Neuropathic Pain in Recessive Dystrophic Epidermolysis Bullosa (RDEB)

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Pain in RDEB

• At least 50% of RDEB patients suffer from intense pain (Fine et al., 2004).
• Chronic pain can be inflammatory, musculoskeletal, or neuropathic
• Treatment for neuropathic pain is different from other chronic pains.
Neuropathic pain

- Pain arising as direct consequence of a lesion or disease affecting the somatosensory system (Treede et al., 2008)
Somatosensory fibres in the skin

**TABLE 10-5** Classes of Somatosensory Nerve Fibers

<table>
<thead>
<tr>
<th>FIBER TYPE</th>
<th>FIBER CHARACTERISTICS</th>
<th>SPEED OF CONDUCTION</th>
<th>ASSOCIATED WITH</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(\beta) (beta)</td>
<td>Large, myelinated</td>
<td>30–70 m/sec</td>
<td>Mechanical stimuli</td>
</tr>
<tr>
<td>A(\delta) (delta)</td>
<td>Small, myelinated</td>
<td>12–30 m/sec</td>
<td>Cold, fast pain, mechanical stimuli</td>
</tr>
<tr>
<td>C</td>
<td>Small, unmyelinated</td>
<td>0.5–2 m/sec</td>
<td>Slow pain, heat, cold, mechanical stimuli</td>
</tr>
</tbody>
</table>
Aim of the study

• To investigate if RDEB patients have neuropathic pain
• and if yes, to find what was causing it (neuropathy)
Results

- We enrolled 29 adult RDEB patients (COL7A1) and 27 age/gender matched controls.
- 92.8% have pain every day.
- Acute pain occurs localised to areas of active skin blistering and resolves following healing.
Pain in RDEB

• However, in addition patients also describe persistent pain coming from areas of skin not actively injured, and especially localised to the feet
Characterization of persistent pain in uninjured skin

- A high prevalence of descriptors suggestive of neuropathic pain
- DN4 questionnaire (screening tool) (Bouhassira et al., 2005).
- Numbness, itching, pins and needles, burning, tingling and electric shocks sensations
If there is neuropathic pain, where is the neuropathy?
• Small (Aδ/C fibres) dysfunction

Hypothesis: fibres in the epidermis will be damaged with repetitive episodes of blistering and healing

Hypothesis: collagen VII is important in nerve fibre structure and the lack of it could cause nerve dysfunction
Small fibre function (Aδ/C): Quantitative Sensory Test

1/3 of patients had paradoxical heat sensations

German Research Network on Neuropathic Pain (DFNS)
Small fibre neuropathy

- Clinical examination showed nerve dysfunction was present in a length dependent distribution
- Only 16% have it in the hands
Intraepidermal nerve fibre density (C fibres)

- 3mm biopsy from unwounded skin
- 10 cm above the external malleolus (reference values Provitera et al 2016)
Large fibre function (Aβ): nerve conduction and Quantitative Sensory Test

<table>
<thead>
<tr>
<th>Sural nerve</th>
<th>SNAP (μV)</th>
<th>NCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>23.3 ± 1.6</td>
<td>50.9 ± 1.7</td>
</tr>
<tr>
<td>RDEB</td>
<td>18.4 ± 2.3</td>
<td>51.7 ± 1.7</td>
</tr>
<tr>
<td>p value</td>
<td>0.08</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Large Aβ fibres were not affected
CONCLUSION

Short Axons

Long Axons

Small fibres of long axons don’t re-grow

Painful Small Fibre Neuropathy
TAKE HOME MESSAGE:

• RDEB patients are at high risk of developing neuropathic pain
• Test your patients using the DN4 questionnaire (S: 82% S: 73%)
• Treat them accordingly
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