Atopic urticaria: phenotypes

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Atopic urticaria: phenotypes

- Atopy (Gr): “inappropriate response to an event”

- Physical urticarias are “orphan” dermatoses:
  - Symptomatic dermographism
  - Cold urticaria
  - Solar urticaria
  - Cholinergic urticaria

- Characterised by inappropriate (urticarial) responses to innocuous physical stimuli
Chronic urticaria: physical urticarias

- Urticarial vasculitis: < 5%
- Physical urticaria: 30%
- Chronic ordinary urticaria:
  - (subsets: autoimmune; non-autoimmune): 65%
Physical urticarias

- Occur within minutes of exposure to triggering stimulus, and resolve within an hour of its removal.
- Resolve in a mean of 2 - 4 years.
- Rarely associated with systemic disease.
- Rarely require laboratory investigation.
- Usually respond to avoidance plus H1 antihistamines.
Physical urticarias: pathogenesis – a hypothetical model

Stratum corneum

- Shearing force
- Cold
- Heat
- UV

Precursor molecule

Neoallergen

Photoallergen

IgE

Histamine and other mediators
Symptomatic dermographism

- Erythema, axon reflex flare, itching in response to light stroking of the skin
- *cf* simple dermographism in which redness and whealing occur without axon reflex or itching
- Using a pressure of 49g/mm² symptomatic dermographism occurs in 4.2% of the population
Symptomatic dermographism: pathophysiology

- Dermal mast cell population is normal, but reduction by application of potent topical steroids under occlusion reduces mast cell population and skin reactivity.

- Elevated tissue histamine levels are present in involved skin and recent evidence also implicates Substance P.

Symptomatic dermographism : treatment

- Treatment is by low sedation H1 antihistamines, but off–label dosage is often necessary.

- H2 antihistamines are often prescribed as well, but several RCT`s have shown that any benefit is statistical rather than clinically useful.

- Narrow band UVB phototherapy (311 nm UV) may also be effective, especially for pruritus (Borsova JAAD 2008; 59: 752)
Cold urticaria

Variants include:

• Secondary acquired cold urticaria with cryoglobulinaemia

• Cold reflex urticaria: exposure to cold atmosphere causes whealing in covered as well as exposed skin, with a negative local cold challenge test

• Hereditary cold autoinflammatory syndromes (FCAS) with negative cold challenge tests and mutation in CIAS1

• Several other very rare subtypes
Acquired cold urticaria: pathophysiology

- Improved cold contact testing (0-45°C) is enabled by a new validated Peltier effect-based method.

- Cold reactivity can be passively transferred by serum to primates, and IgE has been implicated, suggesting a cold-dependent allergenic skin component.

- An anti-IgE autoantibody has also been implicated (Gruber et al, JID 1988,90: 213).

TempTest, Mlynek, A et al, 2010 BJD 162: 198-200)
Acquired cold urticaria: role of virus infections and IgE

Virus infections including EB and HIV have consistently been associated with cold urticaria, and can cause upregulation of IgE

- Low CD4, reduced TH1 and IFN-γ cause increased TH2 cells
- HIV – 1 protein gp 120 and Tat induce TH2 cytokines, or interact directly with specific receptors on B cells causing increased IgE mRNA
- In either case some of this IgE binds specifically to a putative cold induced antigenic determinant
Cold urticaria : management

• Off – label dosages of 2nd generation H1 antihistamines are often needed
• Omalizumab (Xolair) has been effective in selected intractable cases (Boyce JACI 2006;117)
• Bathing in cool water risks anaphylactoid reactions which may be fatal
• A recently recognised hazard : anaphylactoid reaction due to systemic hypothermia (4°C) in open heart surgery; avoided by normothermic cardioplegia
Cholinergic urticaria

- Affects about 10% of young adults
- About one third are atopic
- Attacks are provoked by heat, exercise and emotion and are short - lived
- Systemic symptoms, especially flushing may occur and peak flow may be impaired

Monomorphic symmetrical pruritic red wheals, occasionally angioedema
Cholinergic urticaria: pathophysiology

Heat
Exercise
Stress
Gustatory

Postganglionic sympathetic cholinergic neurones

• Atropinised skin is non-reactive
• Increased plasma histamine levels and mast cell degranulation
• Rat mast cells express acetylcholine receptors and acetylcholine degranulates rat mast cells

Intermediate substance eg protease? (Eftekhari et al BJD 1980)

Sweat gland

Histamine and other mediators
Cholinergic urticaria : autologous sweat and serum reactions

Recent work *(Fukunaga et al JACI 2005; 116: 397-402)* has suggested that cholinergic urticaria are reactive to autologous sweat and can be divided into 2 subtypes :

- Type 1 shows strong reactions to autologous sweat, satellite wheals to id acetylcholine and negative reactions to autologous serum

- Type 2 shows a weak reaction to autologous sweat, a positive reaction to autologous serum and no reaction to acetylcholine

Positive autologous sweat tests have recently been reported in atopic eczema *(Hide et al 2002)* which links cholinergic urticaria and atopy and sweat from cholinergic urticaria patients releases histamine from autologous basophils
Cholinergic urticaria: pathophysiology

Heat, exercise, stress, gustatory

Postganglionic sympathetic cholinergic neurones

Ach

Sweat gland

• ID autologous sweat causes urticarial reaction and releases histamine from autologous basophils

Histamine and other mediators
Cholinergic urticaria: diagnosis

- The diagnosis is clinical and based upon history and challenge testing: usually hot bath, exercise

- Intradermal acetyl choline / methacholine ID testing shows low specificity

- No laboratory investigations are warranted
Cholinergic urticaria: treatment

- H1 antihistamines, often in off-label dosages, are usually effective
- Systemic anticholinergics are usually only effective in toxic dosages
- RCT’s have shown the effectiveness and safety, especially in male patients, of attenuated androgens based upon findings of reduced serum protease inhibitors
- Omalizumab has been used successfully in selected cases
Solar urticaria

- Whealing occurs within 5 min of sun exposure, and fades within 2h
- Action spectrum : 280 – 700nm
- Angioedema and anaphylactoid symptoms can occur
- Prognosis : 5-10y duration
Solar urticaria: pathophysiology

- Reactivity can be passively transferred

- Type 1: abnormal chromophore only occurs in skin and serum of solar urticaria patients and evokes specific IgE antibodies

- Type 2: a normal chromophore evokes specific IgE antibodies
Solar urticaria: pathogenesis

- Irradiation (280-700nm)
- Precursor chromophore
- Photoallergen (type 1 or type 2)

Photoallergen specific IgE

Histamine and other mediators
Solar urticaria: diagnosis

- Most referrals turn out to be PLE (lesions last > 48h, cf solar urticaria < 2h)

- Can be manifestation of erythropoietic protoporphyria

- Phototesting (natural sunlight, solar simulator lamp) confirms

- Monochromator testing establishes action spectrum, enables focussed photoprotection
Solar urticaria: treatment

- H1 antihistamines + photoprotection

- Inhibition spectra and tolerance treatment: wavelengths greater than the action spectra diminish solar urticaria – probably by inactivating photoallergens

- Tolerance treatment has proved effective though necessitating maintenance

- Plasmapheresis and most recently omalizumab have been used in selected cases