Etiopathogenesis of Chronic Spontaneous Urticaria: Immunological Overview and Differential Diagnosis

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Abstract

Urticaria is an inflammatory skin disorder that affects up to 20% of the world population at some point during their life. It presents with wheals, angioedema or both due to activation and degranulation of skin mast cells and the release of histamine and other mediators. Mast cells have a key pathogenetic role in the The pathophysiology of urticaria and can be activated by different mechanisms. The most wellknown activation mechanism is the contact with an agent that induces a hypersensitivity reaction of the I type with production of IgE that binds to FcεRI receptors. A new exposure to the trigger factor induces the receptor cross-linking and the activation of the intracellular signaling resulting in mediator's production. The first indication that urticaria could have an autoimmune basis, with an intrinsic immune imbalance, excluding extrinsic factors as the cause, comes from the so-called "autologous serum skin test"(ASST), in which by intradermal injection of the serum of the CU patient, an erythematous papule is produced at the injection site.It is generally believed now that two types of autoimmunity (type I and type II) contribute to the pathogenesis of CSU, which are mediated by IgE autoantibodies and IgG autoantibodies, respectively. Autoantibodies against IgE or FcεR1 are the most often present circulating antibodies in CSU patients who are ASST positive, accounting for about 40% of all CSU patients. Of the two, anti-FcεRI antibodies are likely to be more prevalent. Dermal MCs and basophils both have the FcεRI receptor on their surface, and autoantibodies to this receptor can cause persistent activation and degranulation of both cells in a way that is IgE-independent. on the other hand, IgG-anti IgE antibodies may bind to and crosslink receptor-bound IgE on the surface of MCs and basophils, resulting in the activation and degranulation of these cells.

Keywords: Chronic Spontaneous Urticaria

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Introduction

The name urticaria is derived from the common European stinging nettle *Urtica dioica* and dates from the 18th century when Cullen and Batemen likened the stinging and burning to that of a nettle sting [1].

Urticaria is an inflammatory skin disorder that affects up to 20% of the world population at some point during their life. It presents with wheals, angioedema or both due to activation and degranulation of skin mast cells and the release of histamine and other mediators [2].

It is more common in people with atopy, but it affects all races and both sexes [3]. However, it appears to be more common among adults, with women affected more than men. The average age of patients suggests that the condition typically begins in the third to fifth decade of life [4].

Clinical features:

Urticaria is characterized by the sudden appearance of hives (wheals), angioedema, or both [5]. Typical hives have three features: (i) a sharply circumscribed superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema; (ii) an itching or sometimes burning sensation; (iii) a fleeting nature, with the skin returning to its normal appearance, usually within 30 min to 24 h. Angioedema is characterized by (i) a sudden, pronounced erythematous or skin- colored deep swelling in the lower dermis and subcutis or mucous membranes; (ii) tingling, burning, tightness, and sometimes pain rather than itch; (iii) a resolution slower than that of wheals (can take up to 72 h) [6]. Angioedema in patients with urticaria most commonly occurs in the face (lips, eyes), and it does not occur in the gastrointestinal tract or the airways [7].

Classification:

The spectrum of clinical manifestations of different urticaria types and subtypes is very wide. Additionally, two or more different subtypes of urticaria can coexist in any given patient. Urticaria is commonly classified, based on its duration, as acute and chronic. In acute urticaria (AU), wheals and/or angioedema occur for less than 6 weeks. In chronic urticaria (CU), wheals and/or angioedema occur for more than 6 weeks. Chronic urticaria can come with daily or almost daily signs and symptoms or an intermittent/ recurrent course. [8].

Urticaria is further subclassified as spontaneous or inducible. In patients with spontaneous urticaria, acute or chronic, the development of wheals and angioedema is unprompted and unpredictable. In patients with inducible urticaria, wheals and/or angioedema occur only in response to specific and definite triggers acting on the skin [9].

Table 1: Classification of urticaria [9].

Type	Subtype	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Wheals and/or angioedema < 6weeks.
	Chronic spontaneous urticaria	Wheals and/or angioedema > 6weeks.
Type	**Subtype**	**Precipitating factor**
Inducible urticaria (Physical urticaria)	Cold urticaria	Cold objects/air/ fluids/wind.
	Delayed pressure urticaria	Vertical pressure (wheals in 3-12 h)
	Heat urticaria	Localized heat
	Solar urticaria	UV and/or visible light
	Dermographic urticaria	Mechanical shearing force (wheals in 1-5 min)
	Vibratory urticaria	Vibratory forces e.g., pneumatic hammer (wheals within 1-2 h)
Other Types	Aquagenic urticaria	Water
	Cholinergic urticaria	Increase body core temperature (due to exercise, spicy food)
	Contact urticaria	Substance Contact
	Exercise induced urticaria	Physical exercise

Acute urticaria(AU):

Acute urticaria is classified as hives of less than 6 weeks duration and accounts for up to 56 % of cases of urticaria. Lesions are short-lived, lasting less than 24 hours but can return [10]. The most common causes of acute urticaria (with or without angioedema) are medications, foods, viral infections, stress, parasitic infections, insect venom, and contact allergens (e.g., latex) [11].

Medications known to commonly cause urticaria (with or without angioedema) include antibiotics (particularly beta lactams and sulfonamides), non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), opiates and narcotics. The predominant foods that cause urticaria are milk, eggs, peanuts, tree nuts, fish, and shellfish. Acute urticaria should be differentiated from anaphylaxis which has similar triggers including food, medication, and insect stings; however,

treatment approaches will be different. In approximately 50% of patients with acute urticaria, the cause is unknown and the condition is referred to as acute spontaneous urticaria (ASU) [12].Up to 36% of patients with ASU can progress to chronic spontaneous urticaria (CSU) [13].

Chronic urticaria(CU):

Urticaria is recurrent, with signs and symptoms recurring most days of the week for six weeks or longer [3]. Chronic urticaria (CU) affects about 1% of the world population of all ages, mostly young and middle-aged women. It usually lasts for several years (> 1 year in 25–75% of patients) and often takes > 1 year before effective management is implemented. It presents as chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU) or both in the same person. [14]. CSU is much more common than CIU.[6]

1-Chronic inducible urticaria(CIndU):

Among chronic urticaria, about 5–25% of patients have CIndU and it is most commonly seen in young adults. CIndU has a longer disease duration than chronic spontaneous urticaria (CSU) and wheals are shorter lasting than CSU. [15].According to the current international classification, there are two types of CIndU: physical urticarias and non-physical urticarias [8].

Physical CIndUs:

Physical urticaria is defined by the ability of a physical stimulus to reproducibly elicit urticarial lesions and can be further divided into many subtypes depending on the physical stimulus [16]:

Symptomatic dermographism:

Symptomatic dermographism is also known as urticaria factitial or dermographic urticaria. It is the most common type of CIndU. It is characterized by strip-shaped itchy wheals observed on areas that are exposed to rubbing, scratching, and scrubbing. Lesions are itchy and/or burning. Shear force is the trigger for symptomatic dermographism. It may also be provoked after friction with a solid object, right clothes, and bedsheets [15].

Cold urticaria:

Cold urticaria is characterized by the appearance of wheals after contact with cold or cooling air, surfaces, or liquids. The symptoms of cold urticaria include erythema, itching, and wheals or angioedema. It may rarely be associated with anaphylaxis [17].

Heart urticaria:

Heat urticaria is characterized by the appearance of wheals, itchy erythema after contact with warm air, surfaces, and liquids [18]. Angioedema may also be seen. Heat urticaria is one of the rarest types of CIndU. Heat urticaria can be localized or generalized [19].

Delayed pressure urticaria:

Delayed pressure urticaria is a rare form of chronic inducible urticaria.

It usually coexists with chronic spontaneous urticaria [20]. In delayed pressure urticaria, skin exposure to vertical pressure is the relevant trigger, e.g. pressure from the shoulder straps of heavy bags, tight shoes, or prolonged sitting. Patients typically develop erythematous angioedema-like swellings, not wheals, and these swellings develop hours after exposure to pressure, rather than fast. Also, these swellings typically persist for several hours, in some patients for several days [7].

Solar urticaria:

In solar urticaria, exposure to UV and/or visible light is the relevant trigger, and skin responses are characterized by itchy wheals that occur within minutes at exposed skin sites [7].

Vibratory urticaria, or vibratory angioedema:

This extremely rare variant of physical urticaria typically presents with angioedema immediately developing after exposure to local vibration [21].

Non-physical CIndUs:

Cholinergic urticaria:

Cholinergic urticaria (ChU) is triggered by a sudden increase of body core temperature, e.g., induced by exercise/exertion, fever, hot baths or showers, emotional stress, hot or spicy foods, and drinks. Its prevalence is higher in young adults and peaks in winter in some patients [22].

A distinct sign of ChU are extensive flares of short-lived, pruritic, tiny (up to 5–6 mm) wheals, so-called pinpoint wheals. Recent studies demonstrated a lack of acetylcholinesterase in eccrine gland epithelial cells and a decreased expression of the cholinergic receptor M3 (CHRM3), probably due to an autoimmune reaction to eccrine sweat glands and/or acetylcholine receptors, resulting in increased tissue levels of acetylcholine that stimulates mast cells degranulation. [23].

Cholinergic urticaria should be distinguished from exercise-induced anaphylaxis which involves the development of systemic symptoms . Adrenergic urticaria is also described as pin-sized wheals but unlike cholinergic urticaria, it is elicited by stress and can by treated with propanolol [24].

Contact urticaria:

Upon contact with the provoking substance, contact urticaria immediately manifests with wheals that disappear within a few hours. The wheals are provoked by either IgE-mediated or non-immunologic mechanisms [25].

Common eliciting factors include foods, plant components (esp. sap, leaves, etc.), latex, drugs, cosmetics, industrial chemicals, animal products, or textiles [26]. Thus, contact urticaria should be

recognized as an occupational skin disease, e.g., in food processing workers, healthcare professionals, and hairdressers [27].

Aquagenic urticaria:

Aquagenic urticaria is a rare variant of CIndUs and shares features of both physical urticarial and contact urticaria. Patients exhibit folliculocentric wheals of 1–3 mm diameter and surrounding larger flares within 20–30 min after skin contact to water, sweat, or tears [28].

2- Chronic spontaneous urticaria(CSU):

Definition:

Chronic spontaneous urticaria (CSU) is defined as the spontaneous daily, or almost daily, occurrence of itchy hives (wheals), angioedema, or both, lasting for 6 weeks or more, with no apparent external trigger [8]. Angioedema is experienced by 40%–50% of patients with CSU. However, around 10% of patients report angioedema as their primary symptom [29].

It affects 1–2% of the general population, and it is more frequent in women and in patients older than 20 years. It represents more than 60% of all cases of CU. [30]. CSU presents a major burden of disease for patients and society with a significantly diminished quality of life [31].

Etiopathogenesis of CSU:

Mast cells have a key pathogenetic role in the The pathophysiology of urticaria and can be activated by different mechanisms .The most wellknown activation mechanism is the contact with an agent that induces a hypersensitivity reaction of the I type with production of IgE that binds to FcεRI receptors. A new exposure to the trigger factor induces the receptor cross-linking and the activation of the intracellular signaling resulting in mediator's production [32].

When mast cells are triggered to degranulate, they discharge cytoplasmic granules. These granules contain histamine, proteases, and other mediators of inflammation that activate sensory skin nerves (itch, skin burning, pain), dilate skin blood vessels (erythema, hyperthermia), and induce plasma extravasation (edema and influx of basophils, neutrophils, eosinophils, and other immune cells). The action of histamine on its H1 receptor plays a crucial role in the development of urticaria signs and symptoms [7].

CSU is recognized as a chronic inflammatory condition characterized by the abnormal activation and degranulation of MCs and basophils [33]. Though numerous cells (MC, basophil, eosinophil, T cell, B cell, endothelial cell, and so on) and mediators are postulated to play a role in the pathogenesis of CSU, skin MC is the well-acknowledged dominating effector cell followed by basophil. Nevertheless, mechanisms involved in the activation and degranulation of MCs are still poorly understood. Over the past few years, several mechanisms were widely investigated and indicated as important participants in the pathophysiology of CSU, which might be roughly divided into autoimmunity-related and non-autoimmunity-related mechanisms [27].

Autoimmunity:

The first indication that urticaria could have an autoimmune basis, with an intrinsic immune imbalance, excluding extrinsic factors as the cause, comes from the so-called "autologous serum skin test"(ASST), in which by intradermal injection of the serum of the CU patient, an erythematous papule is produced at the injection site [34]. It is generally believed now that two types of autoimmunity (type I and type II) contribute to the pathogenesis of CSU, which are mediated by IgE autoantibodies and IgG autoantibodies, respectively [35].

Type I autoimmunity:

Type I autoimmunity, also known as autoallergy, is based on the successful detection of IgE targeting autoantigens in patients with CSU. More than 20 years ago, IgE anti-thyroid peroxidase (TPO) was discovered as an antibody targeting autoantigen in a proportion of patients with CSU [36]. Since then, IgE anti-TPO and IgE anti-dsDNA in CSU were noted and their connections with the pathogenesis of CSU were investigated [37].

Schmetzer et al. [38] further performed a screening of these IgE-form autoantibodies in serum of patients with CSU using protein microarray analysis. They screened out more than 200 IgE anti-autoantigens and identified IgE anti-IL-24 as a specific and functional biomarker in patients with CSU, which is associated with disease activity. Soon afterwards, another study found an increased expression of IL-24 in peripheral blood mononuclear cells (PBMCs) and in local urticarial wheals in a subset of CSU patients, yet no correlation between IL-24 expression and autoimmune status was indicated [39].

Furthermore, reduction of sera IgE anti- IL-24 was suggested as partly contributing to the therapeutic effect of autologous serum therapy [40]. In addition to direct detection of IgE autoantibodies and confirmation by functional tests, the good therapeutic effect of omalizumab in moderate-to-severe CSU indirectly validated the role of IgE in CSU to some extent.IgE autoantibodies bonded to the high-affinity IgE receptors (FcεRI) on MCs result in cross-linking of FcεRI-bound IgE autoantibodies and corresponding autoantigens, which triggers a series of biochemical events that culminate in MC degranulation. [41]

Type II autoimmunity:

Autoantibodies against IgE or FcεR1 are the most often present circulating antibodies in CSU patients who are ASST positive, accounting for about 40% of all CSU patients. Of the two, anti-FcεRI antibodies are likely to be more prevalent. Dermal MCs and basophils both have the FcεRI receptor on their surface, and autoantibodies to this receptor can cause persistent activation and degranulation of both cells in a way that is IgE-independent. on the other hand, IgG-anti IgE antibodies may bind to and crosslink receptor-bound IgE on the surface of MCs and basophils, resulting in the activation and degranulation of these cells [42].These autoantibodies can also activate the classical complement pathway, with the generation of anaphylatoxins such as fractions

C5a and C3a, which bind to its receptor in mast cells and induce their activation and degranulation [43].

The downstream mechanisms after activation of MC or basophil in an autoimmune way which lead to degranulation have also been investigated. One of the mechanisms is the FcεRI-dependent signaling pathway consisting of Src family kinases (Lyn and Fyn), spleen tyrosine kinase (Syk), and a line of downstream pathway molecules [44].

Once FcεRI aggregation happens, Lyn and Fyn transphosphorylate the immunoreceptor tyrosine-based activating motif (ITAM) within FcεRI β- and γ-subunits, subsequently promoting the activation and recruitment of Syk to ITAM, and then propagating the signals through recruitment of downstream secondary molecules including those involved in the phosphoinositide-3 kinase (PI3K) pathway. This process finally results in the mobilization of intracellular calcium and degranulation [45].

Bruton's tyrosine kinase (BTK), a downstream signal transduction molecule, was found to further upregulate the signaling pathways [46]. Oppositely, Src homology 2-containing inositol phosphatases, SHIP-1 and SHIP-2, were recruited to the phosphorylated FcεRIβ upon stimulation, serving as downregulators of this process [47]. In about half of patients with CSU, mast cells isolated from peripheral blood can spontaneously degranulate and release histamine upon FcεRI-mediated IgE sensitization, and a corresponding higher level of Syk and lower level of SHIP was found in these CSU patients [48].

The prevalence of several other autoimmune illnesses is higher among CSU patients. These include rheumatoid arthritis (RA), diabetes, hypothyroidism, hyperthyroidism, and Sjogren's syndrome. Patients with CSU frequently have IgG anti-thyroid antibodies [43].

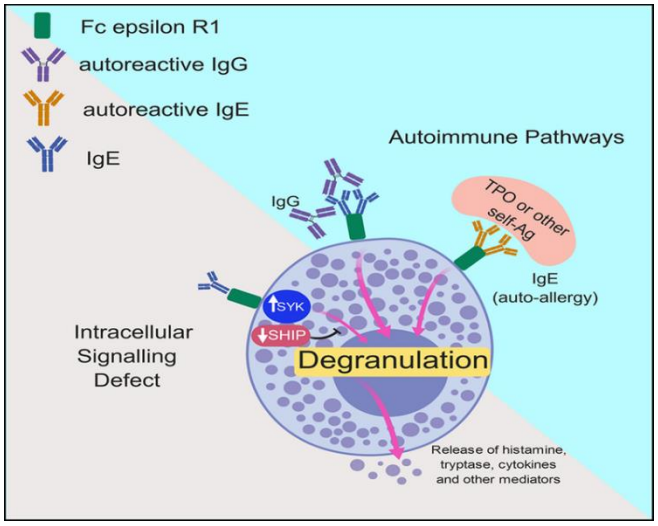

Figure (1): Model of the mechanisms underlying chronic urticaria [42].

Non-autoimmunity:

Whereas autoantibodies are present in only a proportion of patients with CSU, mechanisms other than autoimmunity Coagulation cascade was postulated to take part in the pathogenesis of CSU. This was partly supported by the observation of a higher positive rate of autologous plasma skin test (APST) than ASST (86% vs. 53%) in patients with CSU [49]. Furthermore, elevation of several coagulation biomarkers, such as plasma prothrombin fragment F1 + 2, activated factor VII (FVIIa), and D-dimer, was indicated to be associated with active cases or severe exacerbation of CSU in a line of studies [50].

Besides, an observation that plasma levels of D-dimer turned out to be normal during CSU remission further confirmed the role of clotting process in CSU [51]. Recent studies have evaluated the efficacy of anticoagulant therapy (e.g., heparin, warfarin) and antifibrinolytic therapy (e.g., tranexamic acid), respectively, in refractory CU, reflecting a potentially important role of the coagulation cascade in CSU [52].

The relation between vitamin D deficiency and the pathogenesis of CSU has been reported over the past 30 years [53]. Vitamin D is proved to be endowed with immunoregulatory and anti-inflammatory properties [54]. In CSU, noteworthy lower serum vitamin D levels were reported in most studies [55]. Vitamin D supplementation in a high dosage for 4–12 weeks was suggested to be useful to alleviate disease activity in some CSU patients [56].

The underlying mechanism of vitamin D's role in CSU remains unclear. Nevertheless, vitamin D receptor (VDR) expressed by MCs, which forms complexes with Lyn to inhibit the binding of Lyn to FcεRI β chain and myeloid differentiation primary response 88 (MyD88), was demonstrated as a major molecule in this process. Briefly, vitamin D downregulates the phosphorylation of Syk and inhibits MyD88-dependent signaling pathway by kidnapping Lyn through VDRs, thus maintaining MC stabilization. VDRs were also found to repress the expression of tumor necrosis factor-α (TNF-α) in MCs [57]. In addition, a latest research indicated that 25-hydroxyvitamin D could suppress the generation of vascular endothelial growth factor (VEGF) by MCs [58].

Regardless of acute or chronic urticaria, infections have been postulated to be pathogenic factors. Among various pathogens, chronic infection of Helicobacter pylori (Hp) has been well-studied; however, its potential correlation with CSU remains an ambiguous and contradictory causative property [59]. A recent meta-analysis enrolling 22 studies concluded that Hp might have a relationship with the occurrence and persistence of CSU, and Hp eradication therapy could partly resolve CSU symptoms [60]. An 21–35 kDa Hp associated protein component was regarded as the potential pathogenic factor devoting to the association between chronic Hp infection and CSU [61].

The association between CSU and other pathogenic species such as Staphylococcus aureus [62], toxocara [63] and hepatitis virus [64] was also analyzed, but only weak evidence was revealed. For

example, serum levels of functional IgE against Staphylococcus aureus enterotoxins (SE-IgE) were significantly higher in CSU patients than in healthy controls, and were shown to be strongly correlated with disease activity in CSU patients [62].

Viral infection can also lead to worsening urticaria symptoms [6]. There is evidence that viral infections such as herpes simplex, norovirus, and HHV-4 and -6 are associated with worsening CSU, though data and understanding of the viral role and relationship with CSU are lacking, despite frequent clinical observations of this association . One virus and its role in the exacerbation of CSU that has been reported frequently in the literature is COVID-19 [65].

Dermatologists have observed that COVID-19 may result in newonset CU and CSU, with researchers hypothesizing that inflammation triggered by COVID-19 can exacerbate CU symptoms via the direct or indirect activation of mast cells and basophils by SARS-CoV-2 [66]. Furthermore, studies (2022–2023) have shown that COVID-19 vaccination can trigger disease exacerbation and case reports suggest new-onset CSU in some patients [67, 68].

Emotional factors may contribute to the onset and exacerbation of CSU in part of patients. A series of early observations that stress could exacerbate allergic skin wheal responses in patients with atopic dermatitis encouraged following researches [69]. Growing evidence has shown that stress exacerbates the symptoms of CSU by releasing neuropeptides such as substance P that function through Mas-related G protein–coupled receptor-X2(MRGPRX2) expressed on skin MCs [70].

Non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, may exacerbate allergic symptoms in patients with CSU. A recent study suggested that aspirin might promote the phosphorylation of Syk when FcεRI-dependent signaling pathway was activated, and patients with CU tended to be more sensitive to aspirin compared with healthy controls [71].

Differential diagnosis of Urticaria:

Recurrent wheals without angioedema:

Patients with recurrent wheals without angioedema should be checked for autoinflammatory conditions and urticarial vasculitis as the cause of their symptoms. Autoinflammatory disorders are rare multisystemic, interleukin-1-driven inflammatory diseases mediated primarily via innate immune responses. Clinically, they often manifest with wheals, recurrent bouts of unexplained fever, and pain of the joints, muscles, and/or bones. This is usually accompanied by a general sense of ‘feeling ill’ [72].

Most importantly, hereditary periodic fever syndromes, in particular the cryopyrin- associated periodic syndromes (CAPS: familial cold autoinflammatory syndrome [FCAS], Muckle–Wells syndrome [MWS], and neonatal-onset multisytem inflammatory disease [NOMID]), should be looked for by a detailed family history, age of disease onset (<20 years), and genetic testing of the

NLRP3 gene [73]. if applicable, and Schnitzler syndrome (adult onset) should be checked for by serum immune fixation for the detection of monoclonal gammopathy [74].

Urticarial vasculitis (UV) is an important differential diagnosis to consider in patients with recurrent wheals. Patients with UV may also report intermittent joint pain as well as malaise or even fever. UV typically manifests with wheals of longer than 24-h duration. By histopathological assessment of a skin biopsy from a wheal, histological signs such as leukocytoclastic vasculitis with damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations confirm UV [75].

Systemic vasculitic diseases that may present with UV (e.g., lupus erythematosus or Sjögren syndrome) should be ruled out and patients should be screened for antinuclear and extranuclear antibodies where indicated [7].

Recurrent angioedema without wheals:

Recurrent angioedema without wheals should prompt suspicion of bradykinin-mediated angioedema, which can be hereditary or acquired. One of the latter forms of angioedema, that is, angiotensin- converting enzyme inhibitor (ACE-I)-induced angioedema, is readily diagnosed by simply asking patients whether they are taking an ACE-I medication. Angioedema in patients with ACE-I is ACE-I induced, unless proven otherwise [76].

Patients with recurrent angioedema who do not use ACE-I should be asked for a detailed family history and checked for hereditary bradykinin-mediated angioedema (HAE I-III) and angioedema due to acquired C1-inhibitor (C1-INH) deficiency (AAE) [77]. Normal complement C4 levels, normal C1-INH function and protein levels, the absence of C1-INH antibodies and relevant mutations in the C1-INH or factor XII gene, and efficacy of antihistamines, glucocorticoids or adrenaline all argue against HAE or AAE and should prompt suspicion of urticaria (spontaneous or inducible, depending on the relevance of a trigger) as the underlying cause of the recurrent swellings. Antihistamine- resistant angioedema with neither a history of ACE-I intake nor C1-INH deficiency has been classified as idiopathic angioedema by some authors [7].

Other similar clinical conditions:

Urticaria may be confused with a variety of other dermatologic diseases that are similar in appearance and are pruritic or itchy such as atopic eczema, maculopapular drug eruptions, contact dermatitis, insect bites, erythema multiforme& Pityriasis rosea. Usually an experienced clinician can distinguish urticaria from its mimickers owing to its distinctive appearance, intensely pruritic nature and complete blanching with pressure [78].

Acute urticaria and angioedema should be differentiated from anaphylaxis. Urticaria/angioedema associated with signs and symptoms in organs other than the skin, such as pulmonary (wheezing & cough), gastrointestinal system (vomiting and diarrhoea),nervous system(dizziness and loss of

consciousness) or cardiac symptoms (changes in blood pressure or heart rate) can occur in patients with anaphylaxis [79].

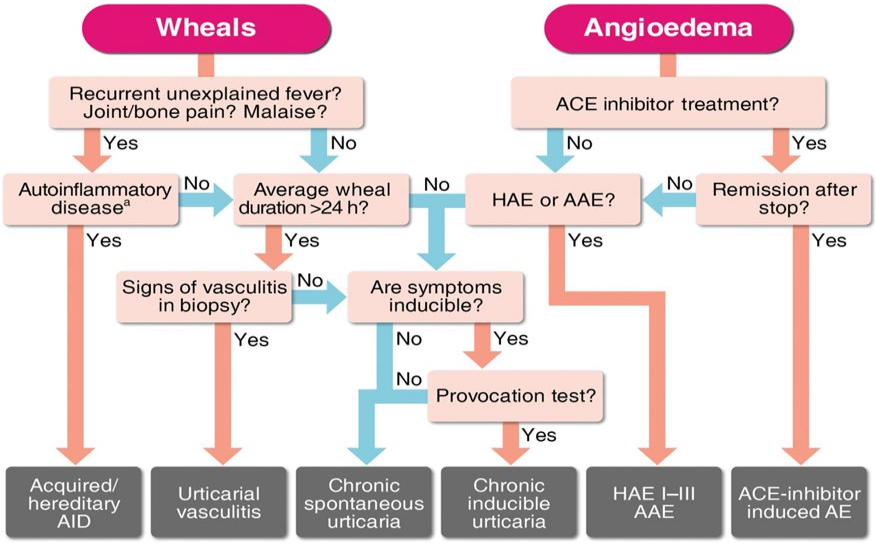

Figure (2) Differential diagnosis of Urticaria [80].

No Conflict of interest.

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