Oral session 8: Charcot neuro-osteoarthropathy

O8.1

Bring Me Sunshine!!........Vitamin D and Charcot Neuropathic Osteoarthropathy

Rosalyn Thomas, Diabetes Centre, Morriston Hospital Swansea, Swansea, United Kingdom
David Price, Diabetes Centre, Morriston Hospital Swansea, Wales, United Kingdom
Jeffrey Stephens, Diabetes Centre, Morriston Hospital Swansea, Wales, United Kingdom
Ujjal Choudhuri, Diabetes Centre, Morriston Hospital Swansea, Wales, United Kingdom
Claire Topliss, Diabetes Centre, Morriston Hospital Swansea, Wales, United Kingdom

Aims: Charcot neuropathic osteoarthropathy is a consequence of various peripheral neuropathies, diabetic neuropathy the most common etiology. The pathology is multifactorial, mediated through a process of inflammation within the foot leading to osteolysis. This circumstantial hypothesis may be indirectly responsible for the dislocations/fractures on presentation (Jeffcoate et al. 2005). Misdiagnosis results in extensive damage, deformity ulceration and infection of the diabetic foot (Armstrong et al. 1997).

We retrospectively examined Vitamin D levels in subjects diagnosed with Charcot from our pathology system.

Methods: 36 subjects with Charcot were identified from our database. Vitamin D levels at presentation reviewed from the pathology system on 32. Subjects, 42% male; 25 % Type 1 diabetes. Mean age 56 years (range 35 -81)

Results: Of 32 subjects tested, 31 had low levels ranging from undetected-31nmol/ml (mean 9.5nmol/ml). One had a serum 250HD>50nmol/L (59nmol/L) indicating sufficient level of Vitamin D, three ranged between 30-50nmol/L and 28 were<30nmol/L demonstrating deficiency. Those subjects tested and identified as having levels of Vitamin D below the recommended All Wales Guidance of 50nmol/ml, received supplements of Vitamin D (Francis et al. 2013) with a total contact cast (Frykberg R 2010).

Conclusion: Preliminary results suggest there may be an association between Vitamin D deficiency and Charcot. Further research is indicated into whether Vitamin D deficiency has a causative role in the development of the condition.

References
Ref Type: Generic
Role of interleukin-17 family members in the pathogenesis of Charcot arthropathy

Agnetha Folestad, Capio Lundby Hospital, Göteborg, Sweden
Jean Cassuto, Sahlgrenska University Hospital, Mölndal, Sweden
Martin Ålund, Sahlgrenska University Hospital, Mölndal, Sweden
Susanne Asteberg, Sahlgrenska University Hospital, Mölndal, Sweden
Jesper Fowelin, Frölunda Specialist sjukhus, Västra Frölunda, Sweden
Jan Göthlin, Sahlgrenska University Hospital, Mölndal, Sweden
Ylva Aurell, Sahlgrenska University Hospital, Mölndal, Sweden

Aim: Charcot arthropathy is a serious complication to neuropathy affecting primarily diabetes patients. The condition is characterized by subluxations and bone erosions ultimately leading to foot deformities or collapse if not diagnosed in time. Trauma or infection causing unregulated activation of proinflammatory cytokines leading to increased osteoclastogenic activity has been proposed as a major initiating factor. Members of the IL-17 family of proinflammatory cytokines have been shown to play a key role in the pathogenesis of several inflammatory conditions affecting bone and joints although there are no studies on their role in the pathogenesis of Charcot. Our aim was to investigate the role of IL-17A, IL-17E and IL-17F in Charcot patients from the acute to the chronic state.

Methods: Twenty-four Charcot patients were monitored during 2 years from diagnosis by by repeated foot radiographs, MRI and circulating levels of interleukin (IL)-17A, IL-17F and IL-17E. Diabetic controls (n=20) and healthy subjects (n=20) served as reference.

Results: IL-17A and IL-17E in Charcot patients at diagnosis did not differ significantly versus diabetes control patients or healthy, whereas IL-17F was significantly lower in Charcot relative diabetes controls and healthy. Off-loading treatment triggered a fast and significant increase in IL-17A and IL-17E lasting up to 18 months before retreating towards levels at inclusion at 2 years. The response of IL-17F to off-loading was significant but gradual reaching a, level not significantly different from control patients at 2 years postinclusion.

Conclusions: we show for the first time that members of the IL-17 family of proinflammatory cytokines play an active role in the pathophysiology of Charcot arthropathy by inhibition of IL-17F-induced osteoblastogenic bone repair during full weight-bearing and by stimulating bone repair through the actions of IL-17A and IL-17E in response to off-loading treatment.
Charcot and PAD: just coincidence?

Patrick Lauwers, Antwerp University Hospital, Edegem, Belgium
Saskia Van Bouwel, Antwerp University Hospital, Edegem, Belgium
Eveline Dirinck, Antwerp University Hospital, Edegem, Belgium
Katrien Clotman, Antwerp University Hospital, Edegem, Belgium
Jeroen Hendriks, Antwerp University Hospital, Edegem, Belgium
Johan Somville, Antwerp University Hospital, Edegem, Belgium
Paul Van Schil, Antwerp University Hospital, Edegem, Belgium
Luc Van Gaal, Antwerp University Hospital, Edegem, Belgium

Introduction: Charcot foot is a known complication of diabetic patients with severe neuropathy. It is a serious condition that can lead to fracture, deformity, and ulceration of the foot. Coexistence of Charcot foot and peripheral arterial disease (PAD) has been reported, but their relation is unclear.

Aim of the study: To evaluate the incidence of PAD in a cohort of diabetic patients with Charcot foot.

Materials and Methods: This is a retrospective evaluation of patients presenting with a charcot foot at the diabetic foot clinic of the Antwerp University Hospital in the period 2011 – 2014.

Results: The cohort (n=51) consists of 3 subgroups, namely patients presenting with an acute first episode of charcot (n=11), patients presenting for the first time with a non-acute charcot (n=6), and patients who have been treated for charcot in the past that are in follow up (n=34). Male:female ratio is 36:15. Thirty six patients were insulin-dependent,. Metabolic control was suboptimal (mean HbA1c 7.4 mg/dl). Twenty six patients also had nephropathy (one dialysis, one kidney transplant). Mean age at the diagnosis of charcot was 58 (31 - 81). The localisation of the charcot was: midfoot in 37, forefoot in 6, and hindfoot in 8). Twenty seven patients presented with an ulcer. At diagnosis, only 3 patients had a history of vascular interventions. Doppler ultrasound was done in 78% (40/51). Nine patients had palpable pulses, but with non-compressible arteries (mediacalcinosis); fifteen presented with below the knee disease and two had femoropopliteal disease,. Only 6 patients underwent revascularization (5 PTA, 1 bypass). In the FU period (mean 5.7 years), 4 patients with initial normal evaluation as well as 5 with mediacalcinosis developed PAD; 2 of them were treated. In the total FU period, 6 patients had PTA.

No reactivation of the charcot was seen after revascularization. Of the total cohort, 61% of the patients (31/51) seen with charcot arthropathy had proven PAD.

Conclusion: A high number of patients with charcot arthropathy present with PAD, or develop PAD during FU. This coincidence should be remembered, especially in patients developing ulcers, as revascularization might facilitate wound healing. In this small cohort of patients, revascularization was safe.
Role of the Wnt/β-catenin pathway in bone healing of diabetic Charcot arthropathy patients

Agnetha Folestad, Capio Lundby Hospital, Göteborg, Sweden  
Jean Cassuto, Sahlgrenska University Hospital, Mölndal, Sweden  
Martin Ålund, Sahlgrenska University Hospital, Mölndal, Sweden  
Susanne Asteberg, Sahlgrenska University Hospital, Mölndal, Sweden  
Jesper Fowelin, Frölunda Specialistjukhus, Västra Frölunda, Sweden  
Jan Göthlin, Sahlgrenska University Hospital, Mölndal, Sweden  
Ylva Aurell, Sahlgrenska University Hospital, Mölndal, Sweden

Aim: Charcot neuroarthropathy is a condition primarily affecting diabetic patients and is characterized by degenerative changes of the bone, joints and soft tissues of the foot and ankle leading to deformity, instability and increased risk of amputation. Little is known of the molecular mechanisms involved in the initiation and recovery of Charcot. The Wnt/beta-catenin pathway, a key regulator of mechanical loading and unloading of the skeleton, bone growth, bone remodeling and fracture repair, has significantly added to our understanding of diseases affecting the bone. We are not aware of any study investigating the role of the Wnt system in Charcot arthropathy. The present longitudinal study investigated the role of this pathway by means of biomarkers parallel to radiographic imaging.

Methods: Twenty-four consecutive Charcot patients were monitored during 2 years by repeated foot radiographs, MRI and circulating levels of sclerostin, dickkopf-1 (Dkk-1), Wnt inhibitory factor-1 (Wif-1) and Wnt ligand-1 (Wnt-1). Neuropathic diabetic controls (n=20) and healthy individuals (n=20) served as reference.

Results: Sclerostin, Dkk-1 and Wnt-1, but not Wif-1, were significantly lower in Charcot relative diabetic controls at inclusion. Dkk-1 and Wnt-1 increased several-fold in response to off-loading treatment and remained elevated during a period of 12-18 months before retreating to inclusion levels after 2 years. Sclerostin was at the level of healthy but significantly lower than diabetic controls whereas Wif-1 was at the level of diabetic controls and significantly higher than healthy at diagnosis to remain so until patients had reached a chronic phase with bone mineralization.

Conclusions: We provide evidence in support of Wnt/β-catenin being an important part the pathophysiology of Charcot by balancing the actions of its agonists and antagonists with the aim of preserving, remodeling and restoring the foot skeleton. We could show that Dkk-1 and Wnt-1 are part of bone remodeling in the acute phase whereas sclerostin and Wif-1 are actively involved in bone regulation both in the acute and chronic state of Charcot. This knowledge is of particular clinical relevance considering promising recent drugs targeting this system.
Corneal confocal microscopy demonstrates severe small fibre neuropathy in diabetic patients with Charcot in Qatar

Talal Talal, Hamad Medical Corporation, Doha, Qatar
Robert Menzies, Hamad Medical Corporation, Doha, Qatar
Ioannis Petropoulos, Weill Cornell Medical College Qatar, Doha, Qatar
Georgios Ponirakis, Weill Cornell Medical College in Qatar, Doha, Qatar
Rayaz Malik, Weill Cornell Medical College in Qatar, Doha, Qatar

Introduction: The pathogenesis of the Charcot foot in diabetes remains unclear. All patients diagnosed with the condition have evidence of a significant peripheral neuropathy with loss of sensation and elevated vibration perception. Small fibres play an important role in blood flow and inflammation and therefore may play an important role in Charcot. We have undertaken corneal confocal microscopy (CCM) in an unselected cohort of patients with a Charcot foot attending a diabetic foot clinic in Doha, Qatar.

Methodology: 9 patients with a chronic Charcot foot were compared to 10 age matched controls. All underwent CCM for estimation of corneal nerve fibre density (CNFD), branch density (CNBD) and fibre length (CNFL).

Results: EGFR (58.5±4.2 v 80.6±8.7, P<0.01) was significantly lower and HbA1c (80.4±22.2 v 38.3±2.4 mmol/mol, P<0.0001) was significantly higher in diabetic patients with Charcot compared to control subjects. There was no difference between diabetic patients with Charcot foot and control subjects for triglycerides (2.22±0.9 v 1.8±0.9 mmol/mol, P=NS) or HDLC (1.1±0.4 v 1.7±0.3 mmol/mol, P=NS). Diabetic patients with Charcot had a significantly greater VPT compared to controls (46.6±4.7 v 10.7±8.3, P<0.0001). CCM demonstrated a significant reduction in CNFD (14.7±6.5 v 36.4±5.7 no/mm², P<0.0001), CNBD (25.6±22.1 v 79.3±29.47 no/mm², P<0.0001) and CNFL (11.4±6.1 v 25.4±3.1 mm/mm², P<0.0001).

Conclusions: Diabetic patients with a Charcot foot had evidence of a severe large fibre neuropathy. Furthermore the also had a significant small fibre neuropathy as evidenced by marked corneal nerve fibre loss on corneal confocal microscopy. Although they had moderate renal impairment and poor glycaemic control, there was no difference in the lipid profile.