Ten years of Charcot: What have we learned?

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Over the last decade, advances have been made in the understanding and management of Charcot osteoarthopathy with new observations on pathogenesis, presentation, diagnosis and treatment.

Pathogenesis

The receptor activator of nuclear factor κB ligand (RANKL) has been identified as an essential cytokine for the formation and activation of osteoclasts and may play a role in the pathogenesis of Charcot osteoarthropathy (Jeffcoate, 2004). RANKL activates the receptor RANK which is expressed on osteoclasts, thus promoting osteoclastogenesis. RANKL is expressed on bone-forming osteoblasts and thus bone resorption and bone formation are coupled through RANKL. The effects of RANKL are physiologically counterbalanced by the glycoprotein osteoprotegerin (OPG), which acts as a decoy receptor for RANKL. The balance between RANKL and OPG determines osteoclast functions. Alterations of the RANKL:OPG ratio are critical in the pathogenesis of bone diseases that result from increased bone resorption and thus may be important in the pathogenesis of Charcot osteoarthropathy.

Furthermore, in Charcot osteoarthropathy there is an excessive inflammatory response to minor trauma in which pro-inflammatory cytokines may play a role (Jeffcoate et al, 2005). A recent immunohistochemical analysis of surgical specimens from patients with Charcot osteoarthropathy has shown excessive osteoclastic activity in the environment of cytokine mediators of bone resorption (IL-1, IL-6 and TNFα; Baumhauer, 2006). Although the local inflammatory response may be excessive, systemic features are often limited. A recent study has shown that C-reactive protein was within the normal range in almost 50% of individuals presenting with acute Charcot osteoarthropathy and only moderately elevated in the remainder (Petrova et al, 2007).

Predisposition

Previous studies have suggested that reduced bone mineral density (BMD) in people with diabetes predisposes them to fracture, which in turn can lead to Charcot osteoarthropathy (Young et al, 1995). Recently, reduced stiffness has been demonstrated in the calcaneum in the Charcot and non-Charcot foot compared with controls (Jirkovská et al, 2001). However, at the onset of Charcot osteoarthropathy, there is pre-existing osteopenia in type 1 diabetes but not in type 2 diabetes (Petrova et al, 2005). One study has shown that people with diabetes and Charcot osteoarthropathy who presented with fractures had a lower BMD compared with people who presented with a dislocation pattern of osteoarthropathy (Herbst et al, 2004).

Diagnosis

It is extremely important to have a high index of suspicion for Charcot osteoarthropathy and to encourage early presentation among at-risk individuals. This should be followed by a rapid diagnosis and early intervention. Early observations of the natural history of Charcot osteoarthropathy indicate 'hot spots' on the diphosphonate bone scan and bone marrow oedema on MRI are often associated with microfracture (Edmonds et al, 2005; Chantelau and Poll, 2006).

Management

Standard treatment has become immobilisation in a total contact plaster cast. The individual

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should use crutches and be encouraged to avoid weight-bearing on the affected side. However, in many cases it is difficult to be completely non-weight bearing because the person can have multiple comorbidities such as loss of proprioception, postural hypotension, a high BMI and, in some cases, neuropathy of the upper limbs, all of which can make it difficult for them to use crutches. Furthermore, a wheelchair existence is often impractical in many home environments and total immobility has disadvantages in itself with loss of muscle tone, reduction in BMD and loss of body fitness. One alternative treatment is a prefabricated walking cast.

The recent CDUK study *A UK-wide, web-based survey of the management of the acute Charcot foot of diabetes* has indicated that the outlook may be superior in the total contact cast compared with the removable prefabricated cast (Game et al, 2007).

Pharmacological therapy

Over the last decade, pharmacological treatment with bisphosphonates has been introduced. A randomised controlled study of a single 90 mg pamidronate infusion has shown significant reductions in the markers of bone turnover in treated compared with controls (Jude et al, 2001). There was a similar finding in a recent study with alendronate (Pitocco et al, 2005). Calcitonin has also been used in the acute stage of the condition, demonstrating a more rapid transition to the stable chronic phase in the treated group compared with controls (Bem et al, 2006). The CDUK study has suggested that there is a significantly longer time to resolution in people treated with bisphosphonates compared with those had none (Game et al, 2007).

Surgical treatment

Although non-operative treatment with use of a total contact cast is considered to be the gold standard treatment for Charcot osteoarthropathy, surgery is eventually indicated for unstable or displaced fracture dislocations, although it should not be performed in the acute phase. Surgical intervention includes open reductions and internal fixation, sometimes combined with external fixation. Surgery can also address the biomechanical problems of Charcot osteoarthropathy and current surgical reconstruction techniques include open reduction with internal or external fixation and intramedullary rodding and arthrodesis of the damaged joints. In a series of 28 individuals with Charcot foot dislocation, external fixation with bone stimulation has been used with no further breakdown after surgery (Wang et al, 2002). Early experience using specific Taylor's spatial external fixation system has also been reported (Roukis and Zgonis, 2006). Surgery can also include exostotomy in cases complicated by chronic recurrent ulceration associated with bony prominence in the Charcot deformed foot.

The future

An understanding of the pathophysiology of Charcot osteoarthropathy and the mechanisms of osteoclastic activity is of critical importance. Specific pharmacological treatments might then be considered including TNFα antagonists and anti-RANKL antibodies as well as bone anabolic agents such as strontium or parathyroid hormone. ■

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