REVIEW ARTICLE

Charcot Theories and Pathophysiology: A Narrative Review

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Received on: 07 April 2023; *Accepted on:* 02 May 2023; *Published on:* 07 August 2023

Abstract

Charcot neuropathic osteoarthropathy (CNO) is defined as relatively painless, progressive, noninfectious, and degenerative arthropathy involving soft tissues and one or more joints with an underlying neurological deficit. Major theories of pathophysiology include neurovascular theory (French theory), neurotraumatic theory (German theory), and neuro-osseous-inflammatory theory. As per the neurovascular theory, loss of sensation due to neuropathy acted as a barrier for feeling pain and discomfort in patients, which predisposed them to repeated trauma and microfractures. Charcot patients have been found to have increased blood flow, which increases venous pressure enhancing fluid filtration due to capillary leakage, which in turn leads to increased compartmental pressure and ischemia compromising the tendons and ligaments. The neurotraumatic theory states that insensate feet are predisposed to repetitive unrecognized trauma and abnormal loading of the joint. The forefoot act as a lever due to increased plantar pressure forcing the collapse of the midfoot. In neuro-osseous-inflammatory theory, emphasis is given to disturbances in the balance between pro and anti-inflammatory cytokines. Increased proinflammatory markers activate cytokine pathways centered on receptor activator of nuclear factor kB (NF-kB) ligand (RANKL). The ratio of RANKL/osteoprotegerin (OPG) is elevated. RANKL induces differentiation of osteoclast precursor to osteoclast and leads to osteolysis. Factors with significant CNO association include hyperglycemia, neuropathy, low bone mineral density (BMD), inflammation, and neuropathy.

Keywords: Charcot joint, Charcot neuroarthropathy, Neuropathy, Receptor activator of nuclear factor-kB ligand.

Journal of Foot and Ankle Surgery (Asia-Pacific) (2023): 10.5005/jp-journals-10040-1305

Introduction

Charcot neuropathic osteoarthropathy (CNO), commonly referred to as Charcot's foot, was first described by Sir William Musgrave in 1703, followed by a detailed description by Jean-Martin Charcot as "pied tabatique" in 1883. CNO can be defined as relatively painless, progressive, noninfectious, and degenerative arthropathy involving soft tissues and one or more joints with an underlying neurological deficit.[1] The CNO develops in both diabetes mellitus type 1 (DM-1) and diabetes mellitus type 2 (DM-2), but the risk of development is 3.9 times higher in DM-1.[2]

This article will focus on the risk factors which have been attributed to the development of CNO and proposed theories to improve the knowledge for a better understanding of pathophysiology.

Theories of Pathophysiology of Charcot

Neurovascular Theory

It is also known as the French theory. It was first proposed by French neurologist Jean-Martin Charcot. He hypothesized that loss of sensation due to neuropathy acted as a barrier to feeling pain and discomfort in patients, which predisposed them to repeated trauma and microfractures.[3] Charcot observed that patients with pied tabatique often had nerve damage or arterial disease that led to reduced blood flow and inadequate healing of fractures culminating in joint destruction over a period of time.

Charcot patients have been found to have increased blood flow as compared to diabetic patients without Charcot.[4] The increased blood flow increases venous pressure enhancing fluid filtration due to capillary leakage.[5] The enhanced pressure also leads to increased compartmental pressure and ischemia, compromising the tendons and ligaments and further leading to joint instability.[6] Capillary leakage leads to increased delivery of monocyte and osteoclasts locally, leading to greater osteoclastic activity.[7] Osteopenia predisposes the foot to have fracture, dislocation, and collapse of joint with trivial trauma (Fig. 1).[8]

Neurotraumatic Theory

It is also known as the German theory. Volkman and Virchow proposed that insensate feet are predisposed to repetitive unrecognized trauma and abnormal loading of joints. Multiple episodes of repetitive trauma and abnormal joint loading lead to joint deterioration (Fig. 2).[3,9] The theory is supported by the work done by Armstrong and Lavery,[10,11] where they found that forefoot pressure is significantly higher in patients with CNO as compared to diabetic patients without CNO. They also hypothesized that the forefoot act as a lever due to increased plantar pressure forcing the collapse of the midfoot.

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How to cite this article: Kumar G, Jose DP, Agrawal U, *et al.* Charcot Theories and Pathophysiology: A Narrative Review. J Foot Ankle Surg (Asia-Pacific) 2023;10(S-1):S3–S5.

Source of support: Nil

Conflict of interest: Dr Inderjit Singh is associated as the Editorial Board member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and his research group.

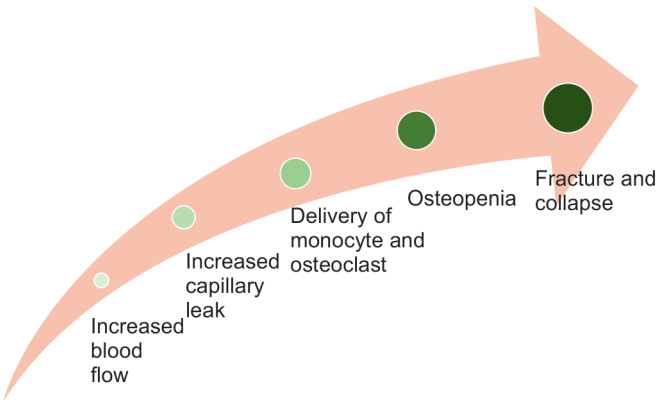

Fig. 1: Neurovascular theory

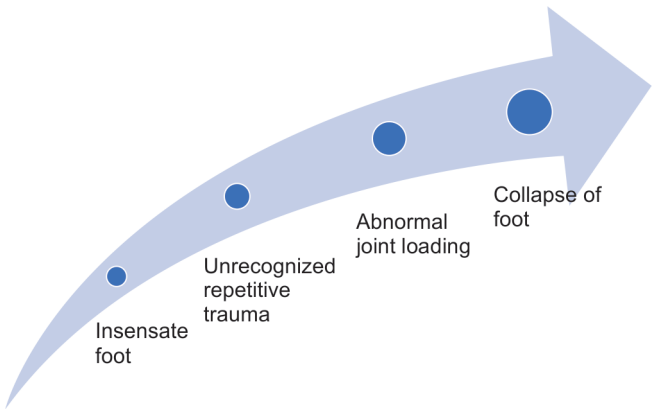

Fig. 2: Neurotraumatic theory

Neuro-osseous-inflammatory Theory

Charcot neuropathic osteoarthropathy (CNO) as a late sequela of osteoporosis was proposed by Childs et al., where an association between osteoporosis and DM was shown. Bone marker studies have shown that there is an increase in osteoclastic activity in acute as well as chronic CNO.[12] There is a disturbance in the balance between pro and anti-inflammatory cytokines with the preponderance of proinflammatory cytokines[13] including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)[14] and a decrease in the level of IL-4 and IL-10 known as anti-inflammatory cytokines. Increased proinflammatory markers activate another cytokine pathway centered on RANKL. Activation of RANKL induces differentiation of osteoclast precursor to osteoclast and leads to osteolysis.[15] In our body, RANKL is antagonized by a soluble glycoprotein called OPG which neutralizes its effects (Fig. 3). In Charcot patients, the ratio of RANKL/OPG has been found to be elevated.[16]

Associated Factors

Hyperglycemia

Studies looking at the role of hyperglycemia have conflicting results.

Previous studies favored hyperglycemia as the cause of CNO. One study hypothesized that age-related modification of collagen might impair the mechanical properties of bone and cause a higher chance of fracture and dislocations.[17] Another proposed hypothesis stated that increased sugar levels potentiate free radical formation triggering the RANKL cytokine storm.[18]

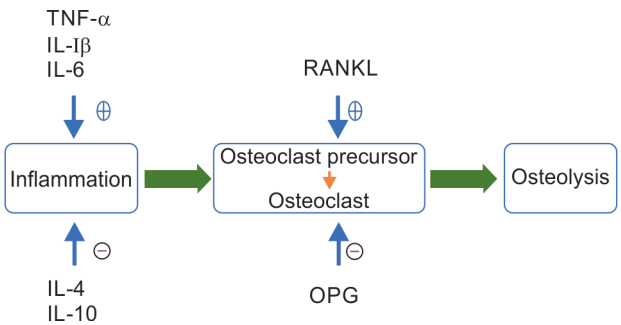

Fig. 3: Neuro-osseous-inflammatory theory

Recent studies have focussed on glycemia control as one of the factors leading to the development of CNO. A recent EPICHAR study,[19] published in 2022, planned to look for the relationship between glycemic control and correction on the development of CNO in patients with DM. In the study, they looked at the levels of glycated hemoglobin at 3 and 6 months before the development of CNO as a surrogate of glycemic control. They proposed that rapid and significant correction may activate CNO.

Neuropathy

The CNO has been associated with atypical neuropathy, which has been found neuropathy of CNO is limited to hot and cold perception compared to lambda sensory neuropathy in diabetes.[20] A study by Stevens et al.[21] on neuropathy and vascular responses has found loss of cold sensation but the preservation of light touch perception.

Bone Mineral Density (BMD)

A case-control study by Sinacore et al.[22] compared 32 patients with DM, peripheral neuropathy (PN), and CNO with age and sex-matched with those with DM, PN, and CNO and found that calcaneal BMD was 545 mg/cm^2 in control subjects, while it was 467 mg/cm^2 in feet not involved of those with DM and PN, which further reduced to 384 in limb having CNO with DM and PN. Another study by El Oraby et al.[23] showed that BMD was significantly lower in patients with DM-2 and CNO groups as compared to those with DM-2 without CNO.

Inflammation

The study by Sinacore et al. showed that there was a significant difference in skin temperature with an average difference of 6.7°F between the involved and noninvolved feet in patients having DM, PN, and CNO. A study by Jansen et al.[24] found that CNO feet were, on average, 2.6°C warmer than contralateral feet in patients with acute CNO, and there is a significant increase in levels of proinflammatory cytokine IL-6. Another study by Sinacore et al.[25] to look at the difference in inflammatory markers and temperature over 1 year found that there was a significant difference in temperature 2°F between the contralateral and feet with CNO and raised the level of C-reactive protein (CRP) and erythrocyte sediment rate (ESR) even at the end of 1 year.

Novel Association with Charcot Foot Worth Looking at in Future Studies

A study done by Munson et al.[26] focused on data mining techniques over the patient data of 1.6 million patients and segregated based on the system involved. The following diseases were found to be associated with CNO, but their temporal association is yet to

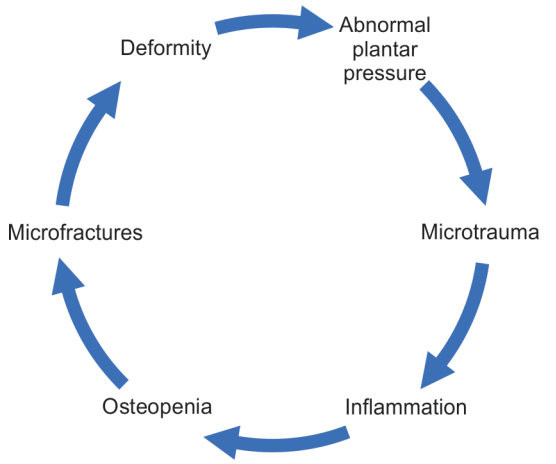

Fig. 4: Sequence of events in Charcot pathophysiology

be established. The major diseases found to be associated were obesity, PN, anemia, cellulitis, abscess of leg/foot, chronic kidney disease, and renal transplant and its complications.

Conclusion

The pathophysiology of CNO is a dynamic topic enriched by the latest research, which answers some previous question but at the same time question the previous hypothesis related to the development of CNO. Neurovascular and neurotraumatic converge into neuro-osseous-inflammatory theory, which is the way forward for further research (Fig. 4).

New studies have tried to address the lacunae of why only a few DM patients, 0.1–0.4%, end up having CNO. The rate of glycemic control and BMD measurement at regular intervals are some of the parameters that may guide us for better prediction of the development of CNO so that we may help in proactively at the early detection of CNO.

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