Study of activation of the coagulation cascade in patients with chronic spontaneous urticaria

Thesis

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By

Mustafa Gamil Mahmoud Shams El dine
MB.,Bch., (Ain Shams university)

Under supervision of

Professor Dr/Maged Mohamed Refaat

Professor of Internal Medicine, Allergy and Clinical Immunology.
Faculty of Medicine-Ain Shams University.

Dr/Mohamed Nazmy Farres

Assistant Professor of Internal Medicine, Allergy and Clinical Immunology.
Faculty of Medicine-Ain Shams University.

Dr/ Nermine Abd Elnour Melek

Assistant Professor of Internal Medicine, Allergy and Clinical Immunology.
Faculty of Medicine-Ain Shams University.

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ACE	**angiotensin-converting enzyme**
ADP	**adenosine diphosphate**
APST	**autologous plasma skin test**
APTT	**activated partial thromboplastin time**
ASST	**autologous serum skin test**
AST	**Autologous serum therapy**
BMI	**Body Mass Index**
CAU	**chronic autoimmune urticaria**
CIU	**chronic idiopathic urticaria**
COAT	**Collagen And Thrombin**
COX-2	**cyclo-oxygenase-2**
CSU	**Chronic spontaneous urticari**
CRP	**C REACTIVCE ROTIEN**
CU	**Chronic urticaria**
DIC	**disseminated intravascular coagulation**
ECM	**extracellular matrix**
ELISA	**Enzyme linked immunosorbent assay**
ESR	**Erythrocyte sedimentation rate**
FcεRI	**functionally active autoantibodies to the high affinity IgE receptor**
FSPs	**fibrin split products**
FVIIa	**activated factor VII**
GpIb	**glycoprotein Ib**
IL-1	**interleukin-1**
INR	**the international normalized ratio**
IQR	**interquartile range**
IU	**International units**
IVIg	**intravenous immunoglobulin**
NSAIDs	**nonsteroidal anti-inflammatory drugs**
PAIs	**inhibitors of plasminogen activator**
PARs	**protease activated receptors**
PAs	**plasminogen activators**

PDGF	**platelet-derived growth factor**
PGI2	**prostacyclin**
PT	**Prothrombin Time**
PTT	**partial thromboplastin time**
PUVA	**Phototherapy with ultraviolet light**
QoL	**quality of life**
SD	**standard deviation**
TF	**tissue factor**
TFPI	**tissue factor pathway inhibitor**
TGF-β	**Tumor Growth Factor Beta**
TNF	**tumor necrosis factor**
TNF α	**Tumor Necrosis Factor Alpha**
t-PA	**tissue- type plasminogen activator**
TxA2	**thromboxane A2**
u-PA	***Urokinase-like PA***
UV	**Urticarial vasculitis**
vWF	**von Willebrand factor**

Introduction

Chronic urticaria (CU) is a relatively common disorder with an estimated 0.5% lifetime prevalence in the general population. The condition can be severe and debilitating and may impair quality of life ***(Sagi et al., 2011).*** This disease is characterized by at least 6 weeks of almost daily episodes of intensely pruritic cutaneous wheals that typically last less than 24 hours and are not associated with residual pigmentation ***(Saavedra and Sur, 2011).***

In spontaneous urticaria, the most common type, the hives seem to arise without provocation ***(Maurer and Grabbe, 2008).***

Studies carried out on chronic spontaneous urticaria during the last two decades have depicted an autoimmune pathogenesis mediated by functionally active autoantibodies to the high affinity IgE receptor (FcεRI) or to IgE, which are able to induce histamine release from basophils and mast cells. However, such a mechanism can explain the disease in less than 50% of patients ***(Ghosh, 2009).***

Asero et al., 2007 have shown that an additional pathogenic mechanism in patients with chronic urticaria is the activation of the coagulation cascade. They described enhanced thrombin generation in patients with CU. They argued that thrombin generation is accelerated by the increase of tissue factor expressed in dermal tissues via the activation of extrinsic coagulation. They advocated that the accelerated generation of thrombin would then activate mast cells and increase endothelial permeability ***(Asero et al., 2006).***

However, Kaplan and Greaves 2009 recently challenged this scenario on several points: (i) lack of evidence for thrombin-dependent activation of human mast cells, (ii) immediate inactivation of thrombin by plasma inhibitors, (iii) possible presence of yet to be defined plasma factor other than thrombin that leads to an increase in endothelial permeability.

Aim of the study:

The present study aims to assess the possibility of activation of the coagulation cascade in patients with chronic spontaneous urticaria, and to correlate this activation with the severity of chronic urticaria.

Chronic urticaria

Introduction

Urticaria (from the Latin word urtica, (to burn) orhives), are a kind of skin rash notable for dark red, raised, itchy bumps ***(OED, 2000).***

It affects 15-20% of the population once or more during a lifetime ***(Caliskaner et al., 2004).***

In around 30% patients of urticaria, attacks often recur for months or years. Chronic urticaria (CU) is definedby recurrent episodes occurring at least twice a week for 6 weeks***(Clive et al., 2002).***

Females are more commonly affected than males ***(Deacock, 2008).***

Establishing the cause of CU is difficult and at times almost impossible. This renderscause specific management difficult and frustration on part of the patient and the treating physician. Also, CU is associated with lower quality of life (QoL) levels ***(Ugu et al., 2008).***

Recent advances in our understanding of its pathogenesis include the finding of autoantibodies to mast cell receptors in nearly half of patients. This possibility of an autoimmune basis to chronic idiopathic urticaria (CIU) is now widely explored ***(Sharma et al., 2004).***

Urticaria represents a transient edema within the dermis; the individual urticarial lesions characteristically clear within hours. It is a vascular reaction of the skin, triggered by many known as well as unknown factors that result in liberation of vasoactive substances such as histamine, prostaglandins, and kinins ***(Buss et al., 2007).*** Most lesions of urticaria are small, less than 10 mm, but individual large lesions of 6–10 cm may occur — the so-called giant urticaria. Clinically, urticaria is classified into the acute (duration < six weeks) and chronic (duration > six weeks) types ***(Grattan et al., 2002).***

'Episodic' urticaria, which occurs intermittently but recurrently over months or years, is also recognized ***(Deacock, 2008).***

CU accounts for 25% of urticaria ***(Greaves, 1995).***And the prevalence of CU is 0.1%-0.6% ***(Gaig et al, 2004).*** Almost 40% of CU patients continue to experience urticarial wheals 10 years later ***(Baiardini et al., 2003)***.

CU has detrimental effects on the quality of life (QOL) and is associated with poorer general health and reduced emotional well-being ***(Baiardini et al., 2003)***.

As a result, CU has a large impact on society in terms of healthcare costs ***(Delong et al., 2008).*** Patients with refractory CU do not respond to standard treatments with antihistamines or

additional immunomodulators that are, in a few cases, unsafe when used for prolonged times.

CU is a heterogeneous disorder and includes idiopathic, autoimmune, and physical urticaria and vasculitis ***(Grattan et al., 2002).*** For more than 50% of patients with CU, the underlying cause has not been identified ***(Greaves, 2003).***

However, up to one-third of patients with chronic idiopathic urticaria have autoantibodies to FcεRI (a high-affinity receptor for IgE), and about 10% have IgE autoantibodies These autoantibodies can cause mast cell degranulation, and most CU symptoms result from the degranulation of skin mast cells ***(Sabroe et al., 2002).***

***Histopathology*:**

The histological appearance of the skin in CIU resembles that of a late phase reaction.Although the infiltrate in patients with CAU is characterized by more prominent granulocyte infiltrate than that of non-autoimmune patients, the frequency of other infiltrating cells is similar in both groups, although there is a slight increase in serum tryptase and cytokines in CAU patients. These small differences are too insignificant to be used as a diagnostic tool ***(Grattan et al., 1990).***

Pathophysiology:

The mast cell is believed to be the major effector cell in most forms of urticaria, though other cell types may be involved. Degranulation of mast cells with release of histamine is central to the development of wheals and angioedema. Urticaria is due to a local increase in permeability of capillaries and venules. These changes are dependent on activation of the cutaneous mast cells, which contain a range of mediators predominantly histamine. The mast cells respond with a lowered threshold of releasability ***(Khalaf et al., 2008).***

Vascular permeability in skin is produced by the interaction of both H_1 and H_2 histamine receptors. Activation of H_1 receptors in the skin induces itching, flare, erythema, whealing and contraction of smooth muscle in respiratory and gastro-intestinal tract. Activation of H_2 receptors contributes to erythema and whealing in the skin. Chronic autoimmune urticaria is caused by anti-FcåRI and less frequently, by anti-IgE autoantibodies that lead to mast cell and basophil activation. A few preclinical investigations have demonstrated an upregulation of TNF-α in patients with CIU. This is in contrast to acute urticaria where TNF-α does not appear to play as important of a role in the inflammatory response. This may explain why patients with CIU do not typically respond to usual therapies for acute urticaria. It