

Heat urticaria – easy to diagnose but also to misdiagnose

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Linked Article: Pezzolo *et al.* *Br J Dermatol* 2016; **175**:473–478.

Heat urticaria is a chronic inducible urticaria (CIndU).¹ CIndUs are characterized by the need for specific external triggers for symptoms to develop, e.g. heat in heat urticaria.² CIndU symptoms are usually, but not always, confined to skin areas that are exposed to the specific trigger and patients may exhibit two or more subtypes of chronic urticaria at the same time.²

While symptomatic dermographism, cold urticaria, delayed pressure urticaria and cholinergic urticaria are relatively common CIndUs,³ heat urticaria is extremely rare. Accordingly, it is difficult to collect conclusive data for this condition.

In this issue of the *BJD*, Pezzolo and coworkers present a review of 60 published cases with heat urticaria,⁴ thereby merging much of what is currently known on this disease. Based on their findings, two clinical subtypes can be distinguished: (i) an immediate form with itchy, short-lived lesions that occur a few minutes after heat exposure, and (ii) a less frequent, usually autosomal dominant inherited form, with delayed weals that burn rather than itch and persist for up to 24 h. In contrast to the delayed form, patients with immediate heat urticaria may develop localized and generalized skin lesions as well as angio-oedema. Potential trigger factors include warm baths, hot air and sun exposure. Notably, more than half of all described patients with heat urticaria also have systemic symptoms such as weakness, headache, nausea, diarrhoea and even syncope.

The facts that prevalent triggers may be relevant (e.g. sun exposure) and that localized but also generalized skin lesions as well as systemic symptoms may occur, make it difficult to clearly distinguish heat urticaria from the much more common cholinergic urticaria, from solar urticaria, and from exercise-induced anaphylaxis, solely based on patient history. Accordingly, the diagnosis of heat urticaria should be secured by appropriate provocation testing,² e.g. by using a Peltier effect-based instrument for critical temperature threshold measurement.⁵ In addition, it is important to rule out cholinergic urticaria, preferentially by a standardized pulse-controlled ergometry test,⁶ solar urticaria by skin testing with ultraviolet and visible light,¹ and exercise-induced anaphylaxis by skin prick testing, laboratory and provocation tests.⁷ Provocation tests are not only essential for ruling out differential diagnoses, they also provide information on disease activity, by assessing trigger thresholds. The knowledge of individual trigger thresholds, e.g. the lowest skin temperature that is sufficient to induce wealing in heat urticaria, can help to counsel patients on the avoidance of relevant triggers and to measure and monitor treatment responses.²

In terms of treatment, Pezzolo *et al.* found that H1-antihistamines work in around 60% of patients with heat urticaria, but

fewer than 20% of patients achieve complete symptom control, even at four times the licensed dose. However, it has to be stressed that the current data on treatment options and efficacy is very limited. As yet, not a single randomized controlled clinical trial has been performed, which is owed, at least in part, to the fact that heat urticaria is a rare disease. All available data are based on case reports and case series and may be skewed by publication bias. An alternative option to obtain more robust data are registry studies. For this reason, the Chronic Urticaria Registry (www.chronic-urticaria-registry.com), the first academia-driven registry for chronic urticaria, was set up recently.⁸ It welcomes all physicians treating urticaria to share their experiences and to improve our knowledge of patient characteristics, symptom patterns, disease course and best treatment options also in rare types of CIndU, such as heat urticaria.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Audio S1. Author Audio.

Protein kinases and phosphodiesterases in psoriasis: time to refocus on biochemistry

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Linked Article: Snape et al. *Br J Dermatol* 2016; **175**:479–486.

In this issue of the *BJD*, Snape et al.¹ report a clinical study of topical phosphodiesterase 4 (PDE4) inhibitors for the treatment of plaque psoriasis. The study is a phase I trial, designed, analysed and funded by industry. It is randomized, placebo-controlled and single-blinded to the clinical investigator. The study reported efficacy with two PDE4 inhibitors as measured by changes in thickness of inflammatory infiltrates in psoriatic lesions. Study numbers were small, but the authors reported lesion improvements that were unidirectional, consistent, dose dependent and statistically significant. Given the preliminary nature of the study, it is easy to point out significant limitations to the methodology and results of the report. However, the findings do fulfil several Bradford Hill criteria for causation with respect to the efficacy of PDE4 inhibitors on inflammatory components of psoriasis. Beyond methodological analysis, a critical element of the criteria is biological plausibility. Accordingly, consideration of potential putative mechanisms by which PDE4 alleviate psoriasis is of great interest and importance.

Cyclic nucleotide phosphodiesterases catalyse hydrolysis of cAMP and cGMP, thus regulating intracellular concentration and function of second messengers in signal transduction through their respective cellular effectors, PKA and PKG. There are 11 structurally related but functionally distinct gene families (PDE1 to PDE11) that comprise the PDE superfamily, with the PDEs exhibiting divergent amino-terminal regulatory regions and a conserved carboxy-terminal catalytic core. Some PDEs specifically hydrolyse cAMP (PDE4, PDE7 and PDE8) while others specifically hydrolyse cGMP (PDE5, PDE6 and PDE9). Alternatively, other PDEs hydrolyse both (PDE1, PDE2, PDE3, PDE10 and PDE11).^{2–4} The N-terminal regulatory regions of PDEs contain structural determinants that target individual PDEs to different subcellular sites and signalosomes⁵ and allow individual PDEs to respond specifically to different post-translational modifications, regulatory molecules and signals.

PDE4 inhibitors exhibit potent cAMP-mediated anti-inflammatory activity in various cellular and animal models, and

have been useful in inflammation-related pulmonary⁶ and skin diseases, in particular atopic dermatitis and psoriasis.⁷ The PDE4 inhibitors act mainly on inflammatory cells like T lymphocytes and macrophages to block tumour necrosis factor- α secretion and interleukin (IL)-17 and IL-23 cytokines.⁷ As such, the PDE4 inhibitors in psoriasis may be mainly anti-inflammatory and may not specifically target changes that are specific to psoriatic hyperproliferation (elongation of rete ridges, parakeratosis, suprapapillary thinning, increased proliferating cell nuclear antigen expression as assessed by the Ki-67 immunohistochemical marker).⁸ Therefore, more studies are needed to see whether PDE4 inhibitors also affect pathophysiological components specific to psoriasis. Normalization of these psoriatic changes have been observed to be necessary for resolution of psoriasis and for achieving prolonged remission after withdrawal from treatment.^{8,9}

One disconcerting effect of PDE4 inhibitors is the finding of tachyphylaxis with roflumilast after repeated dosing in patients with chronic obstructive pulmonary disease.¹⁰ This is due to upregulation of PDE4B, which counteracts the suppression of inflammation by the PDE4 inhibitors. The mechanism involves the synergistic interaction between the PDE4 inhibitor (roflumilast) and bacteria (*Haemophilus influenzae*) to upregulate PDE4B2 expression in the airways. Reports of high prevalence of *Staphylococcus aureus* with superantigen production^{9,11} in psoriasis increases the likelihood that tachyphylaxis may occur with the use of PDE4 inhibitors in this disease.

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