



Pachyonychia Congenita Project

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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.

Treatment of pachyonychia congenita with plantar injections of botulinum toxin

C. Swartling and A. Vahlquist

Department of Dermatology, University Hospital, SE-751 85 Uppsala, Sweden

Summary

Correspondence

Carl Swartling.

E-mail: carl.swartling@akademiska.se

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None declared.

Pachyonychia congenita (PC) is a rare genodermatosis which may be associated with painful, focal hyperkeratosis on the soles. Plantar sweating at high ambient temperatures increases the blistering of the callosities. We report three patients with PC who had great problems in walking, especially during summer time. They were treated with intracutaneous plantar injections of botulinum toxin type A (Dysport[®], 100 U mL⁻¹; Ipsen, Slough, U.K.) after prior intravenous regional anaesthesia of the foot with a low tourniquet and 25 mL prilocaine (5 mg mL⁻¹). Within a week all three patients experienced dryness and a remarkable relief of pain from plantar pressure sites. The effect duration was 6 weeks to 6 months. Repeated injections over a 2-year period confirmed the good results, with no side-effects or tachyphylaxis noted.

Pachyonychia congenita (PC; OMIM 167200/210) is a rare genetic disorder of keratinization which is characterized by hypertrophic nails (pachyonychia or onychogryphosis), focal areas of hyperkeratosis especially on the soles (keratoderma) and occasionally leucoplakia of the oral mucous membranes. PC comes in at least two types: PC-1 (Jadassohn–Lewandowsky) with laryngeal involvement, and PC-2 (Jackson–Lawler) with steatocystoma multiplex. The former type is caused by dominant negative mutations in the keratin genes KRT6A and KRT16, and the latter type by mutations in KRT6B or KRT17; all these mutations predispose for cytoskeletal instability and focal cytolysis in the mid-epidermis.¹ Clinical features very similar to those in PC can in rare cases be caused by connexin 30 mutations² and by KRT5 and KRT14 mutations underlying epidermolysis bullosa simplex (EBS) (A.V., unpublished observation).

Common to all these genodermatoses is a frequent occurrence of painful foot blisters within the hyperkeratotic areas, especially when complicated by hyperhidrosis and a high ambient temperature.³ Alas, traditional therapies for plantar hyperhidrosis, such as topical application of aluminium salts or diluted glutaric aldehyde, produce only short-lasting (< 1 week) suppression of sweating and are hardly effective when massive hyperkeratosis prevents efficient penetration of the chemicals. Lumbar sympathectomy is a more potent method of achieving anhidrosis of the feet but the method has been condemned due to severe side-effects.⁴

A new treatment for focal hyperhidrosis is intracutaneous injections of botulinum toxin (Btx), which produces long-lasting (several months) suppression of eccrine sweat gland activity.⁵ Hyperhidrosis of the axillae is today an established

indication for Btx therapy with minor complications and high feasibility; only rarely is topical anaesthesia needed before the multiple injections of Btx.^{6,7} Treatment of plantar hyperhidrosis is more challenging; Btx injections at this site are impossible to deliver without good anaesthesia. Btx has therefore only been infrequently used in severely hyperhidrotic feet after prior nerve blockade⁸ and there are no previous reports of its use in individuals with pre-existing plantar skin disease.

We wish to report our very promising results using repeated Btx injections after intravenous regional anaesthesia (IVR) of the lower leg in three patients with severe plantar PC.

Case reports

Patient 1

A 26-year-old man was diagnosed in infancy to have PC-1 characterized by onychogryphosis of all toenails and several fingernails, focal keratoderma on the feet and oral leucoplakia. He had no family history of PC and was otherwise healthy. A recent analysis of his blood DNA revealed no hot-spot mutations in relevant KRT genes (Dr Paul Bowden, Cardiff, personal communication). When first seen in 1997 he had for many years been unable to walk for more than a few metres at a time due to his very painful plantar keratoses (Fig. 1). He was treated with acitretin 30 mg daily for more than 1 year with some reduction in plantar hyperkeratosis, but was still in need of a wheelchair for transportation. After informed consent, he was subjected to bilateral IVR with a low tourniquet (middle of the calves) and 25 mL prilocaine (5 mg mL⁻¹) given intravenously to each foot, whereafter he



Fig 1. Patient 1 with plantar hyperkeratoses on pressure sites of the feet.

received a total of 300 U of Btx type A (Dysport[®], 100 U mL⁻¹; Ipsen, Slough, U.K.) to each foot divided into 3-U injections every 15 mm over the sole and toes. An improvement with markedly diminished pain and reduced sweating from his feet was noticed 2–3 days postinjection. He was then able to stop acitretin treatment and to cease using the wheelchair for 6 months, whereafter sweating and pain relapsed. A further treatment was given with equally good results.

Patients 2 and 3

Patients 2 and 3 are sisters aged 38 and 32 years, both receiving thyroxine for hypothyroidism, whose mother had also had PC-1 since birth. Analysis of blood DNA in 1997 revealed a KRT6A missense mutation (I462N) in affected family members (Dr W.H.I. McLean, Dundee, unpublished observation). The mother had been markedly helped in her fifties after a lumbar sympathectomy for moderately increased plantar sweating and severely painful plantar hyperkeratoses. Both sisters were unable to walk long distances due to painful plantar hyperkeratoses and the elder one was in need of a wheelchair. As in patient 1, no obvious blisters with free fluid were seen, but focal accumulations of macerated keratinous material were present on the soles of both patients. After informed consent, both sisters received treatment to one foot while the untreated

side served as control. After IVR with a low tourniquet and 25 mL prilocaine 5 mg mL⁻¹ per foot, they received 250 U (patient 2) and 300 U (patient 3) Dysport[®], 100 U mL⁻¹, divided into 3-U injections every 15 mm over the soles and toes. In both patients the reduction of pain and sweating was substantial within a week in the treated foot compared with the untreated side. Hence the untreated side was injected a month later, with equally good effect in both patients. Even though the extent of hyperkeratosis was only marginally reduced by Btx injections, the affected areas became drier, more solid and thus more easy to manage with pedicure. Furthermore, the intense pain from the hyperkeratotic areas, which was readily provoked by even moderate pressure, diminished significantly in the treated vs. untreated foot in both patients. Repeated bilateral treatments showed effect durations of 6 weeks and 3 months, respectively. At relapse we injected only the pressure sites of the soles/toes, sparing the arch of the foot in an attempt to reduce the dose of Btx. The outcome, including the effect duration, was similar to that produced by the previous injection technique.

Discussion

Pain from pressure sites of soles and toes is a major problem in patients with PC.³ Two of the patients in this study were in need of a wheelchair and all three patients had a long history of musculoskeletal problems due to painful walking. The foot pain in PC is typically exaggerated by excessive plantar sweating, especially at high ambient temperature when frank blistering may occur below the hyperkeratosis, although not seen in our patients. A combination of friction from footwear and tissue maceration from sweat entrapped in the horny material supposedly enhances the cytolysis of fragile keratinocytes, but exactly how this produces the intense tenderness of pressure sites is not fully understood. Hyperalgesia due to inflammation and stimulation of nociceptive nerve fibres is one possible explanation. For example, very painful focal keratodermas have also been noted in association with tyrosinaemia-II.⁹

In all three patients with PC, plantar Btx injections not only elicited anhidrosis within a couple of days, but also made the hyperkeratoses less painful and easier to abrade therapeutically. As a result, the patients became more mobile and had a reduced need for oral analgesics. Furthermore, acitretin therapy was stopped and the wheelchair abandoned in one patient. Based on these positive results, several other patients with painful keratodermas and summer worsening of foot blistering have since been treated in our hospital using the same technique as for the patients with PC. At least two patients with EBS have responded with decreased frequency of painful blistering; however, despite obvious anhidrosis on the treated side, two other patients with EBS benefited only marginally from the therapy (C.S. and A.V., unpublished data). It remains to be studied if the response to Btx injections is intrinsically different in different genotypes of PC and EBS.

Local Btx injections have the advantage of producing anhidrosis for several months without serious side-effects,

but anaesthesia such as a regional nerve block or IVR must be given before injecting the palms and soles.^{10,11} The IVR technique requires an alertness to systemic side-effects from prilocaine, and should not be performed in patients with neuropathies or vascular diseases such as Raynaud's syndrome.

The relatively short effect duration of Btx in two patients (6 weeks and 3 months, respectively) can also be seen in the treatment of primary essential hyperhidrosis, especially at plantar locations. For unknown reasons, the interindividual variation in effect duration after Btx therapy is much more pronounced in the treatment of hyperhidrosis compared with muscle cramp disorders. A recent histometric analysis of palmar sweat glands before and several months after successful Btx therapy of essential hyperhidrosis showed diminished lumen diameter of the coil and attenuated staining for nerve markers around the glands, compatible with a long-lasting suppression of glandular activity.¹² Btx acts via inhibition of acetylcholine exocytosis from the sudomotor end-terminals,¹³ but the toxin might also have an effect on nociceptive C-fibre function in the skin by inhibition of neuropeptide release from the sensory nerve axons. Btx can inhibit the vasodilation (flare) induced by the 'silent' nociceptors also initiating neurogenic inflammation.¹⁴ The tenderness of plantar hyperkeratoses in PC might therefore benefit from Btx injections also via its inhibition of neurogenic inflammation. Further histochemical and neurophysiological investigations are needed before the mechanism of action of Btx in painful foot callosities and blisters can be fully understood. Also larger, placebo-controlled (saline injection) studies of Btx injections in conditions with painful, hyperhidrosis-related keratoderma and foot blisters should be performed before this therapy can be generally recommended for patients with hereditary disorders of keratinization. Meanwhile, we conclude that by using the described IVR technique for anaesthesia, adults with problematic plantar hyperhidrosis can be safely treated with repeated Btx injections and that this therapy appears to be especially effective in patients with PC.

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