Review Article

Charcot neuroarthropathy: pathogenesis, diagnosis and medical management

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Abstract

Charcot neuroarthropathy (CN) is a progressive degenerative arthropathy which rarely complicates diabetes mellitus. Most commonly, though not exclusively affecting the foot, it seems to be determined by the interaction of neuropathy, osteopaenia and proinflammatory cytokines on a calcified peripheral vasculature that maintains its ability to vasodilate despite widespread arteriosclerosis. Although often unrecalled, this arthropathy is probably triggered by trauma. Diagnosis is essentially clinical, given the paucity and non-specificity of radiological and biochemical findings at the acute stage. CN should be considered in the differential diagnosis of any diabetic patient presenting with a warm swollen lower extremity. Bone turnover markers, magnetic resonance imaging and radioisotope scanning may be useful diagnostic aids. Offloading is essential and improves limb survival. There is considerable interest, though limited data, on the benefits of bisphosphonates and calcitonin. The possible roles of ultrasound and radiotherapy need to be assessed in larger trials. Failure to institute corrective measures at an early stage results in a foot that is prone to deformity, ulceration, amputation and loss of function. It is hoped that a better understanding of the aetiopathogenesis at a cytokine level will allow the targeting of new effective agents.

Key words

Arthropathy, neuropathy, cytokines, bisphosphonates, calcitonin

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Introduction

First reported in 1831 by the American physician John Kearsley Mitchell as secondary to tuberculosis induced spinal damage,[1] denervation-induced joint destruction was described by the French neurologist Jean-Martin Charcot in 1868 as a complication of tertiary syphilis.[2] This degenerative neuropathic arthropathy was first associated with diabetes in 1936.[3] Indeed, diabetes is thought to be the commonest cause of CN in the developed world,[4,5] although it may also complicate other diseases associated with peripheral neuropathy such as leprosy, syringomyelia, following traumatic denervation of a limb, and as a complication of alcohol abuse. With a reported incidence of around 0.1-0.5%,[6-8] CN in diabetes almost always, though not exclusively, involves the foot. The midfoot or ankle joints are the most commonly affected joints. Involvement of the knee,[9] hip,[10] spine[11] and wrist[12] has also been reported. CN may develop in up to 16% of patients with diabetic neuropathy.[13] Both type 1 (T1DM) and type 2 diabetes (T2DM) patients appear to be equally at risk, although the former seem to present at a slightly earlier age.[14] There is no sex predilection. Bilateral involvement may occur in up to 30%.[4] Affected individuals generally present in the fourth or fifth decades of life, several years after the onset of diabetes.[6,15] CN has been associated with premature mortality.[16]

Pathogenesis

Although the pathogenesis of acute Charcot foot remains unclear, neuropathy and inflammation are key features. A case series of 101 subjects with CN confirmed the presence of distal sensory neuropathy in all patients.[6] Charcot himself proposed the so called 'French theory',[2] wherein the joint deformity was attributed to damaged central nervous system centres that control bone and joint nutrition. Volkman and Virchow proposed the 'German theory,'[17,18] which suggested that multiple subclinical traumata in a denervated joint were the initial precipitating factor.

It is postulated that minor trauma may trigger an inflammatory cascade through a complex pathway.[19] The precipitating event is unrecalled in around two thirds of affected patients.[4] CN has also been noted to follow local surgery, including revascularisation[20] and orthopaedic procedures.[21] Trauma may lead to microfracture, sublaxation or dislocation. Abnormal joint loading is potentially further exacerbated by the neuropathy, such that a partial or complete lack of pain

Table 1: *Anatomical classification of Charcot neuroarthropathy (CN) of the foot*[5]

Type of CN	Joint/s involved
I	metatarsophalangeal, interphalangeal
II	tarso-metatarsal
III	tarsal
IV	sub-talar
V	calcaneum

Table 2: *Classification of Charcot neuroarthropathy (CN) of the foot*[42]

Type of CN	Joint/s involved
forefoot	metatarsophalangeal, interphalangeal,
midfoot	tarso-metatarsal, tarsal
hindfoot	ankle, calcaneum

leads to continued weight bearing and further joint damage. Interestingly, both neuropathy and diabetes are associated with osteopaenia, the link being stronger with T1DM.[22,23] Osteopaenia seems to carry a higher risk of microfracture compared to dislocation.[24] However, there is no evidence so far for a difference in the presentation of CN between T1DM and T2DM. In a study on a small group of patients presenting with a hot swollen foot, Rawesh *et al.* demonstrated that reduced bone mineral density in the lower limb led to subsequent development of CN compared to patients with a higher bone mineral density at baseline.[25] It is generally accepted that neuropathy impairs healing after an incidental traumatic fracture. The altered integrity of ligaments, possibly compromised in the acute phase by motor neuropathy,[26,27] may account for a predilection for the involvement of joints dependent on ligamentous mechanical stability, such as the midtarsal joint.[28] Limited mobility of the first metatarsophalangeal joint and plantar fascia dysfunction has been associated with mid-foot CN,[31] although it is unclear whether these features precede or follow the onset of the joint damage.[29] Patients with acute CN have been found to have higher plantar pressures in the metatarsophalangeal joints when compared to patients with distal sensorimotor neuropathy or neuropathic ulceration.[30] It is postulated that the forefoot acts as a lever and causes collapse of the midfoot, which is the commonest site of involvement. Electron microscopy of the Achilles tendon has shown an increased packing density of collagen fibrils, decreased fibrillar diameter and abnormal fibril morphology.[31] These changes may lead to shortening of tendons. The abnormal collagen may predispose to CN in these patients.[31,32]

Histological examination of surgical specimens revealed that osteoclasts significantly outnumber osteoblasts in Charcot reactive bone. These osteoclasts showed immunoreactivity for interleukin 1, interleukin 6 and tumour necrosis factor alpha (TNF-α).[33] The inflammatory cascade is thought to be triggered by proinflammatory cytokines, principally TNF-α and interleukin 1 beta, which in turn trigger increased expression of the nuclear transcription factor-kappa B (NF-κB). This transcription factor plays an important part in bone dissolution by favouring osteoclast activation. An intermediate step in the activation of NF-κB may involve an increased expression of a specific transmembrane protein receptor activator called receptor activator of NF-κB ligand (RANKL).[34,35] RANKL and TNF-α appear to be mutually enhancing, such that a vicious cycle is established.[36] Osteoprotegerin, a glycoprotein member of the tumour necrosis factor family, acts as a decoy receptor for RANKL, effectively inactivating it when production is excessive. It is postulated that a coordinated synthesis of RANKL and osteoprotegerin is crucial in bone remodelling, allowing an appropriate balance between bone formation and resorption.[37] The RANKL-NF-κB pathway is implicated in the aetiopathogenesis of arterial wall smooth muscle calcification.[38,39] Vascular calcification (Monckeberg's sclerosis) is a prominent feature of diabetic neuropathy and Charcot foot, being present in up to 90% patients with the latter pathology.[6]

It is thought that, in the absence of neuropathy, pain-induced joint immobilisation halts the above inflammatory osteolytic process by reducing local blood flow.[40] Baseline blood flow is increased in neuropathic feet as a result of a reduced peripheral vascular resistance and sympathetic denervation, but does not increase in response to warming. Charcot feet retain the capacity to increase vascular flow further, exacerbating the inflammatory process.

In summary, it is possible that CN is the result of a precipitating insult on a susceptible individual. The relative contribution of the above factors may vary between T1DM and T2DM, and from one patient to another.[41]

Clinical presentation and diagnosis

CN of the foot may be anatomically classified into five different types, based on the joints involved[5] (Table 1). A different classification system[42] (Table 2) divides CN into forefoot, midfoot and hindfoot CN. Midfoot[43] or type II CN is the commonest variety. Acute CN of the ankle, hindfoot or midfoot heals at a slower rate than forefoot arthropathy.[44]

A high index of suspicion is essential, particularly in the acute stage. The situation is further complicated by the absence of a clear working definition of this disease entity.[45] Not uncommonly, acute CN is misdiagnosed as cellulitis, osteomyelitis or an inflammatory arthropathy.[6] Deep vein thrombosis should also be considered in the differential diagnosis. Avascular necrosis of the navicular bone is less common, but may show similar features to Charcot foot.[46] The diagnosis of acute CN remains predominantly clinical. Investigations largely help to distinguish the condition from others that cause pain and swelling of the foot.

The affected individual often presents with a swollen painful foot or lower extremity. Although patients have severe peripheral neuropathy, pain is the commonest complaint, followed by discomfort.[15,47] On examination, the foot is noted to be warm, with a temperature difference of over 2°C compared to the contralateral side. There may be a clinical joint effusion, usually non-inflammatory or haemorrhagic, which may contain mononuclear cells.[48] The pedal pulse on the affected side may be bounding compared to the contralateral lower limb.[49] A significant proportion of patients with acute CN have a concomitant ulcer, further complicating the diagnosis, and raising the possibility of osteomyelitis. The acute phase may take several months to subside, and is followed by a painless foot, which does not show any temperature difference to the other side. Continued weight bearing results in a deformed foot that is prone to ulceration and amputation (Figures 1 and 2). Moreover, the disease process may become reactivated by further trauma, making the differentiation from osteomyelitis more difficult.[7] Handheld infrared dermal thermometers may be used to assess skin temperature differences,[50] thus allowing monitoring of healing (associated with 'foot cooling') and recurrence (associated with 'foot warming'). Laser doppler shows an increased cutaneous blood flow in CN, differentiating from peripheral neuropathy.[51]

Radiographs, largely useful for their anatomical information, may be normal or show only subtle changes at an early stage. Once established, bone and joint destruction, fragmentation and remodelling are evident (Figure 3).[52] Any associated osteomyelitis cannot be distinguished in the presence of severe bone and joint damage.[53] Early magnetic resonance imaging (MRI) appearances are non-specific, and can also be seen in bone-stressing phenomenon, acute osteomyelitis, reflex sympathetic dystrophy or sepsis.[54] There is significant overlap of signal intensity from the marrow for infection and oedema. Established CN is characterised by a low T1 signal from the joint and a low T2 signal from the marrow.[55] Rapid onset CN with a high bone turnover rate and marked oedema is associated with a high T2 signal, mimicking osteomyelitis.[56] Osteonecrosis and recent surgery may also give this picture,[57] with the signal remaining high for 3 to 6 months after surgery. The greater the signal from the marrow on T2 weighted images, the more likely the bone is infected.[58] Gadolinium treatment does not help differentiating between oedema and infections.[59] MRI is useful for preoperative assessment and to monitor disease progression. Positron emission tomography (PET) can be used in the evaluation of CN patients with metal implants that would compromise the accuracy of MRI. Moreover, PET was also shown to distinguish between osteomyelitis and CN.[60,61]

Three-phase ^{99m}Tc bisphosphonate bone scans are positive in all three phases, reflecting the increased bone turnover characteristic of CN (Figure 4). It is a very sensitive but non-discriminatory test.[58] A four phased bone scan (with a delayed image at 24 hours) is more specific to detect woven bone but does not distinguish CN from severe degenerative changes, fractures and tumours.[53] A ^{111}In-labelled leucocyte scan shows increased activity at the site of an infection, but does not usually accumulate where there is new bone formation in the absence of infection.[53] However, such a scan may be positive with a recent-onset, rapidly advancing CN, due to the accumulation of leucocytes at fracture sites.[62] This can be differentiated by complementary marrow scanning using Tc-nanocolloid alongside a ^{111}In-labelled leucocyte scan.[63] Congruence of both scans (both positive in the same area) indicates absence of infection, and points to CN.[53,62]

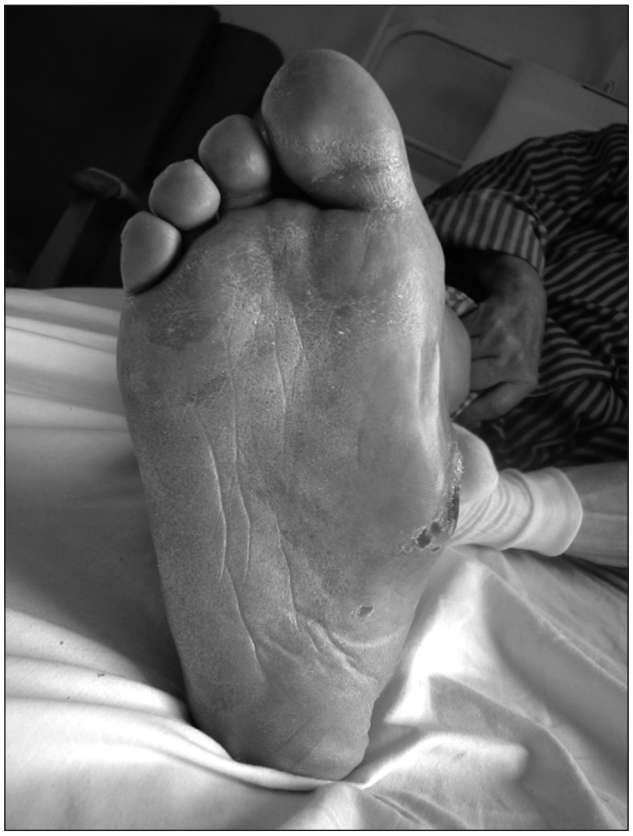

Figure 1: *Foot deformity characteristic of established Charcot foot*

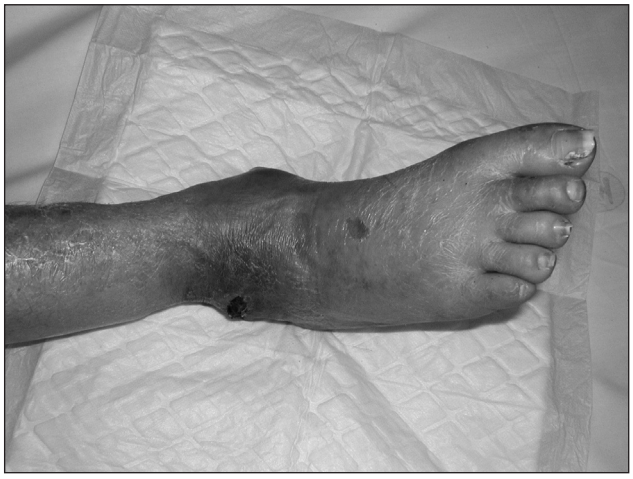

Figure 2: *Foot deformity characteristic of Charcot neuroarthropathy*

Occasionally, an increased C-reactive protein may be observed in acute CN.[64] A very high erythrocyte sedimentation rate favours infection over CN, but is still non-specific.[65] Levels of bone specific alkaline phosphatase (a bone formation marker) and urinary deoxypyridinoline (a bone resorption marker) were found to be increased in acute CN compared to non-Charcot diabetic subjects, reflecting ongoing bone turnover and remodelling.[66] Gough *et al.* found an increase in the bone resorption marker called pyridinoline cross-linked carboxy-terminal telopeptide domain of type 1 collagen in acute CN. In contrast, levels of a bone formation marker called carboxy-terminal propeptide of type 1 collagen were not increased.[67] Jirkovska *et al* not only confirmed an increase in plasma levels of pyridinoline cross-linked carboxy-terminal telopeptide domain of type 1 collagen in acute CN, but also directly correlated it with calcaneal bone density.[68] Levels of cross-linked N telopeptides of type 1 collagen, a urinary marker of bone resorption, were found to be elevated in CN patients in a separate study.[69]

In conclusion, diagnosis of CN, and in particular its differentiation from osteomyelitis remains difficult. The latter is particularly challenging in the presence of an ulcer. Some cases currently diagnosed as having osteomyelitis (particularly of the forefoot) may in fact be cases of CN.[45]

Medical management

CN may be defined as a medical emergency, since failure to act quickly can lead to irreversible consequences.[70] Once established, surgery may be necessary to remove bone deformities and reduce disability. Techniques include arthrodesis, exostectomies, reconstruction and Achilles tendon lengthening.[58] Two studies investigating any benefits of ultrasound are limited by small samples and produced conflicting results.[71,72] Given the non-specific nature of early presentation, it may be appropriate to treat the diabetic patient presenting with a warm swollen foot with antibiotics if an infection cannot be excluded.[73]

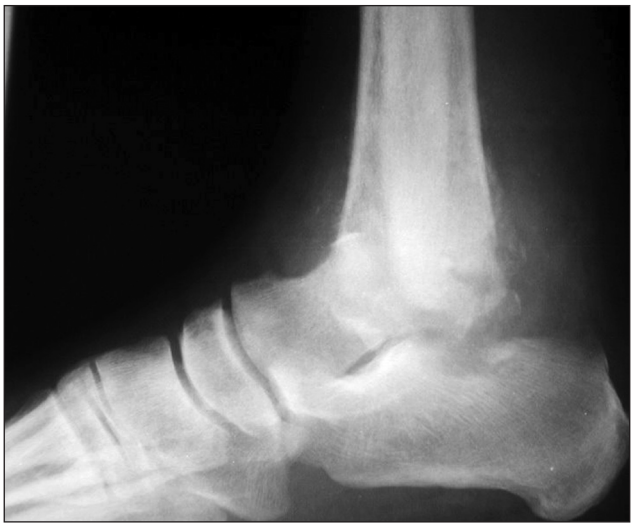

Figure 3: *Radiograph showing bone and joint deformities in Charcot neuroarthropathy of the ankle joint*

Immobilisation

Diabetic patients with acute ankle CN have been shown to have a better limb survival if they were treated with a non-weight-bearing protective device, compared to patients who continued to bear weight.[74] While the use of crutches or other assistive modalities may allow complete non-weight bearing and are acceptable forms of treatment, three-point gait may increase the pressure on the contralateral limb, predisposing it to repetitive stress, ulceration or neuropathic fracture.[75] Better alternatives include the use of a total contact cast (TCC) (made of plaster of Paris or fibreglass), Charcot restraint orthotic walker, a Scotchcast boot (made of Deltalite plaster), or pneumatic walking braces.[15, 52, 76] Ambulation in a TCC was shown to result in a mean healing time of 86 days, with the most rapid healing occurring in forefoot CN.[44] Armstrong and colleagues assessed the efficacy of serial TCC in 55 patients with acute Charcot foot until quiescence.[15] These patients were allowed unprotected weight bearing using a removable cast walker when the temperature difference between the affected foot and the contralateral healthy foot was less than 1°C for two consecutive weeks. Prescription footwear was allowed when the temperature equilibrated within 1°C for one month. On average, patients' feet became quiescent after around 4 months (range 4-56 weeks). Patients could progress to permanent footwear after just over 6 months, although some required treatment for up to 12 months. A study by McCrory *et al.*[77] also assessed the role of

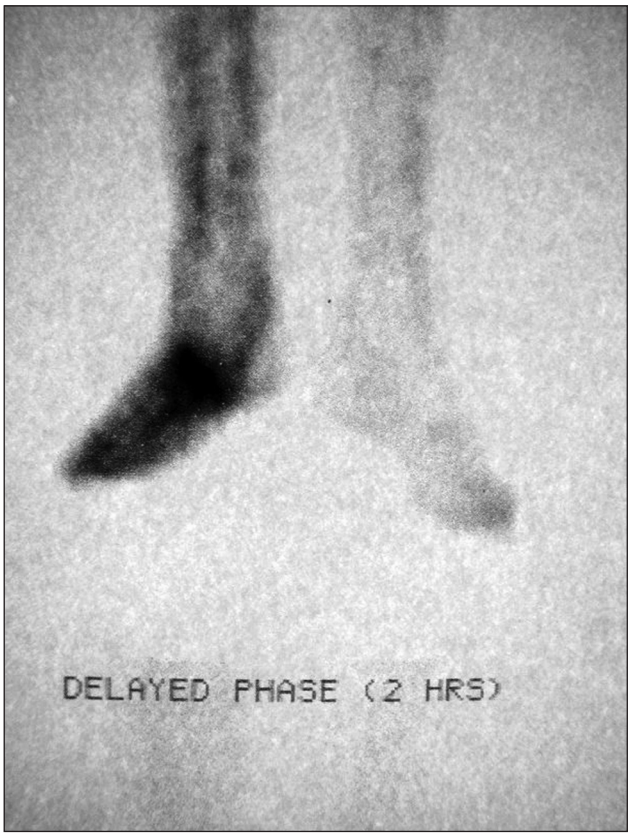

Figure 4: *Radioisotope scan showing increased ankle joint and foot uptake in the delayed phase in Charcot neuroarthropathy*

casting and foot temperature monitoring in acute CN, observing that radiographic healing began by 3-6 months, and that this is correlated with the time the foot began to 'cool.' Both studies confirmed the need for prolonged immobilisation, and that clinical indicators are required to ascertain the total duration of avoidance of weight bearing. TCCs need to be changed at least every 1 to 2 weeks to adjust to limb volume changes as the oedema decreases.[78] There are as yet no published studies assessing the Scotchcast boot in acute Charcot foot.

Bisphosphonates

There is as yet no pharmacological agent licensed for use in acute Charcot foot. A number of clinical trials assessing bisphosphonates in CN suggest clinical benefit. However, they are limited by the small number of participating patients. Bisphosphonates are synthetic analogues of inorganic pyrophosphate that decrease bone resorption by inhibiting the recruitment and activity of osteoclasts, while stimulating osteoblastic activity.[79] Bisphosphonates may shorten the lifespan of osteoclasts and provide pain relief through effects on prostaglandin E2 and other nociceptive substances.[80] They have also been implicated to interfere with the release of neuropeptides and neuromodulators from afferent nerve endings.[81,82]

In 1994, Selby *et al.* studied the effect of pamidronate on 6 patients with CN.[83] These subjects received an initial infusion of 60mg followed by a 30mg infusion fortnightly over 12 weeks. Patients' symptoms and foot temperatures showed a significant improvement. Alkaline phosphatase levels fell by about 25% by the end of the study. Jude *et al.* carried a randomised double-blind clinical trial on 39 diabetic patients with active CN, who were assigned placebo (normal saline) treatment or a 90mg single intravenous infusion of pamidronate.[47] All patients were instructed to immobilise the foot and avoid weight bearing. Both groups had a significant reduction of temperature at 2 weeks. The pamidronate group had a further reduction at 4 weeks, but there was no significant difference when comparing to the placebo group. All throughout the study, the pamidronate group had a significant reduction in symptoms compared to the placebo group. Both fasting plasma bone-specific alkaline phosphatase (a bone formation marker) and second-void early morning urinary deoxypyridinoline (a bone resorption marker, reported as a ratio with respect to urinary creatinine) showed a significant reduction in the pamidronate treated group compared to the placebo group. The first effect was seen around 4 weeks, and remained until 12-24 weeks. Levels returned towards baseline levels 6-12 months after the infusion. Anderson *et al.*[84] reported significantly greater reductions in temperature (measured after 48 hours and 2 weeks) and alkaline phosphatase (measured after 2 weeks) among CN patients treated with intravenous pamidronate compared to standard care alone. However, this study was not randomised, and there was bias in the treatment strategy.

An Italian group studied the effect of the oral bisphophonate Alendronate (70 mg once a week) on 20 patients with acute painful CN.[85] 11 patients were randomised to treatment with the bisphosphonate but all received a TCC for the first 2 months and a pneumatic walker for the next 4 months, followed by the use of special shoes. Alendronate treated patients had a significant reduction of symptoms, a reduction in the levels of the bone resorption markers hydroxyproline and carboxy-terminal telopeptide of type 1 collagen, and an improvement in the bone mineral density of the foot.

Calcitonin

Secreted by the C-cells of the thyroid, calcitonin directly affects osteoclasts and interacts with the RANKL pathway.[86] In a recent study, 32 patients were randomised to receive a combination of intranasal calcitonin (200IU/day) and calcium supplementation (100mg/day) or calcium supplementation alone.[87] Disease activity improved in both groups but there was a significant reduction in bone turnover markers in the calcitonin treated group. In a follow-up study involving 36 acute CN subjects,[88] calcitonin treated patients had significantly faster healing compared to controls.

Conclusion

The diagnosis of acute CN requires a high index of suspicion. Larger trials would allow a better elucidation of the benefits, if any, of bisphosphonates and calcitonin in the acute setting. A better understanding of the underlying aetiopathogenesis, particularly of RANKL and osteoprotegerin, may allow the targeting of new treatment strategies, such as TNF-α antagonists, corticosteroids and nonsteroidal anti-inflammatory agents. Relative risks and benefits would need to be carefully weighed however, especially in those with ulceration of the skin or other risk of infection. In the meantime, immediate institution of effective offloading remains crucial.

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