The Charcot Foot: Neuropathic Osteoarthropathy

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This continuing educational activity will expire for physicians on September 30, 2014.

PURPOSE:
To enhance the learner’s competence with knowledge of the Charcot foot.

TARGET AUDIENCE:
This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:
After participating in this educational activity, the participant should be better able to:
1. Demonstrate knowledge of Charcot foot pathophysiology and diagnosis.
2. Apply knowledge of Charcot foot to its management in patient scenarios.
INTRODUCTION

The Charcot foot is an uncommon complication of neuropathy in diabetes. It is characterized by acute to subacute inflammation of the bones, joints, and soft tissues. If unchecked, the condition can result in extensive damage with resultant deformity, secondary ulceration, and infection. The cause is not known, and there is no specific treatment. The pillars of current best practice are (a) early recognition, (b) off-loading to reduce the deformity that will result from continued weight bearing, and (c) the management of complications.

Reading this article will help the clinician to understand the epidemiology and pathogenesis of the acute Charcot foot, recognize the clinical signs that may lead to a rapid diagnosis of the acute Charcot foot, and to understand how this complication may be associated with or even triggered by a wound on the foot of a patient with diabetes.

HISTORY

Jean-Martin Charcot was appointed medical director of the Salpêtrière hospital in Paris, which at that time was a virtual isolation hospital for women with a variety of undiagnosed neurological, psychiatric, and social disorders. His brilliance lay in a systematic approach to clinical and pathological diagnosis, and this led to the original description of a number of conditions. He first described the process of inflammatory neuroarthropathy in women with tertiary syphilis and tabes dorsalis in 1868. When he presented a detailed clinical and pathological review at the London Medical Congress of 1881, the President of the Congress, Sir James Paget, singled out his work for commendation and suggested that the condition should be named after him. Despite this, his original report made no reference to the foot and ankle.

The first person to describe the process in the foot was an English surgeon, Herbert W. Page, and he presented his case at the same 1881 London congress. He published a second case in 1883, and in this later article, he observed that the condition might occur without overt signs of tabes dorsalis and speculated that it might occur as a complication of peripheral (distal symmetrical) neuropathy. Distal symmetrical neuropathy is now the most common predisposing factor, with diabetes and leprosy being the most common causes worldwide. It can, however, occur in other neuropathies, including alcohol-induced, congenital (eg, syringomyelia), and traumatic denervation.

THE SIGNIFICANCE OF THE UNDERLYING NEUROPATHY

It seems that neuropathy is always present, even though the minimum extent of necessary nerve damage is not known, and the pattern and severity of denervation observed in different cases are very variable. Tabes dorsalis is associated with near total loss of deep pain sensation (as well as loss of proprioception) resulting from damage to the dorsal columns of the spinal cord. As the defect in tabes dorsalis is relatively proximal, the bones and joints affected tend to be the larger ones of the lower half of the body. When, however, the underlying cause is distal neuropathy, deep pain sensation is relatively intact, and the loss of protective sensation is mainly localized to the spinothalamic pathway. The defect is also more distal, and it follows that the bones and joints involved are more likely to be in the foot. In every other respect, however, the process of the disease appears to be same, irrespective of the underlying cause.

PATHOGENESIS

Relatively little is known, largely because of the somewhat rarity of the disease, the lack of a specific diagnostic marker, and the inability to predict its onset and hence to study its earliest stages. Nevertheless, the importance of loss of protective sensation was recognized from the time of the original description (which became known as the “neurotraumatic” or German theory). Charcot himself also speculated that the loss of innervation of arteries supplying the bones themselves may result in osteopenia (known as the “neurotrophic” or French theory). Neither of these theories addressed 3 facts about the condition: (1) that the disease is so rare, whereas neuropathy affects some 30% people with diabetes; (2) that the disease usually is unilateral, whereas the denervation is symmetrical; and (3) that even though the neuropathy is irreversible, recurrence is very rare. Understanding the cause was essentially stalled until the publication of a hypothesis that highlighted the role of inflammation. This hypothesis is generally accepted as being the most likely explanation for the onset of the disorder, even though it has yet to be conclusively proved.

The Vicious Cycle of Inflammation

The essence of the neuroinflammatory theory is that many different facets of denervation may combine to cause a non–self-limiting
inflammatory response to a local insult, which leads to bone lysis (as well as to some ill-defined alteration to the integrity of ligaments and joint capsules) that results in fracture and dislocation. The effect of this structural change to the skeleton is the development of abnormal forces within the foot, and these lead to worsening damage. This is facilitated by loss of protective sensation that prevents protective splinting and allows continued exercise and weight bearing.

**The RANK/RANKL–Nuclear Factor κB Pathway**

The key to the process is the link between proinflammatory cytokines (primarily tumor necrosis factor α and interleukin 1β) and the RANKL/RANK signaling pathway. Thus, proinflammatory cytokines activate expression of RANKL, which is the polypeptide ligand for the RANK receptor, so-called because it is the receptor for the activation of the nuclear transcription factor, nuclear factor κB (NF-κB). Nuclear factor κB has a variety of functions, but the one which is of greatest interest in the context of this disease is the activation of osteoclasts, with resultant bone breakdown. A by-product of the increased expression of RANKL is the formation of a glycopeptide, osteoprotegerin (OPG), which acts as a decoy receptor for RANKL and thereby helps to limit its action. RANKL and OPG are therefore both released at the same time, even though their actions are essentially opposite. Much of the available clinical research has, however, been based on the assay of circulating OPG, because it is easier to measure.

**Predisposition to the Onset of Inflammatory Neuropathic Osteoarthropathy in Distal Neuropathy**

The aspects of distal neuropathy that are most commonly recognized in clinical practice are loss of motor and sensory innervation, but other modalities of denervation may be of either equal or greater importance.

**Motor neuropathy.** Motor neuropathy causes wasting of the small muscles of the foot, and this leads to loss of the smooth transference of forces during normal gait and increased forces applied to particular areas on the sole. There may also be altered balance of long flexor and extensor muscles, leading to a clawing deformity of the foot with increased forces at points, such as the tips of the toes and the dorsal aspect of the interphalangeal joints.

**Sensory neuropathy—loss of protective sensation.** Increased forces applied to any part of the foot would normally cause discomfort or pain, and this would lead to an alteration to gait in order to reduce it. In the presence of neuropathy, gait may be unaltered, and hence the abnormal forces continue to be applied.

**Vasomotor neuropathy (including sympathetic denervation)—loss of normal regulation of small arteriovenous function.** In people who do not have marked macrovascular disease, the presence of distal neuropathy in diabetes may result in the foot pulses being abnormally easy to feel. This is the result of a widened pulse pressure and has 2 main causes: (1) loss of peripheral resistance as a result of the normal control of small arterial blood flow from vasomotor neuropathy and (2) calcification of the tunica media of the wall of medium to small arteries, which is itself largely a consequence of neuropathy. The vasomotor neuropathy causes effective arteriovenous anastomoses, and the altered blood flow could conceivably have an impact on bone integrity, as originally suggested by Charcot.

Vasomotor neuropathy may also have an impact on microvascular function. Specifically, there may be alterations in aspects of vasodilatation that are nerve mediated. Three groups have examined the vascular reactivity (especially in response to warming) of the microvasculature in people who have previously had an acute Charcot foot and have shown that whereas reactivity tends to be lost in people with neuropathy, it is preserved in the small subset in those whose neuropathy has been complicated by neuroarthropathy. The implication is that the onset of neuropathy requires the ability to mount an increase in blood flow as a result of a proinflammatory stimulus, and this is usually lost in people with distal neuropathy.

**Loss of neuropeptides.** A variety of peptides are normally released from nerve terminals. Of these, the peptide that has attracted the greatest attention is calcitonin–gene-related peptide, CGRP. The CGRP normally suppresses the expression of RANKL, and thus, if it is lost as a result of death of the nerve terminals, RANKL will tend to be increased with resultant potentiation of the action of NF-κB.

**Potentiation of neuropathic osteoarthropathy by diabetes.** Although the clinical presentation of neuropathic osteoarthropathy appears to be very similar in all neuropathies, there are metabolic features of diabetes that may make it more likely. Type 2 diabetes is a condition characterized by chronic inflammation (even if there is no suggestion that the acute Charcot foot is more likely in type 2, as opposed to type 1 disease). Moreover, advanced glycation end-products and oxidized lipids both enhance the expression of RANKL. It has been shown that circulating concentrations of OPG (as a marker of activation of the RANK/ RANKL pathway) are elevated in unselected populations of people with diabetes.

**Particular clinical circumstances in which the Charcot foot is especially likely in diabetes.** There is a group of people in whom the incidence of an acute Charcot foot seems especially common and that is in people who have had renal failure managed by a
renal transplant and, in particular, by a combined kidney–pancreas transplant. The likely explanations for this are 3-fold:

1. **Population selection.** People with renal failure almost invariably have the other microvascular complications of diabetes: retinopathy and neuropathy. Those selected for a transplant (and especially for a combined kidney–pancreas transplant) will also be screened to exclude those with any degree of macrovascular disease, and those without macrovascular disease are more likely to have retained the vascular capacity to mount the inflammatory response that is necessary for the onset of the disease.

2. **Metabolic changes.** People who have had end-stage renal disease will also have a high likelihood of having had renal bone disease, with bone thinning being enhanced by both vitamin D deficiency and hyperparathyroidism.

3. **Glucocorticoid therapy.** Immunosuppressive therapy with glucocorticoids (and, possibly, other agents) will potentiate the expression of RANKL.

**Possible genetic predisposition.** Another possibility to be considered is that there is a genetic predisposition to the development of the disorder in some individuals. In this respect, the acute Charcot foot may resemble another disorder characterized by osteoclast activation: Paget disease of the bone. Although a genome-wide association study has not yet been performed in patients who have suffered with an acute Charcot foot, 2 groups have reported increased expression of OPG-related polymorphisms, and in 1 case the abnormality was common to both studies.

**Obesity.** It is often thought that obesity may play a part in the onset of the disease because of the increase in forces subject to the foot and ankle. In fact, the available evidence from case-control studies suggests that it does not.

**THE TRIGGER**

It is thought that a person with diabetes and neuropathy is at risk for the development of an acute Charcot foot by having 1 or more of the previously discussed predisposing factors; however, it is not known to what extent each of these is essential or simply facilitatory. The hypothesis then suggests that the condition is triggered by an episode that causes an episode of inflammation in a foot that is about to be affected. This episode may be several weeks or months before the onset of osteoarthropathy, but a recent large observational survey undertaken in the United Kingdom and Ireland has confirmed the fact that preexisting ulcer, infection, trauma, local surgery, and other potential episodes could have acted as trigger in a high percentage of cases. Given the fact that all had some degree of sensory impairment, it is very likely that unnoticed trauma was the trigger in a sizeable proportion of the remainder.

**THE FREQUENT CONCURRENCE OF ACUTE CHARCOT FOOT AND OSTEOMYELITIS**

**Osteomyelitis Complicating the Osteoarthropathy**

The deformity that can occur in the acute Charcot foot can lead to secondary ulceration and this can sometimes result in infection of underlying bone. When a new case presents with ulceration, it can be difficult to determine whether there is associated osteomyelitis, and it may be necessary to treat the patient with off-loading and antibiotics. Histological and microbiological examination of a bone biopsy specimen may be considered, but many clinicians are reluctant to perform a biopsy on the fragile bone of acute Charcot disease.

**Osteoarthropathy Complicating Osteomyelitis**

Many clinicians will be much less sensitive to the possibility that the local inflammation caused by osteomyelitis (which occurs most often in the midfoot and forefoot) may trigger the onset of an acute Charcot process. This may be typical hindfoot disease, but it may also be centered on the metatarsals. The newly occurring disease may be spatially distinct from the site of original inflammation, and this is a good clue that the new inflammation is not the result of worsening infection.

**CLINICAL PRESENTATION**

At its earliest stage, the acute Charcot foot presents with an episode of inflammation that is usually centered on the midfoot or hindfoot and is unexplained by any recognized predisposing trauma. The inflammation is also relatively, if not totally, painless. There are no specific clinical and biochemical markers, and an X-ray may be normal. Unless the person is under the care of a specialist team at this stage, the diagnosis is almost invariably missed, and a generalist will consider conditions that are more common but less potentially serious: sprain, cellulitis, deep vein thrombosis, and gout. The failure to make the diagnosis at this early stage can, however, lead to irreversible deformity and, ultimately, to loss of the limb.

If undiagnosed, the lack of pain will allow the person to continue to walk on the foot and to be as normally active as possible, without realizing that the bones and joints are vulnerable and at risk for fractures and dislocation. Some cases deteriorate progressively in this way, whereas others do not; the reason for this is not known. The deformity that occurs is typically centered on the bones and joints that are exposed to the
greatest forces during walking: the tarsal bones and the tar-
sometatarsal (Lisfranc) joints (Figure 1).

Disruption of the Lisfranc ligament that anchors the base of the
second metatarsal to the medial cuneiform will allow lateral
dislocation of the second to fifth metatarsals, with or without
bulging of the medial aspect of the foot with displacement of the
cuneiforms. The navicular is often fractured. These changes may
lead to the classic “rocker-bottom” deformity (Figure 2).

Secondary Ulceration
As the acute Charcot foot often leads to a change in shape of the
foot, this will subject different areas of the skin to increased forces
from, for example, shoes. It can also result from the off-loading
used to manage the inflammation. Because of the sensory neu-
ropathy that is nearly always present, the patient does not take
precautions (by resting the limb, for example), and the increased
forces can lead to ulceration. Secondary ulceration occurs in up to
30% of cases, and when it occurs, it can be complicated by in-
fection. Typically, this affects the soft tissue but can involve bone.

Involvement of the Other Foot
The other foot will be involved in 25% to 30% cases. Such con-
tralateral disease may have preceded the presenting case, or it
may follow it after a period of time. Most often, however, the
other foot becomes involved soon after the presenting case—possibly
as a result of increased loading while resting the affected foot.

Resolution
The disease will eventually go into remission. This usually occurs
when there is less than a 2°C temperature difference between the
2 sides. Although this has been shown to be of value, it is not
a particularly robust indicator, and inflammation often recurs
(albeit sometimes only transiently) with renewed weight bear-
ing. The time to remission typically takes several months, but
there is little consensus to be derived from published observa-
tional studies. Single-center reports from the United States and
from Denmark suggest that it takes less than 6 months, but
the median time reported from centers in the United Kingdom is
10 months.12

Late Recurrence
Early recurrence is observed when the inflammation in the foot
is judged to have entered remission when it has not. Late remis-
sion is surprisingly uncommon, but has been reported to recur
on occasion over a number of years.14

DIAGNOSIS
Diagnosis depends largely on clinical suspicion and on pattern
recognition by an expert in the management of disease of the
foot in diabetes. There is no single specific diagnostic criterion.

Prompt Exclusion of Suspicion
Once the possibility is suspected, every effort should be made to
restrict weight bearing until it has been excluded. A plain X-ray
(with views taken anteroposterior, oblique, and lateral weight
bearing) should be undertaken, and the results reviewed promp-
tly with a skilled radiologist. Even if the X-ray is normal,
进一步 investigative imaging should be pursued, and magnetic
resonance imaging (MRI) has been shown to have the greatest
sensitivity. An MRI will reveal the presence of marrow edema,
which should be sufficient evidence to initiate treatment in the presence of suggestive clinical signs, even if it is not entirely specific. Triple-phase bone scanning is as sensitive as an MRI, but is less specific. In fact, computed tomography scanning may be better at revealing microfractures that were not apparent on a plain X-ray. The role of newer imaging techniques is not fully established.

If appropriate imaging is not immediately available, formal off-loading should be initiated. The swelling and any other discomfort settle quickly in the acute Charcot foot with effective off-loading, and such prompt resolution will help support the clinical diagnosis and justify the wait until further imaging is available.

**Circulating Laboratory Markers**

The main difficulty in Charcot foot diagnosis is typically its differentiation from osteomyelitis. And although leukocytosis and elevation of both sedimentation rate and C-reactive protein are more likely in osteomyelitis of the foot, they are not invariable. Elevation of all 3 levels may also be encountered in the person with acute Charcot foot.

**Epidemiology**

There are no robust data on either the prevalence or cumulative incidence of osteoarthropathy in diabetes, partly because systematic surveys have not been undertaken on a population-wide basis and partly because the disease can be difficult to define. Despite this, it is estimated that recognized disease occurs in perhaps 3 of 1000 people with diabetes (in industrialized countries). That accounts for approximately 1% of all people with neuropathy. A specialist clinic in the United Kingdom (where the prevalence of known diabetes is approximately 4%) serving a total (with and without diabetes) population of 1 million may see between 10 and 20 newly recognized cases each year, but it is likely that others are missed or misdiagnosed as osteomyelitis.

**Management**

**Nonsurgical Treatment**

Prompt off-loading is central to the early management of the acute Charcot foot. Off-loading involves resting the foot as much as possible and limiting the forces that are subjected to normally load-bearing bones and joints. There are 2 reasons for this: to break the vicious cycle of inflammation by limiting the triggers to further increased expression of RANKL and NF-κB and to protect the foot while the bones and joints are vulnerable in order to limit fracture, dislocation, and resultant deformity.

The large multicenter observational series published from the United Kingdom and Ireland demonstrated that those who were provided with nonremovable off-loading (a fiberglass cast that requires changing every 1–2 weeks on average) required treatment for a median 2 months less than those provided with removable off-loading (eg, with padded walkers, ad hoc padding of footwear, and fiberglass casts that are split and held in place by tape). The reason for the relatively poor performance of removable devices is partly because the support provided is not as good and also because a device that is removable will inevitably get removed when it is socially desirable.

**Medical Therapy**

A small pilot randomized controlled trial suggested that the intravenous administration of the bisphosphonate pamidronate might be therapeutically useful. Other preparations were used in other studies, but these were not placebo controlled. The most recent double-blind, placebo-controlled randomized controlled trial suggested that the use of a bisphosphonate may not only be ineffective, but also actually prolong the time to resolution. A recent systematic review of bisphosphonate therapy concluded that there is currently no evidence base for the use of bisphosphonates in acute Charcot disease.

The parenteral administration of calcitonin has been extensively used in Eastern Europe but unfortunately without firm evidence of effectiveness. The use of calcitonin has a better theoretical justification than the use of bisphosphonates (because calcitonin reduces the expression of RANKL), but it has been withdrawn from the market by the manufacturer.

There has been no formal assessment of the role of anti-inflammatory agents, including antagonists of tumor necrosis factor α and RANKL, which have been used in other inflammatory arthropathies.

**Surgical Treatment**

**In the acute phase.** The place of surgical intervention designed to secure the retention of a functional plantigrade foot in the acute phase is not established.

**In the chronic, stable phase.** When the Charcot process has gone into remission, surgical intervention (eg, by exostectomy, arthrodeses) is frequently used to improve the function of the foot and to reduce the likelihood of late ulceration of the skin over pressure points.

**Major amputation.** Major amputation (usually below knee because this population does not tend to have severe proximal macrovascular disease) is sometimes necessary because (1) it is judged that it will never be possible to preserve a functional foot, and amputation offers the best option for rehabilitation; (2) it is otherwise judged to be in the patient’s best interest; and (3) it is the patient’s preference.

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Involvement of the Patient in Ongoing Management Decisions

It is essential to involve the patient and his/her family or caregiver in decisions concerning management. The patient needs to understand the problems inherent to making the diagnosis, the lack of effective treatment, and the difficulty that can exist in deciding when the condition has gone into remission. This is primarily because the implications are considerable—at the very least, most patients are forced to adopt a sedentary and socially limited existence for a period of many months. This is more difficult to accept if the patient is aware of the imprecision of the clinical signs being used to make decisions. Thus, it is helpful if the patient is fully involved in decision making from the start.

Reactive depression is very common and may be overlooked by healthcare professionals. The possibility of a patient’s depression should always be considered, and steps taken for its early detection and appropriate management.

Rather than endure months of incapacity, some patients will opt for early major amputation, even though their physician may prefer conservative management.

PREVENTION

Currently, it is not possible to identify the 1 person out of 100 with signs of neuropathy who will suffer this limb-threatening disease. Clinicians must strive to ensure that the diagnosis of any newly occurring disease is made as quickly as possible. It has been shown that a delay in diagnosis of 3 months or more has an adverse effect on both quality of life and long-term functional outcome. Early diagnosis is not usual, however, because nonspecialists may not expect to encounter Charcot foot in their practice. It is more likely that the inflammation will be thought to be caused by a more common disorder. The best solution is to educate the patient.

Whenever a person with diabetes has distal neuropathy diagnosed or confirmed on physical evaluation, he/she should be counseled concerning the risks of loss of protective sensation.

Verbal counseling should be supported by the provision of an educational pamphlet or brochure. That resource should mention the acute Charcot foot, as well as recommend that the patient should suggest the potential diagnosis to the healthcare professional if he/she ever develops unexplained inflammation (or deformity) of the foot. Such patient education may reduce the time to diagnosis.

SUMMARY

Distal symmetrical neuropathy is independently associated with reduced survival in diabetes. Moreover, it is known that the mean 5-year survival of any person presenting with disease of the foot is approximately 50%. It has also been shown in a large single-center cohort that the likely survival of patients presenting with an acute Charcot foot is reduced by 14 years when compared with normative age-related data. As the most likely cause of early death is cardiovascular, it is essential that measures are taken to reduce cardiovascular risk in all people who have suffered an acute Charcot foot (as well as in all persons with diabetes who have had any other form of foot disease).

This article has described the epidemiology and pathogenesis of the acute Charcot foot, and how to recognize the clinical signs to help diagnose the acute Charcot foot and the relationship between Charcot foot and diabetes.

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