

The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes

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The pathogenesis of the acute Charcot foot of diabetes remains unclear. All patients with this condition have evidence of peripheral neuropathy, with loss of protective sensation and abnormal foot biomechanics. However, the acute Charcot foot is also characterised by a pronounced inflammatory reaction and the pathogenic significance of this inflammation has received little attention. We suggest that an initial insult—which may or may not be detected—is sufficient to trigger an inflammatory cascade through increased expression of proinflammatory cytokines, including TNF α and interleukin 1 β . This cascade then leads to increased expression of the nuclear transcription factor, NF- κ B, which results in increased osteoclastogenesis. Osteoclasts cause progressive bone lysis, leading to further fracture, which in turn potentiates the inflammatory process. The potential role of proinflammatory cytokines suggests the possibility of new treatments for this sometimes devastating complication of diabetes.

Introduction

Denervation-induced destruction of joints was described by Jean-Martin Charcot in 1868,¹ although he acknowledged that the condition had been first reported by the American physician John Kearsley Mitchell (1798–1858) in 1831.² Mitchell's cases were secondary to spinal damage caused by tuberculosis, whereas Charcot's were the result of tertiary syphilis. Sir James Paget suggested in 1881 that the condition should be called Charcot's disease. The Charcot foot was recognised as a complication of diabetic neuropathy in 1936,³ and diabetes is probably the commonest cause worldwide today, although leprosy is important in endemic areas. The deformity caused by Charcot's disease can be devastating (figure 1). Charcot was well aware of the part played by painlessness and abnormal foot biomechanics in the pathogenesis of the disorder, but he also emphasised that its onset was marked by an acute, inflammatory phase: “Les articulations étaient tuméfiées, rouges et quelque peu douloureuses, de manière à simuler les accidents de rhumatisme articulaire subaigu” (the joints were inflamed, red and rather painful, similar to exacerbations of subacute rheumatoid arthritis).¹

This acute inflammation, as well as the results of detailed morphological analysis, led him to speculate that in addition to the motor and sensory consequences of denervation, there might be an additional abnormality of bone blood flow or nutrition. He wrote: “[Denervation] devra se traduire encore par des troubles de la circulation ou de la nutrition, si elle affecte, en outre, des tubes appartenant au groupe des éléments nerveux vaso-moteurs ou trophiques” (denervation will also be expressed by changes in the circulation or nutrition if it involves, in addition, nerve fibres which are vasomotor or trophic).¹

This potential aspect of the pathogenesis was largely ignored during the 20th century, and most current

practitioners regard the condition as the simple result of continuing damage caused by loss of protective sensation in a well perfused limb. Recent attention has, however, focused on several anomalies, which together suggest a more complex cause. These anomalies include the rarity of the condition, its asymmetry, and the fact that it is usually self-limiting.^{4,5} The possible relation with reflex sympathetic dystrophy (complex regional pain syndrome, type 1) has also been noted.^{4,6} Of note, early observations on conditions resembling this pain syndrome, including the case series reported by Silas Weir Mitchell, son of J K Mitchell,^{7,8} drew attention to the possible link between inflammation and osteoarthropathy.

Our hypothesis is that the development of the acute Charcot foot is based on an exaggerated inflammatory response to trauma. If the role of proinflammatory cytokines is confirmed, it could lead to the adoption of new markers of the activity of the disease, and of effective new therapies.

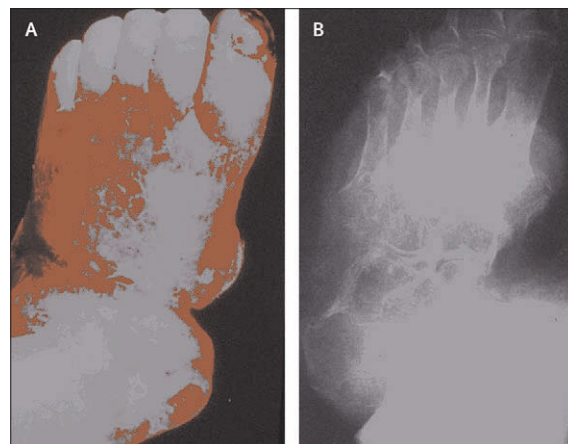


Figure 1: Clinical (A) and radiological (B) appearance of a Charcot foot

Current concepts about pathogenesis

The acute Charcot process is thought to be triggered by a minor injury, whether noticed by the patient or not. The injury might lead to either microfracture or to subluxation or dislocation, which further changes the distribution of forces on the joints and bones of the foot. The damage increases and a vicious cycle is established, which is made worse because the pain is less than would be expected, leading to continued weight-bearing (figure 2). The initial microfracture can be more likely if the bones are osteopenic, and there is evidence that both neuropathy and diabetes are associated with osteopenia, although the association with diabetes is more marked with type 1 rather than type 2 disease.^{9,10}

Although the nature of the predisposition to dislocation remains obscure, major advances have been made in our understanding of the processes underlying bone dissolution and its dependence on the stimulation of osteoclast formation by activation of the nuclear transcription factor κ B (NF- κ B). Activation of this transcription factor, together with other factors,¹¹ is itself dependent on increased expression of a specific receptor activator, receptor activator of NF- κ B ligand (RANKL).^{11–13} A particular reason for suspecting the involvement of the RANKL–NF- κ B pathway in any osteolysis which might occur in diabetic neuropathy is that the same cytokine system is also thought to be

responsible for calcification of the smooth muscle cells of the arterial wall.^{13,14} Vascular calcification (Monckeberg's sclerosis) is a prominent feature of diabetic neuropathy, and especially of Charcot foot, in which it can be present in up to 90% of patients.¹⁵ There is extensive work to suggest mechanisms whereby expression of RANKL might be increased in diabetes, since it is potentiated by free radicals,¹⁶ hyperlipidaemia,¹⁷ increased ambient glucose concentration,¹⁸ and advanced glycation end-products.¹⁹ There is also evidence that the action of NF- κ B is inhibited by insulin *in vitro*.²⁰ Moreover, it has been suggested that neuropathy also leads to increased expression of RANKL as a result of the loss of nerve-derived peptides known to antagonise its effect, including calcitonin gene-related peptide.²¹ Altered circulating concentrations of peptides such as leptin and islet amyloid polypeptide (amylin) can also affect this cytokine system in diabetes.²¹ The relevance of premonitory osteopenia is, however, far from certain, since the presentation of the acute Charcot foot in type 2 diabetes does not differ from that in type 1 disease, even though Herbst and colleagues²² suggest that those with osteopenia at first presentation are more likely to exhibit fractures rather than dislocation. Moreover, the relevance of the metabolic changes of diabetes is also not clear, since the presentation is very similar in those in whom the disease is caused by some other form of neuropathy, such as leprosy or alcohol abuse. Multiple factors probably predispose to development of the acute Charcot foot, and their relative importance probably varies from condition to condition and from individual to individual. Two factors are, however, common to all cases: denervation and acute inflammation.

The role of inflammation

Local inflammation is invariable in the acute phase of the disorder, and is the main symptom or sign which leads to the diagnosis being suspected, whether there is radiological evidence of skeletal changes at presentation or not. The presentation is often mistaken for acute infection, and if bone changes are present, differentiation from osteomyelitis can be very difficult.²³ The fact that soft tissue inflammation can predate detectable changes in bone and joints is indicative of its key role in pathogenesis. Thus, we suggest that the Charcot process is initiated in a susceptible individual by any local insult that can trigger an acute inflammatory response. This insult could be accidental trauma, and in some cases the condition has followed local surgery, including revascularisation²⁴ and orthopaedic procedures.²⁵ It is possible, but unsubstantiated, that the process is triggered by an earlier neuropathic ulcer, or by infection.

The often striking subluxation or dislocation of joints that have ligament-dependent mechanical stability (such as the mid-tarsal or Chopart's joint) suggests that

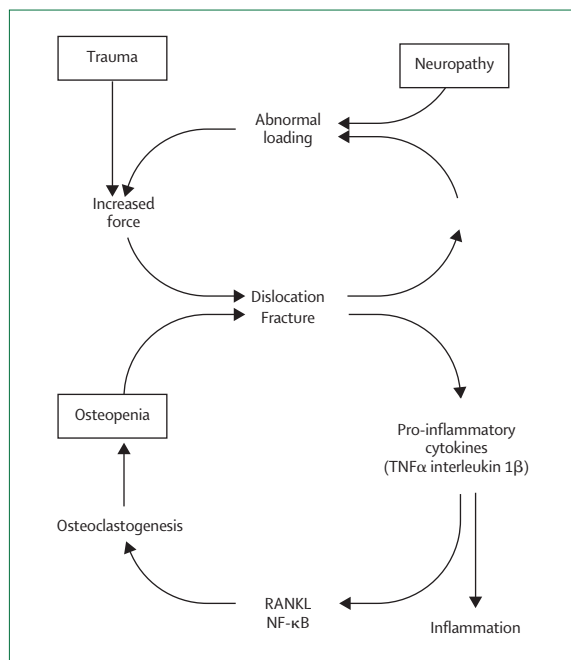


Figure 2: Two separate vicious cycles that we suggest are integral to development of the acute Charcot foot

Items in boxes=predispose to and trigger onset. Upper cycle=essence of well accepted "neurotraumatic" theory. Lower cycle=topic of our hypothesis, indicating how development of condition depends on exaggerated expression of proinflammatory cytokines.

the integrity of ligaments is compromised during the acute phase of the Charcot foot. This result may also be a consequence of the inflammatory cascade.²⁶

The acute inflammatory response is mediated through the increased expression of proinflammatory cytokines, mainly tumour necrosis factor α (TNF α) and interleukin 1 β , and acute phase rises of both follow bone fracture,²⁷ although the functional relation between the two cytokines is not clear. The acute phase inflammatory response is an essential part of the healing process of fractured bone, enabling lysis of bone fragments as a prelude to new bone formation.²⁸ This lysis occurs because TNF α and interleukin 1 β trigger increased expression of RANKL, leading to activation of NF- κ B and maturation of osteoclasts.^{29,30} The mechanism by which post-fracture osteolysis is normally terminated is unknown, but pain could be an important factor, since the perception of pain will lead to immobilisation of affected bone, which reduces local blood flow.³¹ Nerve-derived peptides associated with pain sensation, such as substance P, could also be involved in regulation of the inflammatory process.³²

Whether or not pain perception (or the release of other neuropeptides) is important in limiting the duration of an acute inflammatory phase, impairment of pain sensation will lead to worsening damage to the bones and joints through continued weight-bearing. As the damage continues, the process of inflammation will be further augmented, and the increased expression of RANKL as a result of TNF α activation will lead to further osteolysis. Another vicious cycle is established whereby the release of proinflammatory cytokines worsens the osteolysis, increasing the risk of further fracture, which leads to exacerbation of the inflammatory process (figure 2). After some months, the inflammation settles, and this is closely associated with the end of the lytic-destruction phase. The proximity of this association is such that the fall in skin temperature is the main clinical sign used to dictate when the patient may be allowed to recommence weight-bearing.

The central role of inflammation can also explain the relative rarity of the acute Charcot foot. Blood flow is increased in both feet in those with peripheral neuropathy, because of loss of sympathetic innervation and reduced peripheral vascular resistance. However, Shapiro and colleagues³³ have reported that a difference in vascular reactivity is evident when those with neuropathy and Charcot's disease are compared with neuropathic controls. Although both groups have increased baseline foot blood flow, those with Charcot's disease retained the capacity to increase flow still further, whereas neuropathic controls did not. This finding indicates that the capacity to mount an inflammatory response could be an essential requirement for the development of the acute Charcot foot.

Limitations of the hypothesis

The relation between TNF α and interleukin 1 β in mediating acute inflammation is not known, and nor is the importance of numerous other hormones, cytokines, and metabolic factors that may be involved.³⁴ The role of nerve-derived peptides calcitonin gene-related peptide and substance P is also unclear since their function is essentially proinflammatory and vasodilatory, and there is evidence that they augment the expression of both TNF α and interleukin 1 β .³²

Implications for clinical practice

If the basis of our hypothesis is correct, and the release of proinflammatory cytokines is key to the development and perpetuation of the acute Charcot foot, then measurement of TNF α , or of downstream products such as RANKL, may be used as markers of activity of the disease. Of even greater importance is the possibility that inhibitors of proinflammatory cytokines could be of benefit in clinical practice. Several inhibitors of RANKL, NF- κ B, and interleukin 1 β are available as research tools and have been used to attenuate inflammatory arthritis and osteolysis in experimental animals. More immediately, however, there could be therapeutic potential for short-term use of high dose systemic glucocorticoids (which are known to decrease expression of NF- κ B)³⁴ or of TNF α antagonists (such as infliximab or etanercept), which are currently used for clinical management of conditions such as rheumatoid arthritis. Since the aim would be to break the vicious cycle and promote resolution of the condition, treatment would only need to be continued for a short time. Nevertheless, the relative risks and benefits of such therapies would need to be carefully weighed, especially in those who had ulceration of the skin, or other risk of infection.

Testing the hypothesis

Our hypothesis can be tested simply in patients with an acute Charcot foot in three ways: (1) by measuring circulating concentrations of proinflammatory cytokines and RANKL and correlating concentrations with disease activity, although differences might be more pronounced in samples from the periphery, such as from the dorsal veins of the foot; (2) by measuring cytokine expression in bone specimens from patients with neuropathy with and without reduced bone density, and with and without acute or chronic Charcot changes, although interpretation would need care because knowledge of the morphology and biochemistry of bone affected by the Charcot process is very limited; and (3) by determining the clinical and biochemical response to treatment with systemic glucocorticoids or to TNF α antagonists. There is an urgent need to define a new approach for treatment of this rare, but often devastating disorder.

Conflict of interest statement

W Jeffcoate is contributing editor to *The Lancet*. F Game and P Cavanagh declare that they have no conflict of interest.

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