Diabetic Foot Challenge

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Speaker:

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- Has disclosed that he serves on the Speaker’s Bureau for Pfizer and Lilly

- Will not be discussing the off-label or investigational use of products
Referral

- 50 year old Qatari male with Type 1 DM 32 years.
- HbA1c 6.8%
- BP: 118/64
- ACR: 1.2, eGFR-86
- Lipids normal (Statin)
What Next?
OCT
Corneal Confocal Microscopy
Corneal nerve fibre density (CNFD): 26.0 ± 10.0 no./mm² (control: 36.5 /mm²)
Corneal nerve branch density (CNBD): 83.3 ± 40.3 no./mm² (control: 76.0 /mm²)
Corneal nerve fibre length (CNFL): 21.9 ± 6.6 mm/mm² (control: 25.8 mm/mm²)
# Electrophysiology

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Amplitude (mV)</th>
<th>NCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>5.8</td>
<td>20 (45-70)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>0.5</td>
<td>19 (48-74)</td>
</tr>
<tr>
<td>Radial</td>
<td>0.6</td>
<td>10 (48-70)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>1.6</td>
<td>14 (44+)</td>
</tr>
<tr>
<td>Sural</td>
<td>2.5</td>
<td>13 (46-64)</td>
</tr>
</tbody>
</table>
Gene & cs
NORMAL

But
No Family Hx.
Age 50

NORMAL
Genetics

MLPA* (Multiplex Ligation-dependent Probe Amplification) (deletion or duplication) of PMP22 gene

De Novo Mutation
10%

Son 14 Clumsy

Probes for each of the five PMP22 exons are present in this probemix.

CMT: Incidence 1:2500 (AD)
1) PMP22 duplications (CMT1A) (60%) encodes a 22 KD protein in Schwann Cells
2) PMP22 deletions (HNPP)
3) PMP22 point mutations (both phenotypes.)
ADA 2016: Clinical Pearls

- Most common forms of DN are DSPN and AN.
- DSPN is a length-dependent symmetrical disorder and most commonly predominantly sensory.
- Neuropathy may be present in patients with metabolic syndrome, and/or impaired glucose tolerance.
- Non-diabetic neuropathies may occur in diabetes, may be more prevalent than in non-diabetic populations (e.g., higher incidence of B12 deficiency with long-term metformin treatment; CIDP), and should be actively excluded.
Atypical Neuropathy

- Rapid progression ✗
- Asymmetry ✗
- Motor > Sensory ✓
- Other Complications ✗
- Family History ✓
- Drugs ✗
A swollen foot

- 52 yr old male
- T1D for 25yrs
- Retinopathy: PRP
- HTN 5yrs, eGFR 56
- Long term Urinary Catheter
- Swelling foot 2 months
Presentation

[Image of a foot with lesions]
A&E: Diagnosis?

1. Cellulitis
2. DVT
3. Gout
4. Charcot
5. Osteomyelitis
Investigations

• ESR 80
• CRP 142
• Pro-calcitonin 4.6 ng/mL
Procalcitonin

- Procalcitonin is a 116 amino-acid peptide - precursor of the hormone calcitonin
Procalcitonin in sepsis

- Bacterial toxins (gram+/gram-) and cytokines stimulate production of Procalcitonin in all parenchymal tissues.

- Non endocrine tissues e.g. liver, lung, brain etc. do not have endocrine granules where calcitonin can be stored

- Therefore PCT is immediately released into the bloodstream
PCT: Sepsis diagnosis

- PCT levels accurately differentiate sepsis from noninfectious inflammation*
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

DFU vs Osteomyelitis

DFU vs osteomyelitis

- ESR >67 mm/hr (sensitivity 84%; specificity 75%)
- CRP >14 mg/L (sensitivity 85%; specificity 83%)
- Pro-calcitonin >0.3 ng/mL (sensitivity 81%; specificity 71%)

The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis

- Osteo (n=24) v DFU (n=11).
- ESR, CRP, IL-6, IL-8, TNFα, MCP-1, MIP1α
- Pro-calcitonin (PCT) (P<0.049).

Van Asten et al. Int Wound J 2015;
Imaging?

Probe to Bone

Bone Scan

X-Ray

MRI

CT
Which test?

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Number of patients</th>
<th>Diagnostic test</th>
<th>Gold standard comparison</th>
<th>Pooled results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of 9 cohort trials* (8 prospective, 1 retrospective)</td>
<td>Total N=612</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 trials; N=177</td>
<td>Plain film</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 54% Specificity 68% LR+1.7 LR-=0.68</td>
<td></td>
</tr>
<tr>
<td>4 trials; N=135</td>
<td>MRI</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 90% Specificity 79% LR+4.3 LR-=0.13</td>
<td></td>
</tr>
<tr>
<td>6 trials; N=185</td>
<td>Bone scan</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 81% Specificity 28% LR+1.1 LR-=0.68</td>
<td></td>
</tr>
<tr>
<td>2 trials; N=288</td>
<td>PTB</td>
<td>Histopathology or bone culture</td>
<td>Sensitivity 60% Specificity 91% LR+6.7 LR-=0.44</td>
<td></td>
</tr>
<tr>
<td>Meta-analysis of 21 cohort trials* (8 prospective, 13 retrospective)</td>
<td>Total N=1027</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 trial; N=35</td>
<td>Ulcer &gt;2 cm³</td>
<td>Bone biopsy</td>
<td>LR+=7.2 LR-=0.48</td>
<td></td>
</tr>
<tr>
<td>3 trials; N=75</td>
<td>PTB</td>
<td>Bone biopsy</td>
<td>LR+=6.4 LR-=0.39</td>
<td></td>
</tr>
<tr>
<td>4 trials; N=108</td>
<td>ESR &gt;70 mm/hr</td>
<td>Bone biopsy</td>
<td>LR+=11 LR-=0.34</td>
<td></td>
</tr>
<tr>
<td>16 trials; N=567 (data pooled for 7 trials; N=217)</td>
<td>Plain film</td>
<td>Bone biopsy</td>
<td>LR+=2.3 LR-=0.63</td>
<td></td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MRI, magnetic resonance imaging; PTB, probe to bone test.

* Numbers of trials and patients don’t add up because multiple diagnostic tests were used in some trials.

† 10 trials were graded as a level II or III (included a blind comparison to the gold standard) and the rest were of low quality because they lacked blinding.
Diagnosis?

1. Cellulitis
2. DVT
3. Gout
4. Charcot
5. Osteomyelitis
Case 2

• 45yrs old male.
• Type 1 diabetes 30 yrs.
• eGFR 38.
• Swelling right foot >1 month.

• CRP 2
• ESR 5
• Pro-calcitinon 0.1ng/ml
Is There a Systemic Inflammatory Response in the Acute Charcot Foot?

- 36 consecutive patients who presented to the Diabetic Foot Clinic with a red, hot swollen foot
- Skin foot temperature 3.1°C (2.4 – 4.2) > in the Charcot compared with the contralateral foot

**HOWEVER**

- Median CRP: 5.8 mg/l (5–11) and <5 mg/l in 47.2% of patients
- Median ESR: 21 mm/h (13–36)
- WCC: 7.0 (4 –11).
Offloading treatment is linked to activation of proinflammatory cytokines and start of bone repair and remodeling in Charcot arthropathy patients

Folestad et al. Foot & Ankle Research 2015; 8: 72-84
Imaging
Diagnosis

1. Cellulitis
2. DVT
3. Gout
4. Charcot
5. Osteomyelitis
Charcot: Pathogenesis

Neurovascular
Charcot 1868

Neurotraumatic
Volkman 1870

Pro-inflammatory cytokines (IL-1β, TNF-α)
Activation (RANKL- NFκB)
OSTEOCLASTS (CGRP/VIP)

Wnt/β-catenin pathway, sclerostin and dickkopf-1.
OSTEOBLASTS (SP/CGRP)
Charcot: Imaging

MRI: Sen-76.9%, Spec-75%
T1 increased
T2 decreased

$F^{18}$ FDG PET:
Sen-100%, Spec-93%
Management?

Off-loading

Bisphosphonates

Calcitonin
5 yr malignancy: 4.1 v 2.9%

Surgery
Exostectomy, Arthrodesis

Denosumab
RANK-L inhibitor (Osteoclasts)

Teriparatide
Recombinant PTH (Osteoblasts)
Thank you