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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Efficacy of botulinum toxin in pachyonychia congenita type 1: report of two new cases

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ABSTRACT: Pachyonychia congenita (PC) is a rare genodermatosis caused by a mutation in keratin genes, which can lead to hypertrophic nail dystrophy and focal palmoplantar keratoderma (predominantly plantar), amongst other manifestations. Painful blisters and callosities, sometimes exacerbated by hyperhidrosis, are major issues that can have a significant impact on patient quality of life. Many alternative treatments for this condition have been applied with variable and partial clinical response, but a definitive cure for this disease has yet to be discovered. After obtaining informed consent, two patients with genetically confirmed PC type 1 were treated with plantar injections of botulinum toxin type A. Both patients showed a marked improvement in pain and blistering with an average response time of one week, a six-month mean duration of effectiveness, and a lack of any side effects or tachyphylaxis.

KEYWORDS: botulinum toxin, hyperhidrosis, pachyonychia congenita

Introduction

Pachyonychia congenital (PC) is a group of autosomal dominant congenital keratinopathies caused by mutations in any of five genes: KRT6A, KRT6B, KRT6C, KRT16, or KRT17. With a prevalence of 1:1,00,000 for this condition, there are estimated to be 5,000–10,000 cases worldwide. Historically PC has been broken down into two clinical subtypes: PC type 1 (Jadassohn-Lewandowskii) and PC type 2 (Jackson-Lawler), but clinical phenotypes overlap between both types.

PC-1 is characterized by thickened toenails and fingernails in the first stages, extremely painful focal areas of hyperkeratosis and blistering, particularly on the soles of the feet (plantar keratoderma), and occasionally by oral leukokeratosis, follicular hyperkeratosis, laryngeal involvement, or other ectodermal defects (cysts or natal teeth).

Diagnosis of PC is determined through clinical examination and confirmed by molecular genetic testing, which is provided free to all patients enrolled in the PC registry (PC Project) http://www.pachyonychia.org (1).

Painful foot blistering and callosities are common problems in patients with PC which are often exacerbated by hyperhidrosis and high ambient temperature. Hyperhidrosis can be blocked by plantar injections of botulinum toxin (BTX) (2). We report two patients who experienced remarkable improvement in terms of reduced plantar pain and foot blistering after BTX injection.
injections without loss of efficacy thus far. Anaesthesia was achieved in both cases via superficial sedation with spontaneous ventilation.

Case reports

Case 1
The first patient, a 32-year-old woman, had been diagnosed with PC-1 when she was 3 months old. She presented thickened and discolored nails, focal palmoplantar keratoderma with painful blisters and erosions on the soles exacerbated by plantar hyperhidrosis (FIG. 1A), follicular hyperkeratosis on the extensor surfaces of the extremities, oral and laryngeal leukokeratosis causing vocal hoarseness. She had no family history of PC and was otherwise healthy. Foot blisters and calluses were so painful that she was unable to walk and required the use of a wheelchair. At the age of 29, blood testing revealed a \textit{KRT6A} missense mutation (Dundee, Scotland), making the diagnosis of PC type 1 definitive. She had previously been treated with acitretin 25 mg/day, which was later tapered to 10 mg/day, and keratolytic agents for more than 10 years with only partial effectiveness. In 2010, following informed consent, she was offered toxin plantar injections. After paring down the callosities by curettage, we administered intradermal injections of 100 U of botulinum toxin type A (BTX-A) (Botox®, Allergan, Inc, Irvine, CA) in each sole and 50 U in each palm. Postinjection clinical improvement began in week one. Plantar pain and blistering were significantly mitigated and the patient was able to mobilize without her wheelchair (FIG. 1B). The effect of this treatment lasted approximately 6 months, so injections were subsequently administered biannually. In later sessions, the dosage was reduced (75 U in each sole and 50 U in each palm), concentrating the injections below blisters and callosities. The outcome was similar to the previous technique. Thus, BTX injections have led to substantial improvement in the patient’s quality of life, allowing her retinoid treatment to be withdrawn and enabling her to plan a pregnancy. The treatment has shown no reduction in efficacy during 5 years of follow-up.

Case 2
The second patient, a 27-year-old man, presented focal plantar hyperkeratosis with associated hyperhidrosis, painful blisters on the soles and on the back of the feet (FIG. 2A), thickened nails and oral leukokeratosis. The appearance of lesions began during infancy, and at the age of 23, a blood test revealed a \textit{KRT6A} missense mutation (Dundee, Scotland). Lesions in palms were less severe. He had a son with the condition, although no formal genetic testing had been conducted on him. Keratolytic agents and oral retinoid treatment had previously been applied with poor clinical response. Five months ago we started treatment with BTX-A at a dose of 150 U for each foot, concentrating the...
injections in the affected areas. A remarkable clinical improvement and reduction in plantar pain was seen at Day 7 postinjection (FIG. 2B), with a sustained response thus far. He had previously been treated over an 18-month period at another hospital with no preinjection curettage of foot lesions and a total dose of 100 U, resulting in only moderate improvement.

**Discussion**

Painful plantar hyperkeratosis is a very common feature in PC (95% of cases) and the most disabling one, reducing quality of life due to plantar pain (1). Currently there is no specific and effective therapy for patients with PC, although certain clinical trials have shown promising results. Targeted therapeutic strategies including small interfering RNA, topical or systemic rapamycin or simvastatin have recently been developed, but they cannot be offered on a regular basis (3–6). Many alternative treatments have previously been applied in this condition with variable and partial clinical response. These include: topical emollients, keratolytic agents, mechanical removal of excessive hyperkeratotic skin, avoidance of physical activity, analgesia, and so forth (7). Among the systemic agents for treatment of PC, oral retinoid therapy represents the treatment of choice (8).

Epidermolysis bullosa simplex and PC are congenital keratinopathies in which painful foot blisters and callosities severely reduce patient quality of life. Since 2006, a handful of studies have begun to report the efficacy of BTX-A in treating both conditions.

In 2010, a retrospective evaluation of 14 patients with epidermolysis bullosa simplex and PC showed a remarkable reduction in plantar blistering and pain after BTX injections (9–11). BTX inhibits eccrine sweat glands by blocking the acetylcholine pathway, thus reducing hyperhidrosis, maceration, and blistering of the fragile epidermis. But even patients with no overt hyperhidrosis or blisters reported pain relief. This may be explained by a more direct effect of BTX on nociceptive C-fibers inhibiting neuropeptide release from the sensory nerve axons. Also, BTX can decrease the release of pain mediators including substance P, calcium generelated peptide and glutamate, and also inhibit the vaso-dilation induced by the silent nociceptors that initiate neurogenic inflammation. These mechanisms may explain the effect of BTX on tenderness in both keratinopathies. Activation of TRVP3 on keratinocytes leads to the release of algogenic and pruritogenic substances inducing cutaneous pain. However, no reports have been found to date regarding the effect of BTX-A in these new receptors (12–15).

The technique applied was similar to treatment for axillary and palmar hyperhidrosis, but the same outcome is achieved when concentrating the entire dose directly below blisters and callosities. Mechanical removal of callosities by curettage prior to intradermal injections of BTX-A may play a role in pain reduction due to reduced friction. The optimal anaesthesia method may vary amongst different patients, but superficial sedation with spontaneous ventilation was applied in our cases. The dose of BTX-A each session ranged from 75 to 150 U per foot. Table 1 shows improvement scores and our results in comparison with those of previous studies. The mean effect lasted 6 months in both patients, no side effects were

![FIG. 2. Case 2 (A) Painful blisters and erosions on the back of the feet. (B) Improvement after BTX injections.](image-url)
reported and effectiveness was sustained over time.

**Conclusion**

There is, thus far no curative treatment for PC, and agents previously used to treat this condition have led to variable clinical outcomes. Until targeted therapeutic treatment can be offered on a routine clinical basis, our findings support the usefulness of BTX-A plantar injections in providing sustained symptomatic relief to PC patients and reducing painful foot blistering and callosities with good tolerance and lasting effects. As such, BTX-A treatment may offer a marked improvement in the quality of life for patients affected by this rare and incapacitating disease.

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**Table 1.** Global outcome and details of therapy comparing our results with those of previous studies

<table>
<thead>
<tr>
<th></th>
<th>Our cases (n = 2)</th>
<th>Swartling and Vahlquist 2006 (9) (n = 3)</th>
<th>Swartling et al. 2010 (11) (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of BTX</td>
<td>A (Botox)</td>
<td>A (Dysport), 7 A (Dysport), 3 B (Neurobloc)*</td>
<td></td>
</tr>
<tr>
<td>Dose (U) of BTX (range)</td>
<td>50 U (each palm)</td>
<td>125–300 U (each foot)</td>
<td>BTX-A: 200–350 (each foot)</td>
</tr>
<tr>
<td></td>
<td>75–150 U (each foot)</td>
<td></td>
<td>BTX-B: 2500</td>
</tr>
<tr>
<td>Improve in callosities (average)*</td>
<td>1.5</td>
<td>u</td>
<td>2</td>
</tr>
<tr>
<td>Improve in blistering (average)†</td>
<td>3</td>
<td>u</td>
<td>1.6</td>
</tr>
<tr>
<td>Improve in pain (average)‡</td>
<td>2</td>
<td>u</td>
<td>2.1</td>
</tr>
<tr>
<td>DLQI score before/after treatment (average)§</td>
<td>23 (before)/3 (after)</td>
<td>u</td>
<td>u</td>
</tr>
<tr>
<td>Effect duration (range and average)</td>
<td>5–6 months (5, 5)</td>
<td>6 weeks–6 months (3, 5)</td>
<td>2–12 months (3)</td>
</tr>
<tr>
<td>Number of treatments (range and average)</td>
<td>1–9 (5)</td>
<td>u</td>
<td>1–19 (8)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>Case 1: 60; case 2: 5</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Type of anaesthesia</td>
<td>Superficial sedation</td>
<td>IVRA§</td>
<td>3 General, 5 IVRA</td>
</tr>
<tr>
<td>Side effects</td>
<td>None</td>
<td>None</td>
<td>3/8 mild¶</td>
</tr>
</tbody>
</table>

*Due to treatment resistance, three patients were later switched to BTX B (Neurobloc).
†0, no effect; 1, a little better; 2, much better; 3, very much better.
‡DLQI (Dermatology Life Quality Index): 0–1: no effect at all on patient’s life; 2–5: small effect on patient’s life; 6–10: moderate effect on patient’s life; 11–20: very large effect on patient’s life; 21–30 extremely large effect on patient’s life.
§IVRA: intravenous regional anaesthesia.
¶Dysphagia in one case, and dry mouth, accommodation problems and urinary stress incontinence in two cases. n: number of patients. u: unknown.

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**Conflict of interests**

None of the authors have any conflict of interest to declare.

**References**

5. Hickerson RP, Leake D, Pho LN, Leachman SA, Kaspar RL. Rapamycin selectively inhibits expression of an inducible keratin (K6a) in human keratinocytes and improves...