
Delayed Pressure Urticaria

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Delayed pressure urticaria is a physical urticaria where erythematous, often painful swellings occur at sites of sustained pressure on the skin, after a delay of several hours. If sought, it is present in up to 40% of patients with ordinary chronic "idiopathic urticaria" to a varying degree. Compared with other urticarias, the pressure-induced lesions impair the quality of life of patients most severely. The pathogenesis is not well characterized, but whealing is dependent on mast cell activation, with the histology of lesions also showing a deep dermal inflammatory

infiltrate of neutrophils and eosinophils, without vasculitis. Treatment of delayed pressure is generally unsatisfactory, and is often resistant to antihistamine and a range of anti-inflammatory medication. Oral steroids, although the most effective therapy, are unsuitable for long-term use. Delayed pressure urticaria may persist for many years, and improved or novel methods of management are under investigation. *Journal of Investigative Dermatology Symposium Proceedings* 6:148-149, 2001

Delayed pressure urticaria (DPU) is important because it can interfere severely with the quality of life, the condition may be underdiagnosed, its pathogenesis is not defined, and its treatment is very difficult.

QUALITY OF LIFE

The severity of the impact of DPU on the quality of life has only recently been documented in a specialist urticaria unit. When the quality of life of patients with delayed pressure urticaria and chronic urticaria was compared with patients with uncomplicated chronic ordinary urticaria, using a Nottingham health profile, a general health status measure, the patients with DPU were significantly more restricted in mobility and types of clothing that they could wear, had a higher pain score, and had more problems related to employment and hobbies (O'Donnell *et al*, 1997). Similar results were obtained by using a skin disease specific questionnaire (Dermatology Life Quality Index; Poon *et al*, 1999). In addition, patients with DPU had the highest impairment of quality of life compared with the other types of urticaria questioned (Poon *et al*, 1999). This impairment of quality of life of patients with DPU was comparable with that seen in atopic outpatients (Poon *et al*, 1999). Patients may not reveal that DPU can cause sexual difficulties (McFadden *et al*, 1998).

CLINICAL CHARACTERISTICS

DPU is characterized by the development of erythematous swellings at sites of sustained pressure application on the skin after a delay of 30 min to 12 h (Dover *et al*, 1988). The swellings are usually pruritic and/or painful, may persist for several days, and occasionally may blister (Mijailovic *et al*, 1997). Systemic features such as flu-like symptoms and arthralgia may be present and on a few occasions delayed pressure urticaria has led to obstruction of

urinary flow (Poon and Kobza Black, 1998). The severity of DPU varies in individuals with time (Lawlor *et al*, 1989). Nearly all (94%) patients have associated ordinary idiopathic urticaria (Sussman *et al*, 1982).

The incidence of DPU was previously stated to be approximately 2% of all urticarias (Champion, 1988). It is now recognized that DPU is more common, as 37% of patients with ordinary urticaria attending hospital have associated DPU (Barlow, 1993). Other types of urticaria may be associated with DPU (Dover *et al*, 1988), including angioedema, symptomatic immediate, and delayed dermatographism.

DIAGNOSIS

The patient and physician may be unaware of the presence of DPU unless direct questioning reveals the association of pressure and development of wheals after a delay. Lesions appear at pressure sites under tight clothes, on palms after using tools, and on soles of feet after prolonged walking or standing.

Confirmation of the diagnosis is made after application of a standardized weight applied to a defined area of skin for a specified time results in a palpable wheal when inspected after 2-8 h (usually 6 h). The presence of wheals resulting from rods of 1.5 cm diameter weighted with 2.5 or 3.5 kg applied for 20 min to the skin were designated as a gold standard for DPU. Using a pen-like instrument calibrated at 100 g per mm² (dermographometer) pressed for various times against the back, the best combination of specificity and sensitivity of the diagnosis of DPU was at 70 s application (Barlow *et al*, 1993).

PATHOGENESIS

The pathogenesis of DPU is not well characterized, although a number of potential mechanisms and mediators have been postulated.

It has been postulated that the pressure-induced wheals may be due to a late phase reaction (Sussman *et al*, 1982), but an antigen has never been identified. This reaction is dependent on mast cell activation and reduced stainable mast cells have been demonstrated in wheals of DPU (Barlow *et al*, 1995a) associated with a

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neutrophil- and eosinophil-rich infiltrate present in some early and late wheals (Barlow *et al*, 1994). There is upregulation of E selectin (Barlow *et al*, 1994). These responses suggest the presence of cytokines derived from mast or inflammatory cells. Increased interleukin 6 (Lawlor *et al*, 1993) and TNF α and IL3 expression related to the inflammatory cell infiltrate were demonstrated in lesions of DPU (Hermes *et al*, 1999).

TREATMENT

Treatment is generally unsatisfactory and there are only a few controlled trials. Antihistamines are generally not effective (Sussman *et al*, 1982; Dover *et al*, 1988), though high doses of cetirizine (10 mg three times) reduced the areas of whealing in 14 patients with DPU (Kontou-Fili *et al*, 1991), but in clinical practice the results have been generally disappointing.

Nonsteroidal anti-inflammatory drugs (NSAID) have been used to treat DPU, with conflicting results. Acetyl salicylic acid (3900 mg per d in divided doses) clinically suppressed experimentally induced wheals in six of eight patients with DPU (Sussman *et al*, 1982); however, in a double blind trial of indomethacin 25 mg three times a day in 14 patients with DPU, there was no significant reduction of dermatographometer-induced weal areas (Dover *et al*, 1988). It is important to note that NSAID may exacerbate ordinary chronic idiopathic urticaria.

Colchicine at a dose of 0.5 mg and placebo twice a day in 13 patients with DPU in a double blind cross-over trial, did not demonstrate a reduction of dermatographometer-induced wheals compared with placebo (Lawlor *et al*, 1989).

There has been an isolated case report of the usefulness of dapsone 50 mg daily in five patients (Gould *et al*, 1991), of sulfasalazine up to 4 g daily in two patients (Engler *et al*, 1995), and of montelukast, a leukotriene antagonist, in one patient (Berkun and Shalit, 2000) with DPU, but larger double blind, placebo-controlled studies are necessary to evaluate these treatments.

In a study of 44 patients with DPU, one group was randomised to nimesulide 100 mg daily for 3 wk, ketotifen 1 mg b.d. was added for 2 wk, and in the next 2 wk nimesulide was ceased but ketotifen was continued. In another group prednisolone orally was reduced from 40 mg daily for 3 wk, 30 mg daily for 2 wk, and 20 mg daily for 2 wk. There was a reduction of 93% of symptoms in the first group and 85% in the second, but longer follow-up studies are necessary (Vena *et al*, 1998).

Oral steroids are the most effective treatment, but doses above 30 mg per day may be necessary, so it is unsuitable for long-term use (Dover *et al*, 1988). Topical steroids under occlusion may be helpful in pretreating small localized areas (Barlow *et al*, 1995b).

It is unclear whether immunotherapy including oral cyclosporine and intravenous immunoglobulin, which have been used to treat the most resistant autoimmune chronic urticarias, may be beneficial for delayed pressure urticaria.

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