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Case Report Open Access

The Successful Use of Vitamin D in Physical Urticaria

Veronica A Varney[1]* and Amena Warner[2]

[1]Respiratory Department, St. Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM5 1AA, UK
[2]Allergy Clinic Immunology Department, St. Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM5 1AA, UK

Abstract

Physical urticarias are disorders of the skin occurring in response to a number of physical stimuli (pressure, temperature and ultra violet light). The condition is characterized by painful swelling and burning at the site of the stimulus. High dose anti-histamines combined with montelukast seldom control the condition completely. The exact cause of the skin pathology is not fully understood and this has limited new treatment options. We describe a case series in which significant daily symptoms of physical urticaria were occurring without an adequate response to treatments other than steroids. The patients were asked to commence an oral Vitamin D3 supplement in view of its widespread anti-inflammatory effects on the immune system. In all cases symptoms resolved within 2-4 months allowing regular medication to stop. We discuss briefly the possible actions of Vitamin D3 on the immune system in this case series.

Keywords: DPU urticaria; Physical Urticaria; Solar urticaria; Vitamin D

Abbreviations: DPU: Delayed Pressure Urticaria; SU: Solar Urticaria; IL-6: Interleukin-6; LT: Leukotriene; HDM: House Dust Mite; IgE: Immunoglobulin E; CU: Chronic Urticaria

Introduction

Physical urticaria is a heterogeneous group of diseases with differing stimuli of which pressure, temperature and ultra-violet light are well described [1]. Atopy and chronic urticaria are frequently associated with the condition [2]. Acute and chronic urticaria generally responds well to antihistamines but this is not the case for physical urticaria, where response is usually unsatisfactory [3]. As a result combination treatments have been used and many of these are described in the literature. They include antihistamine combinations with other drugs such as montelukast, ketotifen, NSAIDS and dapsone [4,5]. Oral steroids are very effective but long-term treatment is limited by adverse effects. For intractable cases, treatment with anti-IgE infusions and infusions of intravenous immunoglobulin appear successful, but are expensive, time consuming and unlikely to be generally available [6,7].

The physical urticarias appear to be associated with a different pathology to acute and chronic urticaria where mast cell histamine release is predominant. Studies in Delayed Pressure Urticaria (DPU) and Solar Urticaria (SU) suggest dermal inflammation with inflammatory cells (neutrophils, eosinophils and basophils) and a late phase-like reaction. Interleukin-6 is raised in lesional skin along with raised eosinophil-derived major basic protein and leukotrienes B4, C4, D4 and E4 suggesting non-mast cell dependant mechanisms [8-11]. The exact pathogenesis is still a puzzle and this influences the development of effective treatment especially for severe cases. We describe 5 cases of physical urticaria in which oral Vitamin D supplements were given with resolution of symptoms over a few months. The sites of action of Vitamin D on the immune system and inflammation are multiple and we discuss its possible actions in these patients.

Case

Case 1

Gave a history of acute urticaria to penicillin and eggs from the age of 11 years, which she subsequently avoided (Table 1). As an adult, she would develop acute urticaria with every virus requiring steroids to settle the giant urticaria. In addition she had severe symptoms (previously diagnosed by a dermatologist) of both pressure and cold temperature induced urticaria for 14 years which had significantly reduced her life quality. DPU occurred severely on her legs and buttocks on sitting with burning pain. After her spinning classes she would develop forearm, wrist and hand swellings along with buttock swelling that would be very uncomfortable until it resolved. With cold weather or cold exposure she would develop giant urticaria. Her symptoms had never been controlled by antihistamines and montelukast, hence her frequent steroid courses. She had deteriorated further in the last 2-3 years and was referred to the allergy clinic. We explained to her our observation in the allergy clinic of a significant benefit from Vitamin D3 in physical urticaria. She commenced 3000 IU/day from the health shop which was increased to 5000 IU/day in view of her very low blood level of 25OH Vitamin D (Table 1). All other bloods were normal including inflammatory markers, thyroid, complement, immunoglobulin's and auto-antibodies.

At 2 months review her DPU symptoms had settled and review was planned for mid-winter when she suffered the addition of cold temperature induced urticaria and giant urticaria with virus infection requiring prednisolone. At winter review all her symptoms had settled and she had stopped all medication (antihistamines and anti-leukotrienes) except for Vitamin D. After her spinning classes she developed no DPU symptoms and even a recent severe virus had passed uneventfully. Her cold temperature induced urticaria had gone and she described herself as normal. She was advised to continue 1000-2000 IU/day long-term. On discharge she commented that she had suffered this condition for years and couldn't believe that the cure came from a Vitamin! This comment prompted us to collect together our

***Corresponding author:** Veronica A Varney, Respiratory Department, St. Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM5 1AA, UK, Tel: 004402082962401; Fax: 004402082963163; E-mail: veronica. varney@esth. nhs. uk

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most recently remembered cases for publication, as we have found this treatment so effective in our allergy clinic.

Case 2

Gave a history of irritable bowel syndrome with loose stools, abdominal pain and bloating which was the main focus of her referral to the allergy clinic (Table 1). Skin testing confirmed tree, grass and wheat allergy and wheat avoidance settled the abdominal symptoms completely at her first review. At that review she then enquired about her long history of DPU which was affecting her life quality especially now the bowel symptoms had resolved. She reported that this symptom had not changed on the wheat free diet. It occurred on her shoulders and arms if carrying bags and on her buttocks and legs on sitting for long periods. She had to avoid crossing her legs due to DPU of her knees and tight shoes would cause it to develop on her feet. She had taken cetirizine 30 mg and montelukast 10 mg long term without any benefit to the DPU, but found it useful for her seasonal rhinitis. We asked her to commence Vitamin D 2000 IU/day for the DPU and on review at 4 months, she reported that her DPU was only fleetingly noticed as one mild episode a month compared with daily before. As a result of the improvement she had stopped the montelukast and taken cetirizine only as required for rhinitis. We recommended that she continue 1000-2000 IU/day long term.

Case 3

Described a lifetime history of asthma with atopic rhinitis, and allergy to house dust mite. In the past two courses of house dust mite desensitization for her asthma and rhinitis had occurred (1948 and 1974) and she was referred due to deterioration of her asthma and rhinitis (Table 1). On attendance she informed us of her need for high dose anti-histamines due to severe solar urticaria. She had to avoid all sunlight and reported that to even drive her car wearing total sunblock cream and leather gloves she would still develop painful urticaria through the gloves if the sun shone on the steering wheel from spring until Autumn. She was under the guidance of a leading hospital photo-dermatology clinic that had established that she had solar urticaria to UVA (380-400 nm wavelength) with an immediate erythema and a papular response (even though gloves) at 30 minutes that resolved after 2-3 hrs. The antihistamines and total sunblock to reduce exposure was not working. The reaction had started approximately 2 years before and the patient wondered whether a course of oral doxycycline was the trigger initially. We suggested she started some oral Vitamin D 3 due to our observations of improvement with physical urticaria and she

Cases	**1**	**2**	**3**	**4**	**5**
Diagnosis	DPU Cold urticaria	DPU	SU	DPU	DPU Cold urticaria
Duration	14yrs Worse from 2011	Years worse >2yrs	1-2 yrs	10yrs	1 yr
Age(sex)	44(f)	63(f)	71 (F)	47(F)	19(F)
Ethic Group	Caucasian	Caucasian	Caucasian	Afrocarribean	Caucasian
Atopic	Yes HDM	Yes Airborne Wheat	Yes HDM Sulphite reactions	Yes Grass, tree, HDM, nuts, banana, yeast	Yes Wheat banana
Other conditions	Nil	Irritable bowel syndrone Hypertension Lichen planus	Past immunotherapy 1948 and 1974	Hypertension Seasonal asthma Steroid-induced psychosis	Eczema
Chronic urticaria	no	no	yes	yes	no
Acute urticaria	Viruses Eggs penicillin	Aspirin Grass pollen	Solar UVA (380-400 nm)	Grass pollen	banana
Previous treatment	Steroids Cetirizine Loratidine montelukast	Cetirizine Montelukast Steroids Candesartan Moduretic Omeprazole nifedipine	Cetirizine/ fexofenadine Total UV block creams	Prednisolone Ranitidine Montelukast Phenergan Chlorpheniramine Eurax cream Assorted H2 Antihistamines Cetirizine, loratidine	Loratidine Prednisolone montelukast
Routine and immune blood tests+	normal	Normal	Normal ↑ IgE HDM	Normal ↑ IgE grass	normal
25OH Vitamin D at referral nmol/l*	30	44	48	43	Not measured
Vitamin D dose commenced	5000 IU/day	2000 IU/day	2000 IU/day	4000 IU/day	2000 IU/day
Time to improvement	2 months	4 months	3 months	4 months	2 months
Outcome	Resolved to DPU, cold and viral illness	DPU Resolved Vitamin D	SU Resolved All drugs and creams stopped No clothing Protection needed	Resolved All drugs stopped	Remaining mild DPU on fingers only
Follow-up/relapses	2 and 6 month. none	2 yr Resolved as long as she stays on vitamin D	4 yrs Resolved and holiday in California gave no problems	3 yrs	3 years and stable without symptoms

* <20 nmol/l: severe deficiency 20-50 nmol/l: insufficiency 50-200 nmol/l: replete

+ blood count, liver and kidney function, thyroid, protein and calcium levels, C-reactive protein, complement and auto-antibodies,ANCA,C3,C4,C1assay and function

Table 1: Case Summary.

Cell	Action	Mechanism	References
Macrophages/monocyte	Promotes differentiation Inhibit dendritic cell differentiation Reduced inflammatory Cytokines Reduces co-stimulatory molecules	↑ 1α hydroxylase ↑ 1α hydroxylase ↓ IL-6,8,12, TNF* ↓ CD40, CD80, CD86 and HLA-DR*	[13,14,18-20]
T cells	Homing to inflamed tissue Homing to skin Increased T regulatory cells Reduced inflammatory cytokines	↑CCR5, CXCR3, CXCR6* ↑CCR10 ↑IL-10, TLR-9* ↓ IL-17, IL-2, IFN-gamma	[13,14,16,18,20]
Dendritic cells	Increased T cell regulation Reduced immune response Reduced co-stimulatory molecules Reduced cytokine release	↑ IL-10, TGFß ↓ IL-17 ↓ CD1a, CD14, CD40, CD86 ↓ IL-12, IL-23	[12,13,14,18,20]
Mast cells	Stabilise mast cell Reduces IgE dependant pro-inflammatory mediators	↓ histamine release ↑ IL-10	[18,21,23]

*CCR and CXC-chemokine receptors IL-interleukin TLR-toll-like receptors, TGFß-transforming growth factor-beta, TNF-tissue necrosis factor. HLA: Human Leukocyte Antigens. IFN--gamma-interferon-gamma. CD-cluster designation of immune system cells

Table 2: Effects of 1,25 hydroxy-vitamin D on immune cells that may effect physical Urticaria [22,23].

was assessed and commenced on sublingual HDM desensitization. On follow-up for her immunotherapy at 3 months, she reported that she was not developing SU and she slowly progressed to not wearing gloves and stopped sunscreen by 6 months and subsequently anti-histamines. No relapse of her SU nor her asthma/ rhinitis occurred. The HDM immunotherapy improved her rhinitis and asthma. She was delighted with these events; we did not feel that the sublingual immunotherapy was responsible for the improvement in the SU, although both had been commenced together. She continued oral Vitamin D long-term and reports that she visit California as a holiday without solar Urticaria.

Case 4

Referred due to multiple allergies, associated with severe chronic urticaria, DPU and cold urticaria that was extremely difficult to control (Table 1). She had known hayfever and asthma in the grass season with acute on chronic urticaria at that time resulting in significant angioedema which would take many months to settle after the grass pollen season. She denied chronic asthma or eczema. Pressure and ice testing was strongly positive. Skin testing confirmed she was atopic to airborne allergens, nuts, yeasts and banana. With oral prednisolone above 20 mg/day she had developed severe steroid psychosis in the past when used by the dermatologists. This dose had been required due to the severity of the Chronic Urticaria (CU) with daily DPU which had not responded to other drugs. She suffered high blood pressure and in the allergy clinic we discontinued her aspirin and changed her Angiotensin Receptor Inhibitor (ACEI) to a calcium channel blockers in order to reduce any possible aggravation by these drugs. This gave some improvement to her chronic urticaria. Her prednisolone remained at 5-10 mg without which her symptoms were intolerable. Every anti-histamine was tried in increasing doses and in combination with ranitidine, montelukast and phenergan along with antihistamine creams and topical eurax cream. Little progress was made and frequent review in the allergy clinic was required over 7-8 years. In the grass season acute angioedema would require increased steroids, due to the increased severity of her daily DPU causing great distress. At this time we had not observed the benefit of Vitamin D in any patient.

We decided upon some sublingual grass pollen immunotherapy to see if settling the seasonal aggravation of her CU and DPU could facilitate a reduction in steroids use. Improvement by 40-50% in her summer hay fever and acute urticaria did occur. This did little for her DPU and cold urticaria. We suggested in 2011 she took some Vitamin D 800 IU/day when we were first observing a benefit in other patients. No apparent benefit was observed in her in the first year. After another admission for severe DPU to her feet, hands, legs and buttocks she admitted that she had never followed our advice of taking Vitamin D. We then suggested that she took high dose Vitamin D (4000 IU/d) as her Vitamin D levels were low and she was clinically a severe case. Within 2 months the DPU had dramatically reduced along with the Cold urticaria. Steroid reduction was begun at 1mg every 4-6 weeks. No relapses occurred during weaning and cessation and all symptoms resolved. In the following grass pollen season minimal eye and nasal symptoms occurred and the allergy problems were settled. She was advised to stay on 1000-2000 IU/day long term.

Case 5

Referred to the allergy clinic due to 37 attacks of pressure induced swelling (Table 1). This affected her fingers, arms, back, feet, lips and tongue. Swelling would occur rapidly after a hot or chilled drink or if ice-lolly or ice cream was licked or put into her mouth. She had small patches of eczema over her buttocks but tests showed no sensitivity to gluten. She was strongly positive on the pressure and ice testing developing immediate positive ice test and significant DPU at 2 hrs after the test. SPT showed her to be highly atopic to airborne allergens with large reaction to wheat and banana and smaller reactions to rye, tomato and cashew nut. She gave no history of irritable bowel syndrome. On oral challenge off her anti-histamines she confirmed that bananas caused rapid lip swelling independent of the temperature induced symptoms. We advised her to commence oral Vitamin D in view of her physical urticaria and on review at 2 months, all lip, tongue and mouth swelling had ceased and she was now able to drink hot and chilled drinks and ice cream etc. The bulk of her DPU had resolved from her arms, back and feet. She described milder swelling of her fingers on carrying very heavy shopping only. Avoiding wheat products had cleared her eczema patches Progress was maintained at 4 month review and she was advised to stay on Vitamin D at 1000-2000 IU/day and discharged from the clinic.

Discussion

Urticaria and allergic conditions are increasing and Vitamin D3 deficiency (25 hydroxy-Vitamin D) is now recognized as a global issue with effects on health including dysregulation of the immune system [12]. The understanding of its effects on the immune system has grown dramatically in the last decade and some of the recognized effects are summarized in Table 2.

1,25 hydroxy-Vitamin D receptors are present on mast cells, macrophages, T and B lymphocytes and other antigen presenting and

dendritic cells where the main effect is to reduce inflammation and increase T cell regulatory function [13]. The immune system generates 1,25 hydroxy-Vitamin D from serum 25 hydroxy-Vitamin D [14]. The latter reliably reflects Vitamin D status of the individual. 1,25 hydroxy-Vitamin D is important for glucocorticoid receptor functioning with widespread anti-inflammatory effects [15]. Micro-array work shows that within the CD4 T-cell alone, 102 genes are targeted with 57 down-regulated and 45 up-regulated [16] by 1,25 hydroxy Vitamin D. Within the skin, the presence of inflammation and inflammatory cytokines increases the local production of 1, 25 hydroxy-Vitamin D usually by macrophages which can then reduce the production of inflammatory cytokines (Interleukin-6,8,12,17,23 and tissue necrosis factor-α) [13,17]. This reduces the infiltration of neutrophils, eosinophils and basophils [13,18]. When 25 hydroxy-Vitamin D levels are <50 nmol/l, human monocytes and macrophages are unable to initiate some innate immune responses [19]. In mast cells, 1, 25 hydroxy-Vitamin D activates mast cell Interleukin-10 production without degranulation which suppresses mast cell derived pro-inflammatory mediators in-vitro [18,20]. This would reduce the generation of leukotriene C4 which generates D4 and E4 and activation of eosinophils as observed in the dermal inflammation described in the physical urticarias [21]. T-cell "homing" to skin sites of inflammation via the CC-chemokine receptor-10 is increased by 1,25 hydroxy-Vitamin D, where it can attenuate antigen presentation by skin dendritic cells and increase T-cell regulation of inappropriate Th-1 and Th-2 responses. This could potentially suppress late phase-like reactions observed in physical urticaria [22-24]. In our case series 4 out of 5 patients who measured their serum 25 hydroxy-Vitamin D levels were deficient with values between 30-48 nmol/l. These levels are below that required for bone health (75 nmol/l), although much debate does exist around minimal and optimal levels of 25 hydroxy-Vitamin D [25]. A National study of Vitamin D levels in British adults in various UK regions (south, middle, north, Scotland) showed an average 21% variation between winter and summer values with lowest levels in the North. For the south of England mean adult blood 25 hydroxy-Vitamin D levels were 42.6 nmol/l in winter and 62.4 nmol/l in summer [26]. This would have the closest correlation with our patients in Surrey who were all indoor workers. Our supplementation with Vitamin D was designed to elevate their blood levels to values >100 nmol/l, since it is thought that optimal immune health requires higher blood levels of Vitamin D3 than those required for bone health [12,17]. For subjects with a Vitamin D receptor polymorphism that affects Vitamin D "effector" function, elevation of Vitamin D levels in the blood appears to minimize the defect and is the subject of much research currently [27].

In our case series, the slow responses (2-4 months) of the physical urticaria to oral Vitamin D could reflect slow re-adjustment of the immune system with down-regulation of on skin inflammation. The cessation of all prior treatments for the condition upon improvement suggests an independent and sustained anti-inflammatory effect on the skin independent of the drugs. Skin biopsies in physical urticaria comparing changes before and after Vitamin D treatment and its effect on cellular infiltration in the skin would be interesting. *In situ* hybridization could also be used to assess changes in cytokine expression and may give further understanding of this condition.

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