The Charcot Foot Reflects a Response to Injury That Is Critically Distorted by Preexisting Nerve Damage: An Imperfect Storm

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It has been recognized since comprehensive descriptions by Jean-Martin Charcot in 1868 and 1883 that development of what is usually known as neuropathic osteoarthropathy (or the Charcot foot) requires the coincidence of neuropathy and inflammation. Despite this, detailed understanding of the causes has remained remarkably limited in the succeeding century and a half. The aim of this descriptive account is to draw particular attention to the processes involved in both the onset and resolution of the inflammation that is an essential component of active disease. The principal observation is that while neuropathy is common in people with diabetes, the inflammation and secondary skeletal damage that characterize neuropathic osteoarthropathy are observed in only a small minority of people with diabetes and with neuropathy. We therefore argue that the key to understanding the causes of the Charcot foot is to focus equally on those who have active disease as well as those who do not. Although neuropathy is essential for development of the disorder, neuropathy also has an adverse impact on the mechanisms involved in the onset of inflammation, and these may be critically affected in the majority of those who are susceptible. The Charcot foot is uncommon in people with diabetes (or any other cause of neuropathy) because the large majority of those with neuropathy may have also lost the capacity to mount the specific inflammatory reaction that is essential for its development.

THE CHARCOT FOOT OF DIABETES

Neuropathic osteoarthropathy and its involvement in the bones of the foot in people with peripheral neuropathy were described in 1868 and in 1883 by the eminent Parisian physician, Jean-Martin Charcot (1829–1896) (1). Although the cases that Charcot described were in people with tertiary syphilis complicated by tabes dorsalis, syphilis is now an uncommon cause and most cases are the result of other distal symmetrical neuropathies such as those complicating diabetes or other conditions, which include leprosy, and ethanol abuse.

The diagnosis is suspected when a patient with neuropathy presents with an inflamed part of the lower limb with or without evidence of underlying fracture or dislocation. It may follow an accident or injury, but in many cases there is no apparent trigger (2). The inflammation and any associated skeletal damage may worsen over a number of months and may be complicated by ulceration of the skin, which

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can lead in turn to secondary infection of both soft tissue and bone. The process usually causes months of incapacity and may be complicated by permanent deformity and can lead to limb loss through major amputation.

The presentation with clinical inflammation has most often been described as "acute" Charcot disease even though it can persist for many months and the term "acute" is not always appropriate. More recently, it has been suggested that this phase should be referred to as the "active" phase of Charcot disease (3,4), but it could also be called the "inflammatory" phase.

But despite a number of reviews published in recent years (5–8), there remains little consensus on either the details of the processes involved in the evolution of a Charcot foot or the relative contribution made by different factors involved in its predisposition, precipitation, and progression. In the absence of full understanding of these processes, along with the lack of specific diagnostic tests and therapy, current management relies heavily on prompt recognition of the condition and on the early introduction of off-loading designed to conserve as much as possible of the structure and function of the affected foot. Such reliance on early recognition and prompt intervention is not helped by widespread ignorance of the Charcot foot in nonspecialist clinical practice. Some 78% of doctors working in a major teaching center in the U.S. admitted in a recent survey that their knowledge of the Charcot foot was either scant or nonexistent (9).

The aim of this review is to highlight the range of overlapping interactions that may lead to the development and persistence of this limb-threatening complication of diabetes. There is a clear need for greater understanding of the complex interaction of the factors that initiate and then moderate the active phase of the disease and using this to plan research into best practice for prevention, diagnosis, and management.

THE ROLE OF INFLAMMATION IN THE USUAL RESPONSE TO INJURY

Animals are continually exposed to injury and have evolved defenses that clear tissue debris and encourage repair in order to maximize the possibility of return to normal function. The process of clearing injured tissue is facilitated by inflammation, which is itself dependent on increased blood flow to the injured part. The process is triggered by the complex interaction of multiple *proinflammatory* cytokines, which include interleukin-1β (IL-1β), interleukin-6 (IL-6) and nuclear factor-κB (NF-κB), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and granulocyte-macrophage colony stimulating factor (GM-CSF), which are themselves derived from mesenchymal stem cells in response to stimulation predominantly by T-helper cells and macrophages. Part of their role is to stimulate the maturation of osteoclasts such that damaged bone can be removed and the remnant remodeled.

The proinflammatory process is normally moderated by, and balanced with, parallel *anti-inflammatory* pathways that limit the extent of tissue destruction and initiate its recovery and replacement. One of the principal sources of such anti-inflammatory activity lies in the terminals of peripheral nerves and is mediated by neurotransmitters such as substance P (SP), calcitonin gene–related peptide (CGRP), and vasoactive intestinal polypeptide (VIP), which themselves potentiate the release of anti-inflammatory cytokines, such as IL-8 and IL-10 (10–14). Anti-inflammatory agents promote maturation of osteoblasts and encourage new bone formation. Wang et al. (14) have emphasized that in experimental animals osteoclastogenesis and bone resorption are stimulated by RANKL-induced activation of NF-κB, while osteogenesis is activated by CGRP.

The usual recovery from injury is relatively rapid, but it can be protracted by, for example, repeated trauma or persisting infection. It may also be protracted if the balance between pro- and anti-inflammatory cytokines is distorted and the proinflammatory state remains dominant. Such imbalance is particularly likely in someone with preexisting neuropathy because this will be associated with reduction in (or absence of) the release of anti-inflammatory neurotransmitters such as SP, CGRP, and VIP. This will lead to persistent inflammation and continued tissue breakdown—which are the cardinal features of Charcot foot disease. The Charcot foot can, therefore, be regarded as the result of a reparative process that is critically distorted by the presence of preexisting nerve damage.

There is evidence that the pro- and anti-inflammatory signaling pathways may also be influenced by diabetes itself through advanced glycation end products and the production of reactive oxidative species (15,16).

CAUSES OF THE CHARCOT FOOT SYNDROME: PREDISPOSITION

Neuropathy

Neuropathy is the single factor that is essential for the development of the Charcot foot. The effects of the nerve damage are multiple and involve *1*) the effect of neuropathy on the integrity of underlying bone and joints, *2*) the effect of denervation on the release of both proinflammatory and anti-inflammatory cytokines, *3*) the effects of neuropathy on distal limb blood flow, and *4*) loss of protective sensation.

Effect of Denervation on Skeletal Integrity

Distal neuropathy of whatever cause is associated with loss of bone mass in the foot, and this is now thought to be mediated primarily by imbalance between the release of pro- and anti-inflammatory cytokine pathways. Barbaro et al. (17) have summarized the evidence that foot ulceration in people with diabetes and peripheral neuropathy (but without Charcot foot) is associated with reduced calcaneal bone density—in contrast to people with diabetes but without neuropathy.

Role of RANKL and Osteoprotegerin in Osteopenia. The elucidation of the role of receptor activator of NF-κB (RANK) and its ligand (RANKL), as well as that of its inherent inhibitor, osteoprotegerin (OPG), led to greater understanding of the link between activated mesenchymal stem cells and bone breakdown—and the recognition that osteopenia was linked to neuropathy because the loss of CGRP, SP, and NGF leads to reduced synthesis of the RANKL antagonist, osteoprotegerin (OPG) (18–20).

The expression of RANKL is also enhanced by advanced glycation end products that characterize diabetes (7,16). This effect of neuropathy dominates the well-recognized difference in bone density between people with type 1 diabetes (in which case it is lesser) and type 2 diabetes (in which case it is greater) (21) and may explain the apparent lack of

difference in the incidence of Charcot foot in the two types of diabetes. It is now also known that other signaling systems involved in the maintenance of bone integrity are also likely to be involved, and these include the Wnt/β-catenin pathway (22,23).

It is likely that it is not just the bones that are weak, but the joint capsules may also be affected in people with neuropathy. Osteopenia may contribute to dislocation by impairing anchorage of tendons and joint capsules to bone, but joint capsules are also normally richly innervated (24) and defective innervation will expose the foot to increased risk of both fracture and dislocation. Fracture and dislocation will create abnormal forces within the foot and will predispose to further skeletal damage. Seemingly isolated dislocation of major joints of the foot is also known to occur in diabetes (25), and this could constitute a forme fruste of the same process.

The Complex Relationship Between Neuropathy and Distal Limb Blood Flow

Neuropathy and Increased Distal Limb Blood Flow

A number of studies have demonstrated increased distal limb blood flow in people with established somatic and autonomic neuropathies. In reviewing this literature it is important, however, to differentiate between studies undertaken in people with or without associated Charcot foot disease. Edmonds et al. (26) and Boulton et al. (27) reported an increase in distal limb blood flow in people with neuropathy in the absence of Charcot disease, even though it was more marked when the two were combined.

Potential Effects of Arterial Calcification on Distal Limb Blood Flow

Nevertheless, there is now clear evidence that people with distal neuropathy are also likely to develop vascular calcification (28). This is usually referred to as medial artery calcification (MAC), but it should be noted that the changes in the arterial wall are the result not of "calcification" but, rather, of new bone formation (29,30) and this ossification of the arterial wall is now recognized to be the direct corollary of the osteopenia of the skeleton and is similarly based on activation of the RANKL/OPG and NF-κB signaling systems. The new bone forms in the media of the arterial wall as the result of heightened activation of the proinflammatory RANKL–NF-κB pathway when the protective effect of OPG is limited by the effects of neuropathy (31–33).

It is interesting to observe that in a recent report of a prospective study of 573 people with type 1 diabetes, higher serum concentrations of OPG were associated with the later development of neuropathy, peripheral artery disease, and diabetic foot ulceration and this association persisted despite adjustment for other likely confounders (34). It is possible that this early elevation of OPG occurred as a compensatory response to increased activation of RANKL in a population at risk for these complications of diabetes but that the expression of OPG would be later obscured by worsening nerve damage.

What has not been clearly shown, however, is the impact MAC has on distal limb blood flow. Underlying autonomic neuropathy is thought to lead to arteriovenous shunting in small arteries and arterioles, with decreased peripheral resistance that is often indicated in clinical practice by distension of veins on the dorsum of the foot in many people with neuropathy, as well as increased oxygenation of venous blood samples taken from them (26,27). But it is very possible that the development of MAC has an effect on distal limb blood flow opposite that of the neuropathy which originally caused it. Thus, MAC may reduce the capacity for arterial dilatation and any associated decrease in peripheral resistance and thereby result in a reduced capacity for the local tissues to become inflamed.

Other Factors That Might Predispose to the Development of the Charcot Foot

Genetic Predisposition

While genetic predisposition may contribute to the increased risk in the individual as suggested by study of a small number of candidate genes (35–37), the evidence is not currently strong. Even though it is likely that genetic susceptibility plays a part, the necessary genome-wide association studies have not been performed.

Obesity

It has long been suspected that obesity will increase the risk of Charcot foot disease developing, and firm supportive evidence was provided by a large study conducted by the Department of Veterans Affairs that demonstrated an increase in risk of ~60% (38).

CAUSES OF THE CHARCOT FOOT SYNDROME: PRECIPITATION

Trauma

Trauma can trigger the onset of an acute Charcot foot in an individual with neuropathy—whether it is an isolated accident or the result of elevated forces arising from associated abnormalities of foot structure and gait, often with loss of protective sensation. Trauma was the most common precipitant of the active Charcot syndrome and reported in 36% of 288 consecutive cases presenting to 1 of 76 specialist services in U.K. and Ireland (2). It should, however, be noted that the occurrence of bilateral Charcot disease is relatively uncommon.

Other Inflammatory Insults

People with diabetic neuropathy are at greatly increased risk of ulceration from loss of protective sensation, and this can be complicated by infection of soft tissue, bone, or both. As such, it is possible that this might serve to trigger the onset of active Charcot disease by causing local inflammation. Prior foot ulcer was reported in 35% of cases of active Charcot disease documented in the survey of cases in U.K. and Ireland reported above (2), while the condition was thought to be have been triggered in other cases by either local surgery or osteomyelitis in 12% and 7%, respectively. The realization that preceding foot disease may trigger the onset of active Charcot foot syndrome is important—not least in recognizing that an apparent deterioration or relapse in a case of osteomyelitis of the foot could in fact represent the onset of new Charcot disease despite effective treatment of preceding bone infection.

Lower Limb Revascularization

Episodes of active Charcot disease have been described as being triggered by surgical revascularization (39). It is possible that the revascularization enabled the expression of an inflammatory response

that had hitherto been masked by reduced distal limb blood low. Alternatively, the increased perfusion could conceivably have triggered the onset of a new inflammatory response.

Simultaneous Kidney-Pancreas Transplantation

A very high incidence of active Charcot foot disease has been reported in the months that follow simultaneous kidney-pancreas transplantation, with up to 15% reported to develop the condition within 12 months of transplantation (40–43). Most of the affected population will have had type 1 diabetes, even though there are no other data to suggest a greater susceptibility to the development of Charcot disease in either main diabetes type. It has been suggested that the high incidence may relate to the use of high dose immunosuppressants, including glucocorticoids (42). It is relevant that it has also been suggested that immunosuppressive use may occasionally be associated with some other aspects of presentation in active Charcot foot (44). It has also been suggested that it might be triggered in part by the abrupt return of euglycemia (45).

THE PERMISSIVE ROLE OF THE CIRCULATION TO THE LOWER LIMB

There is one major anomaly relating to the association of neuropathy with the Charcot foot in diabetes. While it is accepted that foot osteopenia is widespread in people with diabetes complicated by neuropathy, and that such osteopenia could predispose to the fracture and dislocation that occur in active Charcot disease (46), there has been very limited discussion of the reason why active Charcot disease occurs in only 0.1–1.0% of all people with diabetes (47), even though it was first noted by Stevens et al. (48) in 1992. This group also noted that people with an active Charcot foot had relative preservation of both skin warming on the foot and persisting warm sensitivity in the foot—in contrast to a matched population with neuropathy and foot ulcers but without Charcot changes. Stevens et al. speculated that those who develop a Charcot foot might have relatively restricted loss of sensory modalities and it was this that was linked with the capacity to mount an inflammatory response. Relative preservation of the capacity for vasodilatation in people with active Charcot disease was also noted in the same year by Shapiro et al. (49), and similar observations were made more recently by Baker et al. (50).

Retention of the Capacity for Vasodilatation in the Presence of Neuropathy

While it is possible that the capacity for vasodilatation is linked to a specific, but relatively uncommon, type of neuropathy as suggested by Stevens et al. (48), it should be noted that there is no other evidence that clinical differences in sensory modality may be linked to the loss of capacity to mount an inflammatory response.

Moreover, there are a number of other reasons why the potential for vasodilatation may be reduced in a population with nerve damage. In addition to the occurrence of cardiac autonomic neuropathies, peripheral neuropathy in diabetes has long been recognized to be associated with functional abnormalities of distal limb blood flow with, in particular, arteriovenous shunting as described above.

It is similarly well-known that therapeutic denervation by lumbar sympathectomy is associated with a marked rise in radiological signs of arterial calcification (51) and such "calcification" of the distal vasculature (Mönckeberg sclerosis) has the histological features of ossification, also as described above (29,30). As the walls of distal arteries become ossified, they will lose the capacity to dilate. Moreover, the capacity for increasing distal limb blood flow in people with diabetes may also be limited by the marked thickening of endothelial cells that can occur (52).

An additional consequence of neuropathy that will limit the capacity for vasodilatation in neuropathy will result from the reduced release by peripheral nerves of the neurotransmitter, nitric oxide (NO)—which is both proinflammatory and a potent vasodilator. The reduced release of NO when added to the oxidative stress of diabetes will increase activity of vascular matrix metalloproteinases, which will in turn inhibit vasodilatation (16,53).

It follows that in addition to any coincidental effects of proximal atherosclerosis in this population, the net effects of neuropathy will range from a state of increased distal limb blood flow associated with arteriolar-venular shunting to one with a reduced capacity for distal vessels to dilate in response to proinflammatory stimuli. If the capacity for vasodilatation is restricted in this way, it is likely to be the main reason why the majority of people with diabetes complicated by neuropathy do *not* develop active Charcot syndrome.

There are three strands of observational evidence to support this last conclusion. The first is the very occasional report of active Charcot foot being precipitated by therapeutic revascularization, suggesting that increase in distal limb blood flow is an important trigger of the onset of the syndrome, as referred to above (39).

The second strand of evidence derives from the three important studies where it was reported that people with active Charcot foot can retain some capacity for distal blood vessels to dilate—in contrast to people with neuropathy but without Charcot (48–50).

The third, rather more indirect, strand of evidence derives from the observation of the much increased incidence of active Charcot foot in the months following simultaneous kidney-pancreas transplant in people with diabetes (40–43,45). This population will be remarkable in that they will have been selected for transplantation and the process of selection is likely to have excluded those with evidence of overt macrovascular disease. The implication might be that they are more likely than others to have retention of relatively normal vascular responsiveness despite their end-stage renal failure.

CAUSES OF THE CHARCOT FOOT SYNDROME: PERPETUATION

Response to Bone Injury

The best understood pathway relating to fracture healing is characterized by three distinct but overlapping phases. The initial inflammatory phase is triggered by proinflammatory cytokines that are released within the first hours or days. This phase is usually short-lived but leads to the removal of necrotic tissue by neutrophils as well as to the recruitment of mesenchymal stem cells to the area (54–56). In the second phase,

stem cells undergo differentiation into chondrocytes leading to formation of a soft cartilaginous callus. Mesenchymal stem cells differentiate into osteoblasts and osteoclasts, the cartilage is calcified and gradually replaced by woven bone, and the callus becomes more stable. At the same time new blood vessels grow into the area. Finally, a late phase of expression and release of proinflammatory cytokines occurs and woven bone is absorbed by osteoclasts and replaced by lamellar bone produced by osteoblasts, the fracture gap is closed, and normal bone strength is achieved. A recent review sheds some light on how normal fracture healing may be disturbed in inflammatory conditions and is relevant to the usual delay in healing and chronicity of the active Charcot foot (57).

Evidence of the Involvement of Inflammatory Cytokines During the Evolution of Active Charcot Syndrome

Following speculation that the continuing process of active Charcot foot disease might be mediated through a vicious cycle of activation of the RANKL/OPG/NF-κB pathway (58), a number of groups published potentially supportive evidence of activation of one or more relevant cytokine pathways.

In a single small study of bone tissue from four people with either neuropathy or active Charcot disease evidence was found suggesting decreased expression of both innervation-dependent NO synthase and CGRP compared with controls (59). Uccioli et al. (60) also reported evidence of increased expression of proinflammatory cytokines (and reduced expression of anti-inflammatory cytokines in monocytes from people with active Charcot disease). Petrova et al. (61) provided evidence of activation of TNF-α in the stimulation of osteoclast activity in peripheral blood monocytes from people with active Charcot syndrome, and the same group also provided evidence of activation of both the NF-κB/RANKL pathway and a possible alternative monocyte-dependent pathway (62). Bergamini et al. (63) also found evidence of changing expression of NF-κB in peripheral blood mononuclear cells at different stages of activity of acute Charcot foot disease. Nevertheless, it remains very possible that the role of RANKL/OPG/NF-κB pathway in the development of the Charcot foot is concentrated not so much in the evolution of inflammation in the active Charcot foot but, rather, in the underlying osteopenia that predisposes to it (34).

In this respect, some of the most illuminating observational evidence to date came from the work of Folestad and colleagues in Göteborg and was based on following the changing expression of circulating cytokines over a 2-year period in venous samples from up to 28 people attending a single center with active Charcot syndrome (64–66). They were able to demonstrate the effect of time and disease evolution on the changing patterns in the circulating concentrations of different pro- and anti-inflammatory cytokines. Specifically, they observed in the full population that serum concentrations of proinflammatory cytokines IL-6, IL-1β, and TNF-α were no higher (and often lower) than in control subjects at presentation, although concentrations of IL-6 and TNF-α both rose transiently after ~4 months (64). In a separate study of IL-17 cytokines in 26 of the full cohort, investigators again found that baseline concentrations were not elevated but that those of IL-17A, IL-17E, and IL-17F all rose in the first 4 months of management before decreasing gradually (65). Finally, they observed that when circulating concentrations of OPG, RANKL, and markers of activation of the Wnt/β-catenin pathway were similarly followed in 24 members of the full cohort, although OPG and RANKL were significantly higher than in control subjects at presentation and fell over the 2 years of observation, the RANK-to-OPG ratio remained constant throughout (66). In contrast, the measures of activity of the Wnt/β-catenin pathway were significantly lower in the Charcot patients at presentation and rose after the introduction of off-loading.

These findings suggest that the RANKL/OPG system may be involved in the late, possible remodeling, phase of bone healing but not necessarily during the early, actively inflammatory phases of the evolution of a Charcot foot. This echoes the findings of Petrova et al. (67), who similarly found no changes in RANKL or OPG levels at presentation, after 3 months of off-loading, or at resolution of the active Charcot.

The work of Folestad and colleagues also provides good evidence of a possible role of the Wnt/β-catenin system in the development or evolution of the acute Charcot foot despite its role in bone anabolic pathways being based on osteoclast recruitment and differentiation. These findings suggest that this signaling pathway may play a greater role in the regulation of bone repair and modeling than is generally recognized, but further studies are required.

Collectively, these observations, together with those of other groups in the field, emphasize the need for care in the interpretation of measures made in cross-sectional studies and suggest that more longitudinal studies are needed to advance understanding of the processes involved in the predisposition, precipitation, perpetuation, and ultimate resolution of this complex disorder.

CAUSES OF THE CHARCOT FOOT SYNDROME: PERMANENCE OF RESOLUTION

Close study of the evolution of active disease will also provide greater insight into the way in which the relative, or changing, expression of different pro- and anti-inflammatory cytokines might indicate when the condition has entered effective remission. Such work might provide a clue to the reasons why it is unusual for the Charcot syndrome to recur in the same part of the foot once it has entered true remission. This may be because the episode of active Charcot syndrome itself has had a critical impact on the remaining capacity of the smaller arteries and arterioles to dilate in the way that it is now suggested may be essential for onset of the condition.

CONCLUSIONS

Although neuropathy is essential for the development of the disorder, neuropathy also has an adverse impact on the mechanisms involved in the onset of inflammation, and these may be critically affected in the majority of those who are susceptible. The Charcot foot is uncommon in people with diabetes (or any other cause of neuropathy) because the large majority of those with neuropathy may have also lost the capacity to mount the specific inflammatory reaction that is essential for its development.

These conclusions are based on available evidence as well as on plausible

speculation derived largely from a clinical perspective. Such an approach is justified by the relative paucity of scientific study of all diabetic foot disease over the years and especially that of the Charcot foot syndrome. Nevertheless, the emergence of some understanding of the pathways involved in mediating the responses to injury has highlighted the need for more systematic study of the complex causes of the condition. Coordination of care between diabetologists, podiatrists, vascular and orthopedic surgeons, and other specialist clinical and nonclinical teams will provide the framework for more systematic management. Moreover, the relative uncommonness of the disorder should prompt the creation of multicenter platforms for much-needed prospective studies of the causes and impact of the disease as well as of effectiveness of care. Given the complexity of the cytokine cascades that may be involved and the lack of understanding of their interaction, it is not surprising that trials of single pharmacological therapeutic agents designed to have an effect on bone integrity have been disappointing to date. Without clear guidance on a definition of the Charcot foot and particularly on what constitutes the transition from active to inactive (or resolved) phases, the design and interpretation of future studies will require great caution.

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