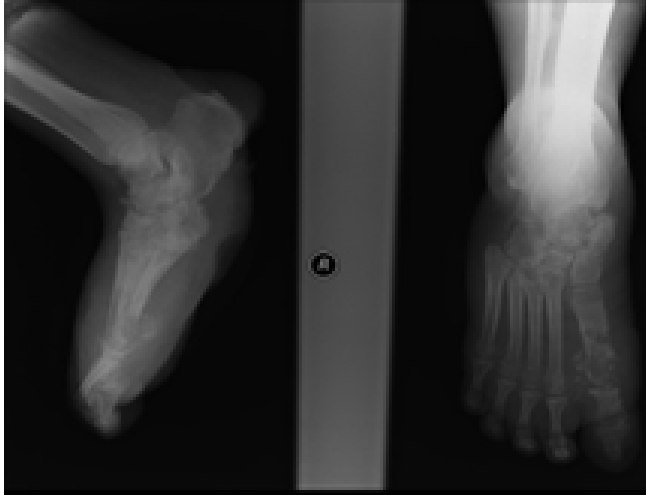
Figure 7: X-ray of destroyed fore, mid and hind foot Charcot.

However, radiographic changes of CN are typically delayed and have low sensitivity. Radiologic features of CN are the same irrespective of the etiology and distribution. Early stage radiographic findings include persistent or progressive joint effusion, narrowing of the joint space, soft-tissue calcification, minimal subluxation, osteopenia, and fragmentation of eburnated subchondral bone. In the late stage, there is radiographic evidence of destruction of articular surfaces, subchondral sclerosis, osteophytosis, intra-articular loose bodies (bag of bones), subluxation, Lisfranc fracture/dislocation of midtarsal bones, and rapid bone resorption demonstrating pencil-in-a-cup deformity. Radiographic features found in the severe form of neuropathic arthropathy are pathognomonic. Bone eburnation, fracture, subluxation, and joint disorganization can be more profound in this disorder. However, early changes may resemble osteoarthritis, and the bone collapse seen in the late stage may resemble osteonecrosis and posttraumatic osteoarthritis [32].

Magnetic resonance imaging (MRI) allows detection of subtle changes in the early stages of active CN when X-rays could still be normal. MRI primarily images protons in fat and water and can depict anatomy and pathology in both soft tissue and bone in great detail. Because of its unique capability of differentiating tissues with high detail, MRI has a high sensitivity and specificity for osteomyelitis and has become the test of choice for evaluation of the complicated foot in diabetic patients. MRI is very useful in making the diagnosis at its earliest onset before changes become evident on plain films. MRI would show, joints involved appear diffusely swollen and demonstrate low signal intensity. The fat plane adjacent to the skin ulceration appears hypointense. Signs on MRI consistent with Charcot neuroarthropathy include ligamentous disruption, concomitant joint deformity, and the center of signal enhancement within joints and subchondral bone. MRI will show subchondral bone marrow edema.

The subcutaneous soft tissues are not much involved. MRI can also differentiate Charcot neuroarthropathy from transient regional osteoporosis. The latter has a different anatomic location and does not cause fractures and dislocations, and patients do not have a clinical history of pain. Signal intensities on MRI may not discriminate between active Charcot Joint and osteomyelitis. MRI had a sensitivity of 76.9% and an accuracy of 75 % [6,33].

Due to the cost factor, we prescribe an MRI only in essential cases, for example in a patient with a Filarial leg (Kerala being endemic for Filariasis), and acute Charcot. Much like radiographs, Computed Tomography (CT) uses X-rays to generate an image. CT, while more sensitive than radiographs for detecting osteomyelitis, may still fail to detect osteomyelitis in the early stage of disease. Additionally, CT may not be able to distinguish neuropathic osteoarthropathy from the sequelae of chronic infection. Contrast-enhanced CT can detect soft-tissue and osseous abscess formation. The discovery of an abscess may alter clinical management, as treatment for abscess is typically surgical debridement. CT lacks sensitivity for differentiating changes associated with infection, edema, fibrosis, and granulation tissue.

The risk of use of iodinated contrast in diabetic patients may not be a trivial one as chronic renal insufficiency is commonly a comorbidity in patients with diabetes [34]. Nuclear medicine includes a number of exams based on the use of radioisotopic tracers. Three-phase bone scans, based on technetium-99m (^{99m}Tc), are highly sensitive for active bone pathology. However, diminished circulation can result in false-negative exams and, perhaps more importantly, uptake is not specific for osteoarthropathy. However, due to cost factor, we routinely resort to a ^{99m}Tc nuclear scan as the main diagnostic modality. Role of radioisotopic studies is also to detect osteomyelitis in a neuropathic joint. Three-phase phosphate scintigraphy has a high sensitivity (85%) but a low specificity (55%) because of bone remodeling of other causes. Studies using uptake of the gallium-67 (Ga) citrate have a high false-positive rate. Scanning using indium-111 labeled leukocytes has the highest sensitivity (87%) and specificity (81%) for detecting osteomyelitis in a neuropathic foot. Labeled white blood cell scanning (using ^{111}In or ^{99m}Tc) provides improved specificity for infection in the setting of neuropathic bone changes [6,35], but it can be difficult to differentiate soft tissue from bone. Therefore, this exam can be combined with a three-phase bone scan or sulfur colloid marrow exam when superimposed osteomyelitis is suspected [6,36]. More recently, positron emission tomography scanning has been recognized as having potential for diagnosis of infection and differentiating the Charcot foot from osteomyelitis [6,37,38]. However, this remains investigational at this time.

The role of positron emission tomography (PET) scanning with fluorodeoxyglucose (FDG) is promising. In diabetic patients in the setting of concomitant foot ulcer, FDG-PET scanning accurately rules out osteomyelitis with a 100% sensitivity and 93.8% accuracy in the diagnosis of Charcot foot [39]. Evaluation of bone density may be useful in those with diabetes to assess onset of CN as well as fracture risk.

BMD can be assessed using dual-energy X-ray absorptiometry or calcaneal ultrasound. BMD has been related to the pathological pattern of CN, whereby joint dislocation is more prevalent in those with normal mineralization versus fracture in those with diminished BMD [6,40]. A negative result obviously should not offer any confidence regarding lack of disease. In a patient with low clinical suspicion of osteomyelitis and no sign of CN on radiographs, either three-phase bone scan or noncontrast MRI is very effective at excluding osseous disease. If the patient has ulceration with a high likelihood of deep infection, MRI is the best diagnostic modality. Nonetheless, one test may not be adequate for full evaluation. In this setting where MRI diagnosis is indeterminate, a subsequent labeled white blood cell scan can provide more specificity and should be correlated with clinical findings. The decision of nuclear imaging versus MRI is largely based on personal preference, availability, and local experience. In general, if metal is present in the foot, nuclear medicine exams are preferred, whereas diffuse or regional ischemia makes MRI the preferred examination [6].

Diagnostic recommendations for active CN [6]

a) The diagnosis of active Charcot foot is primarily based on history and clinical findings but should be confirmed by imaging.

b) Inflammation plays a key role in the pathophysiology of the Charcot foot and is the earliest clinical finding.

c) The occurrence of acute foot/ankle fractures or dislocations in neuropathic individuals is considered active CN because of the inflammatory process of bone healing, even in the absence of deformity.

d) X-rays should be the initial imaging performed, and one should look for subtle fractures or subluxations if no obvious pathology is visible.

e) MRI or nuclear imaging can confirm clinical suspicions in the presence of normal-appearing radiographs.

Medical Management

The most important aspect in the medical treatment of CN is to offloading the foot and prevent further foot and ankle fractures and deformities [41]. Increasing bone redeposition and reducing further resorption of bone are also looked into.

Offloading

Offloading at the acute active stage of the Charcot foot is the most important management strategy and could arrest the progression to deformity. Total offloading with graduated compression with an elastocrepe bandage is applied for the initial 5 to 7 days, till the edema, redness and pain have subsided. Then, in a hind foot CN, involving the ankle and/ or the calcaneum, a non-walking or an irremovable total contact cast (TCC) is applied. Patient is ambulated in a 'walker' if possible. If not, a wheelchair is advised. Care of the TCC is informed to the patient and bystanders. The patient is reviewed as an out-patient once in 3 to 4 weeks, when clinical examination carried out to see for the progress of the condition, or for any maceration or ulceration of the skin. Dorso-plantar, lateral and oblique X-ray of the foot and ankle are taken to see for signs of progression of the condition and bony union. In case of a midfoot and/or forefoot CN, a walking fiberglass TCC is given [42,43].

The advantage is that the patient can carry out limited ambulation and this can be removed at night before going to bed. The foot can then be inspected for any abnormalities, and proper foot care carried out. However good compliance from the patient is required. The walking TCC offloads the forefoot and the midfoot by 80%. The pressures are transferred to the hind foot. Hence the walking TCC must not be used in a hindfoot Charcot. Here again, the patient is reviewed every once in four weeks in the out-patient clinic, and clinical and radiological findings are noted to see for progression of the condition. The casting is continued until the swelling has resolved and the temperature of the affected foot is within 2°C of the contralateral foot and X-ray shows good bony reunion [44].

It is important to take into consideration that TCC may actually have unfavorable consequences on the non-Charcot limb and induce unnatural stress patterns causing ulcerations and even fractures. Furthermore, patients with CN have increased instability and risk for falling and fracture as a result of multiple comorbidities including loss of proprioception and postural hypotension. Nonetheless, it should be noted that total immobility has disadvantages in itself with a loss of muscle tone, reduction in bone density, and reduced muscle tone and strength. Duration and aggressiveness of offloading (nonweight bearing vs. weight bearing, non removable vs. removable device) are guided by clinical assessment of healing of CN based on edema, erythema, and skin temperature changes [41,42]. Evidence of healing on X-rays or if required an MRI or a nuclear scan, strengthens the clinical decision to transition the patient into footwear. To prevent recurrence or ulceration on subsequent deformities after an acute or active episode has resolved, patient is prescribed diabetic footwear with custom molded plastazote insole, or a Charcot restraint orthotic walker (CROW). Frequent monitoring, once in 12 weeks or so, is required.

Bisphosphonates

Bisphosphonates are sometimes advised due to high bone turnover in patients with active CN. However, there is little evidence to support their use, but both oral and intravenous

bisphosphonates [45] have been studied in the treatment of CN in small randomized, double-blind, controlled trials [46,47] or in retrospective controlled studies [48]. Some patients cannot tolerate oral bisphosphonates but may benefit from intravenous therapy using pamidronate or zoledronic acid [49]. Bisphosphonates help by reducing osteoclastic resorbtion and increasing the osteoblastic redeposition of bone. Intranasal calcitonin is another antiresorptive agent that has been studied in CN.

This treatment was associated with a significantly greater reduction in cross-linked car boxy-terminal telopeptide of type I collagen and bone-specific alkaline phosphatase than standard treatment in the control group that received only calcium supplementation and offloading. Calcitonin has a safer profile in renal failure when compared with bisphosphonate therapy [50-53]. However, a single dose of intravenous bisphosphonate generally does not require renal adjustment. As yet, there is no conclusive evidence for using bisphosphonates in active Charcot foot. More trials are currently underway. In our center, we do prescribe bisphosphonates, either oral Alandronate or intravenous Zolandronate, with dosages adjusted as per the required blood investigations including serum calcium, renal functions and liver function tests. A repeat of the medication may be given after six months, if indicated. Our experience is that bisphosphonates do help in bony consolidation and early healing of the acute Charcot.

Bone growth stimulation

There is limited evidence for the use of external bone stimulation in CN. Ultrasonic bone stimulation was reported for the treatment of CN of the ankle and for the healing of fresh fractures. Direct current electrical bone growth stimulators have been used specifically in CN patients undergoing arthrodesis and clinically tested to promote healing of fractures in the acute phase of CN in small case series. Although these findings are promising, there have been no subsequent studies to validate this method, and its use has been supported only as an adjunct therapy during the postsurgical period [52-56]. In brief, offloading the foot and immobilization with a graduated compression elastocrepe bandage, are the mainstay conservative therapy in CN, which helps in bony consolidation and prevents further destruction. As of now, there is little evidence to guide the use of available pharmacological therapies to promote the healing of CN. After the active episode has resolved, ambulation is done with prescription footwear, especially a plastazote molded custom made insole. Lifetime surveillance is advised to monitor for signs of recurrent or new CN episodes as well as other diabetic foot complications.

Surgical Reconstruction

Surgical treatment of Charcot arthropathy has generally been advised for resecting infected bone (osteomyelitis), removing bony prominences that could not be accommodated with therapeutic footwear or custom orthoses, or correcting deformities that could not be successfully accommodated with therapeutic footwear, custom ankle-foot orthoses, or a Charcot Restraint Orthotic Walker [57]. It is also advised for arthrodesis of destroyed joints of the foot and ankle, and thus provides a functional foot and ankle [58].

Several investigators have suggested that Achilles tendon lengthening combined with total contact casting has the potential to decrease the deforming forces at the midfoot and decrease the morbidity associated with CN [59-64]. Exostectomy offers the potential to reduce pressure caused by bony prominences. This treatment is often combined with accommodative bracing and appears to obtain more favorable results in patients without associated ulcers [65-67].

Surgery has generally been avoided during the active inflammatory stage because of the perceived risk of wound infection or mechanical failure of fixation. Two recent case series would suggest potentially favorable outcomes with early correction of deformity combined with arthrodesis [68,69]. Salvage fusions of the foot and ankle present a unique set of problems to the surgeon. In these cases, the surgeon must frequently deal with extensive scar tissue, bone and soft tissue loss, osteopenic bone, or anatomic changes that have occurred since the primary injury or surgery. Although there have been numerous advances in surgical techniques during the past few years, many of the adaptations involve the use of internal or external fixation devices to stabilize the bony construct while awaiting consolidation [70]. These devices can include screws, blade plates, intramedullary nails, and external fixators [70,71].

Most case series have focused on reconstruction of the deformity by reduction and arthrodesis using standard methods of internal fixation. Because of the poor bone quality, an extended period of nonweight bearing of about four months is required after surgery to account for the poor bone healing and inherent weakness of the underlying osseous structures. Early surgical series showed improvement in restoring a plantigrade foot and preventing recurrence of ulceration, although nonunion, failure, and loss of initial correction were common [72-76]. The use of internal fixation and some forms of external fixation, however, may not be possible or optimal when there is extensive bone loss, local metabolic dissolution, non-union, osteopenia and osteoporosis. The concept of an internal fixation 'super construct' that extends internal fixation beyond the zone of fusion has evolved to address these issues [77]. Studies have shown an overall 56% complication rate and 55% non-union rate with the use of an external fixator. The combination of poor bone quality and a tenuous soft tissue envelope in a relatively immune-impaired population has led many surgeons to use a modification of the external fixation method of Ilizarov to correct deformity with a limited risk for surgical-associated morbidity [77-83].

Charcot arthropathy of the ankle

Charcot arthropathy of the ankle is particularly challenging, because there is often resorption of the taller body, or significant angular deformity with or without instability. Several small studies have recommended augmented internal fixation followed by prolonged periods of immobilization and nonweight bearing in neuropathic patients who sustain acute ankle fractures [84-86]. In addition, there is a prolonged time for complete stable fusion, which may cause a loosening of fixation as the process evolves. This is especially true once the patient is ambulatory. A resulting deformity may further complicate the clinical scenario. To provide salvage operations to this group of patients, alternative methods of fixation are necessary to provide stability for a prolonged period of time [87-94]. Ring fixators may be helpful for such salvage fusions. These ring fixators use tensioned, small-diameter wires to achieve the necessary stability [95]. Acute ankle fractures in patients with complicated diabetes are associated with significantly higher rates of noninfectious complications and need for surgical revision when compared with diabetic patients without other organ system comorbidities [96]. Numerous techniques have been reported without comparative effectiveness [97-100]. All of the surgical studies are retrospective in nature without a control group and are based on a limited number of patients. Complications of external fixation are very common, and pin tract infections are the most frequent (Figure 8).
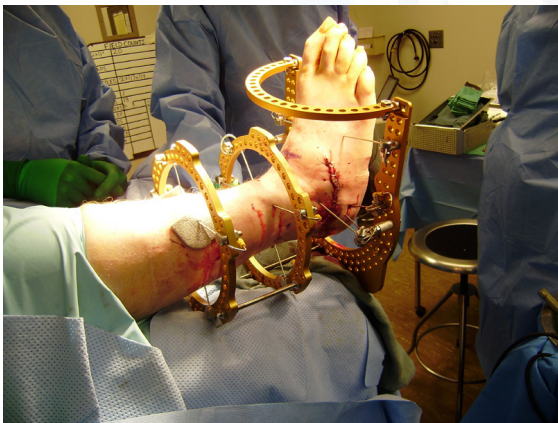
Figure 8: External Fixator.

Literature reports the rate of pin tract infections to be between 5%–100%, with most studies reporting in the range of 10–20% [88,91,95]. Moreover, cost is an important factor in a country like India, where less than 50% of patients are covered by medical insurance. Most of the cases taken up for foot and ankle reconstruction are severely osteopenic. In these cases, the compression screws or even threaded Kirschner wires do not hold well, with the chances of re-collapse being very high. To overcome this complication and the problems associated with external fixation, we have developed an alternative technique of foot and ankle stabilization after internal fixation, called the 'Amrita Sling Technique'[101]. In this method, after internal fixation with intramedullary nails or compression screws, one or more loops of number '2' fiberwire suture is passed deep to the soft tissues, close to the mid and hind foot bones, and fixed

to the lower end of the tibia, through a hole drilled with a k-wire. The Fiberwire (Arthrex) is one of the strongest non-absorbable suture materials available. Fiberwire suture is constructed of a multi-stranded long chain polyethylene core with a polyester braided jacket that gives it superior strength, soft feel and abrasion resistance [102].

In a newer technique, we have replaced foot bones destroyed due to CN or osteomyelitis, with poly methyl methacrylate (PMMA) as a prosthetic bone (Figure 9 & 10). Especially in osteomyelitis, a bone culture and sensitivity is taken pre-operatively, and the culture specific antibiotic added to the PMMA. These antibiotic laden PMMA prostheses may be able to achieve higher local concentration of antibiotics well below the toxic level of systemic administration. This has helped us avoid amputation and provide patients with a cosmetically acceptable and functional foot [103]. Patient selection is very important before surgery. Only patients who will comply with the postoperative instructions should be given this option of prosthetic replacement. It is necessary that the patient have sufficient vascularity in the lower limbs based on ankle brachial index (0.9-1.2) and trans cutaneous partial oxygen pressures (over 50 mm Hg pressure) values to permit adequate healing of the surgical wounds [103].

Figure 9: PMMA replacement of proximal phalanx, great toe.

Figure 10: PMMA replacement of destroyed hind-foot bones.

Conclusion

Charcot neuroarthropathy (CN) is a limb-threatening destructive process that occurs in patients who suffer from sensory, motor, and autonomic neuropathy associated with medical diseases such as diabetes mellitus [3]. All physicians treating diabetic patients should be vigilant in recognizing the early signs of an acute process such as unexplained pain, warmth, edema, or pathologic fracture in a neuropathic foot. Early detection and prompt treatment can prevent joint and osseous destruction, which may result in morbidity and high level amputation [27,29].

Prompt immobilization and offloading are indispensible. Patients in the quiescent stage with significant deformity are at high risk for amputation and should be referred to an appropriate center for management. Diagnosis begins at the physician level with monitoring protective sensation of diabetic patients along with strong suspicion of an acute Charcot process when the patient presents with classical signs [30].

Treatment must then be determined on an individual patient basis in which it must be determined whether or not a patient can be treated conservatively or will require surgical intervention when entering the chronic phase. A firm understanding of the aetio-pathogenesis, diagnostic modalities, and treatment protocols must be achieved by both the clinician and patient in order to obtain success. If diagnosed early, medical and conservative measures will usually suffice in this regard. Surgery is most often reserved for those patients with severe or unstable deformities, which if untreated will end up in major amputations, which should be prevented whenever possible [57,58].

When walking even with the best of prosthesis, mortality at 5 years after unilateral Below Knee amputation is 50%, and there is 50% mortality after Above Knee amputation in 3 years, in a diabetic amputee using lower-limb prosthesis [104]. In diabetes mellitus the target organ involved are the blood vessels. It thus affects all organs. By the time the blood supply to the foot has been compromised due to peripheral obstructive vascular disease, cardiac compromise would have occurred. Even with the best of prosthesis the cardiac strain is increased to over 15%, leading to cardiac failure over a period of time, which is the reason of the high mortality rates of diabetic patients on prosthesis after major amputations. About half of amputees suffer a serious lesion on the contralateral limb within two years [105]. A team approach is recommended to prevent patients with these high risk foot deformities from succumbing to limb loss.

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