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Charcot Pathophysiology

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Abstract: Charcot osteoathropathy is a rare complication of neuropathy with devastating complications. Charcot bone damage leads to altered bony architecture of the foot and bony prominences. Inadequate offloading can lead to ulceration and eventual infection, which ultimately may lead to amputation. The pathophysiological mechanism for the Charcot disease process is poorly understood. Previous neurovascular or neurotraumatic theories did not fully explain the classic clinic features of Charcot on a molecular level. A new theory of the underlying disease progression relates to the increased activation of osteoclasts.

Key words: Charcot, Osteoarthropathy, RANKL, OPG, Neuropathy

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Charcot osteoarthropathy is an often undiagnosed complication of long standing neuropathy. This condition causes progressive bone and joint destruction. Charcot is characterized by joint subluxation and pathologic fractures that may eventually lead to ulceration and amputation. Yu et al. state that the early diagnosis of Charcot osteoarthropathy is based solely on very unremarkable clinical presentation of symptoms. Patients may have no overt history of trauma to the affected area. Pain may or may not be present with asymmetrical edema. Pulses may be bounding or barely palpable while the capillary fill time may be normal[1]. Jeffcoate et al. assert that the past French neurovascular and German neurotraumatic theories do not fully explain the pathology of Charcot.

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Neuropathy is symmetrical, while Charcot usually affects unilateral joints. Neuropathy is irreversible, but Charcot self-limiting. Neuropathy is common, though Charcot is quite rare. It is possible that neuropathy only worsens Charcot, but is not the direct cause of the disorder[2].

Pathogenesis

In the neuropathic patient, minor trauma or even a minor infection may cause an exaggerated inflammatory response[3]. This early unremitting inflammatory stage features an increased level of cytokine production; most pertinent to our discussion is the resulting elevation of Tumor Necrosis Factor-alpha, interleukin-1, and interleukin-6. An increased level in TNF-α and IL 1β will trigger an overproduction of Receptor Activator of Nuclear Factor Kappa B ligand (RANKL). RANK ligand is a surface molecule that is expressed by osteoblastic stromal cells and activated T-lymphocytes. Receptor Activator of Nuclear Factor Kappa B ligand has been

identified as an essential cytokine for the formation and activation of osteoclasts and may play a role in the pathogenesis of Charcot[2]. Ligand binding to osteoblasts activates Nuclear Transcription Factor Kappa-B, which initiates osteoclast activation and bone resorption[3]. Osteoprotegerin (OPG) is an important regulator of bone remodeling as it acts as a decoy receptor for RANKL to balance osteoclastic activity[4]. In cases of exaggerated inflammatory response as in Charcot, the overproduction of RANK ligand saturates the system, exceeding the protective capacity of OPG and thus leading to unopposed osteoclastogenesis[3]. Compounding this imbalance is the single nucleotide polymorphism altering the promoter region of OPG that has been discovered in patients with Charcot[4]. This abnormality modifies the normal binding of transcription factors and OPG gene expression may create an imbalance of the RANKL/OPG system, again leading to unopposed osteoclastogenesis.

The calcification of vascular smooth muscle, aka Monckeburg's sclerosis, is commonly found in conjunction with Charcot osteoarthropathy and is thought to be controlled by the RANKL/OPG system[5]. Ndip et al. determined that RANKL stimulates vascular smooth muscle cell mineralization[5]. Low level inflammatory responses stimulate an increase in receptor Activator of Nuclear Factor Kappa B Ligand that induces osteoblastic-like cell formation. This cascade of events leads to matrix deposition and mineralization then ultimately vascular calcification[6].

The proposed mechanism for overexpression of RANKL and altered expression of OPG leading to unopposed osteoclastogenesis will correlate with the Eichenholtz stages of Charcot progression[7]. An increase in pro-inflammatory cytokines is made evident in the prodromal stage and visualized radiographically by joint effusion and an increase in soft tissue density[8]. An overexpression of RANKL enhances osteoclast activity triggering the bone fragmentation and resorption that defines the

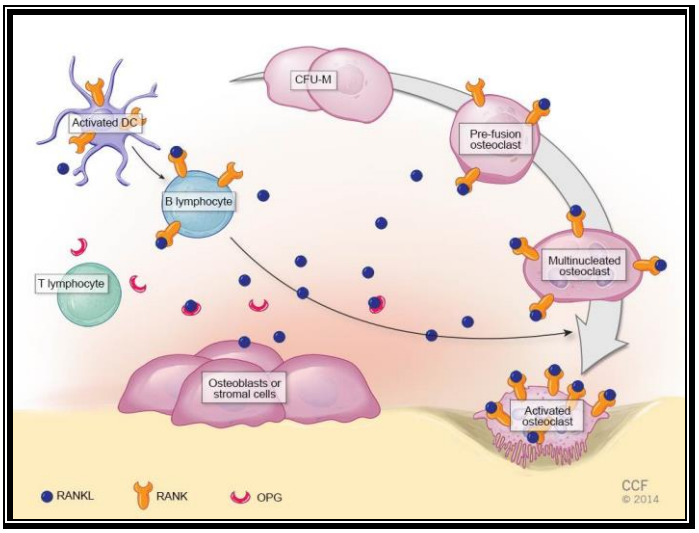

Figure 1: The activation of osteoclasts by Receptor Activator of Nuclear Factor Kappa B ligand binding

development stage. The rebound osteoprotegerin counterbalance initiates osteosclerosis, healing of fractures, and resorption of small bone fragments that are common findings of the coalescence stage. As the patient enters the reconstruction stage, an overall homeostatic return of the RANKL/OPG balance produces bony consolidation and joint fusion.

The connection between the osseous destruction of Charcot and neuropathy has not been established. La Fontaine et al. used immunohistological studies of bone samples to show that patients with Charcot had the least amount of Calcitonin Gene Related Peptide (CGRP). Also studied was the level of endothelial nitric oxide synthase (eNOS), which controls nitric oxide production. Nitric oxide has been shown to suppress osteoclast activation. Immunohistochemical studies showed eNOS was significantly reduced in the Charcot bone samples[9]. Mrak et al. state that CGRP can be released by nerve fibers and may play a role in bone remodeling and fracture healing. CGRP prevents apoptosis of osteoblasts and reduces osteoclast resorption[10]. CGRP may help to regulate the Wnt/β-catenin signaling pathway, which is critical for bone development, fracture healing, and the maintenance of bone density[11].

Imaging

Rogers et al. state that magnetic resonance imaging

remains the gold standard for diagnosing early Charcot osteoarthropathy. MR imaging displays bone marrow edema, ligamentous disruptions, and associated joint deformities. However, MRI still does not easily distinguish between early Charcot and osteomyelitis, due the poor specificity[12]. Pickwell et al. assert that positron emission tomography using radiolabeled fluorine 18 fluorodeoxyglucose combined with computed tomography offers the most sensitive diagnosis for Charcot. Significantly higher uptake in osteomyelitis has been shown, as compared to low to intermediate metabolism of the radiolabeled sugar in Charcot[13].

Currently, no early diagnostic test exists to identify Charcot osteoarthropathy in the prodromal period. Early treatment of immobilization is limited by a purely clinical diagnosis. Symptomatic Charcot is commonly overlooked until osseous destruction is apparent[3]. Genetic expression testing utilizing real-time quantitative polymerase chain reaction holds the potential to detect RANKL/OPG variations in Charcot patients and high risk asymptomatic individuals. No studies to date have sought to investigate the use of RANKL or OPG as potential biomarkers for patients at an increased risk of developing Charcot osteoarthropathy.

Conclusion

The relationship between neuropathy and Charcot is not fully understood. The initial presentation of Charcot lacks any significant radiological findings and is often overlooked in the clinical examination[8]. Due to its vague symptomatology, patients often go undiagnosed for months to years as they are treated for suspected cellulitis, gout, or injury. Early diagnosis and treatment with immobilization has the potential to prevent bone dissolution and joint subluxation, preserving normal foot function and boney alignment[1,14]. A better understanding of the underlying mechanism of osseous destruction and neuropathy will provide a potential pharmaceutical target for possible treatment. The availability of laboratory markers for identification of patients at increased risk of Charcot would allow for an objective assessment of this difficult to diagnose disease and raise clinical awareness leading to a more proactive course of therapy and possible prevention of the associated neuropathic ulceration and amputation that is the common sequela of Charcot osteoarthropathy.

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Figure 1 provided by Cleveland Clinic medical art department. Permission required for use or duplication.

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