Karolinska Dermatology Symposium 2014 "URTICARIA and ANGIOEDEMA – An Update on Pathogenic Mechanisms and Therapy"

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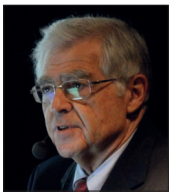
The Karolinska Dermatology Symposium 2014 was made possible by a successful collaboration between the Dermatology Unit at Karolinska University Hospital and the pharmaceutical company Novartis. During the day the participants got a complete and well-structured review of urticaria and angioedema. The talks were divided into 3 categories: pathomechanisms, hereditary angioedema and therapy.



Dr *Allen Kaplan* from the Medical University of South Carolina started with a talk on "Basic pathomechanisms in urticaria". He described the *wheal and flare*-reaction of urticaria where the *wheals* are caused by vasodilation and an increased vascular permeability in the small venules in the skin and the *flare* is caused by a stimulation of type C unmyelinated afferent cutaneous neurons. Urticaria is divided into acute and chronic urticaria, and chronic urticaria is defined as almost daily symptoms for 6 weeks or more. Chronic urticaria can be further subdivided in inducible and spontaneous urticaria. *Chronic inducible urticaria* (CindU) is triggered by different stimuli, such as cold, heat, pressure, sun light etc., and typically the wheals persist for <2 h and there is a good therapeutic response to antihistamines but not to glucocorticosteroids. In *chronic spontaneous urticaria* (CSU) a triggering factor cannot be identified by the patient but in some patients an autoimmune/autoallergic cause can be identified with an *autologous serum skin test* (ASST) or a *basophil-release test*. There are several factors in serum that can activate the mast cells, such as IgG antibodies against IgE and IgG against the alpha-subunit of the IgE receptor (anti-IgE-rec). There also is an association between CSU and autoimmune diseases such as diabetes mellitus type 1, Hashimotos thyroiditis and vitiligo. In contrast to CindU the single wheal persists longer in patients with CSU, but not longer than 24 h. By different elegant experiments the lecturer has been able to show that anti-IgE-rec caused histamine release is inhibited when the IgE receptors are saturated and is augmented by complement C5 (Fig. 1). Finally, the coagulation system seems to be affected in CSU. In animal studies a release of *tissue factor* from eosinophilic granulocytes and endothelial cells has been observed which activates the extrinsic coagulation. As a working hypothesis a thrombin-mediated activation of basophils and mast cells via the PAR 2 receptor has been suggested.

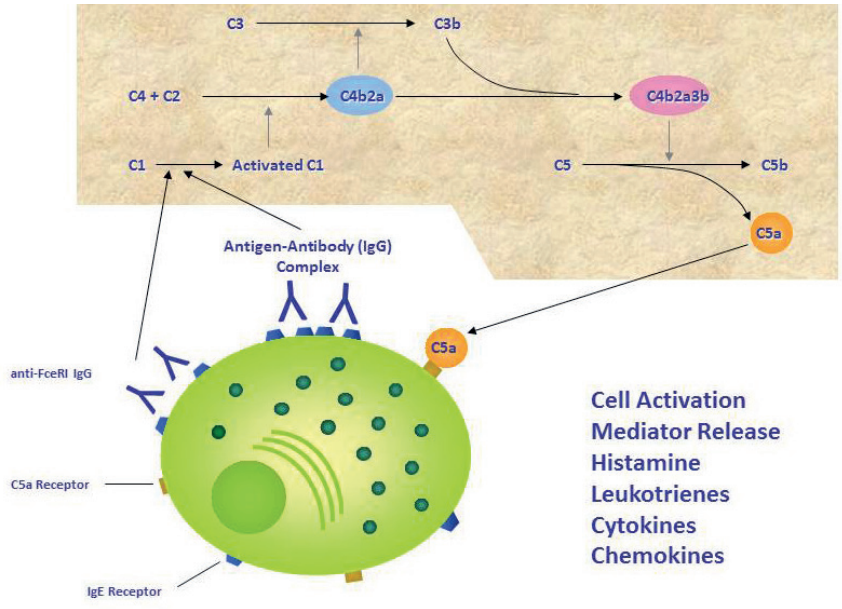


Fig. 1. Physiology and molecular mechanism of autoimmune urticaria. Reproduced with permission from Dr Kaplan.

The next topic of the day was "Red meat allergy and skin symptoms". Professor *Marianne van Hage* from the Karolinska Institute and University Hospital lead us through this topic and reported that researchers have discovered a new food hypersensitivity to red meat during the last couple of years. The allergy is caused by the production of IgE antibodies directed at a carbohydrate epitope called galactos-α-1,3-galactos (α-Gal), that is abundantly expressed in red meat from mammals with the exception of humans and monkeys. The lecturer has investigated red meat allergy in Sweden and has identified 39 patients that reported both allergic symptoms after consumption of red meat and had an elevated titre of IgE against α-Gal. Most patients debuted with red meat allergy late in life and almost all patients got the allergic symptoms one or several hours after the exposure. The allergic symptoms included urticaria in 95% and there was a personal history of an anaphylactic shock in as many as 45% of the patients. Due to the delayed reaction the association to the ingestion of red meat is often difficult to identify. In USA it was observed that the geographic distribution of IgE towards α-Gal was similar to the occurrence of the tick-borne disease *Rocky Mountain spotted fever*, which indicated that tick bites could be relevant in the aetiology of red meat allergy. Therefore, the association between red meat allergy and tick bites from a Swedish tick, *Ixodes ricinus*, was investigated in the Swedish cohort. It was found that almost all patients had been tick bitten and had antibodies against *Ixodes ricinus*. Furthermore, by histopathological examination of ticks, the occurrence of α-Gal could be demonstrated in their gastrointestinal canal. Since the α-Gal epitope is structurally related to blood group B antigen, the distribution of blood groups in the Swedish cohort of red meat allergic patients was investigated and it was shown that 95% had blood group A or O which is significantly different from the distribution of blood groups in the Swedish population.

Next, Professor *Marcus Maurer* from Charité Universitätsmedizin in Berlin told us about "Differential diagnosis and diagnostic work-up in chronic urticaria". He managed to make the audience believe that CSU is a fun and almost easy diagnosis to manage! He started by identifying 3 "musts" in the work up, that is explained in further detail below:

1. Confirm CSU by excluding differential diagnosis.
2. Rule out severe inflammatory disease.
3. Measure disease activity and impact on the patient.

Beyond these musts it is desirable to try to identify the cause in selected patients. Dr Maurer showed the audience a simple and useful algorithm that can be used in No. 1) to exclude differential diagnosis (Fig. 2). With simple questions autoinflammatory syndromes (recurrent fever/malaise, bone- or joint pain?), urticaria vasculitis (duration of a single wheal?) and CindU (can you make your urticaria appear?) can be excluded. In patients who also/only manifest with angioedema,

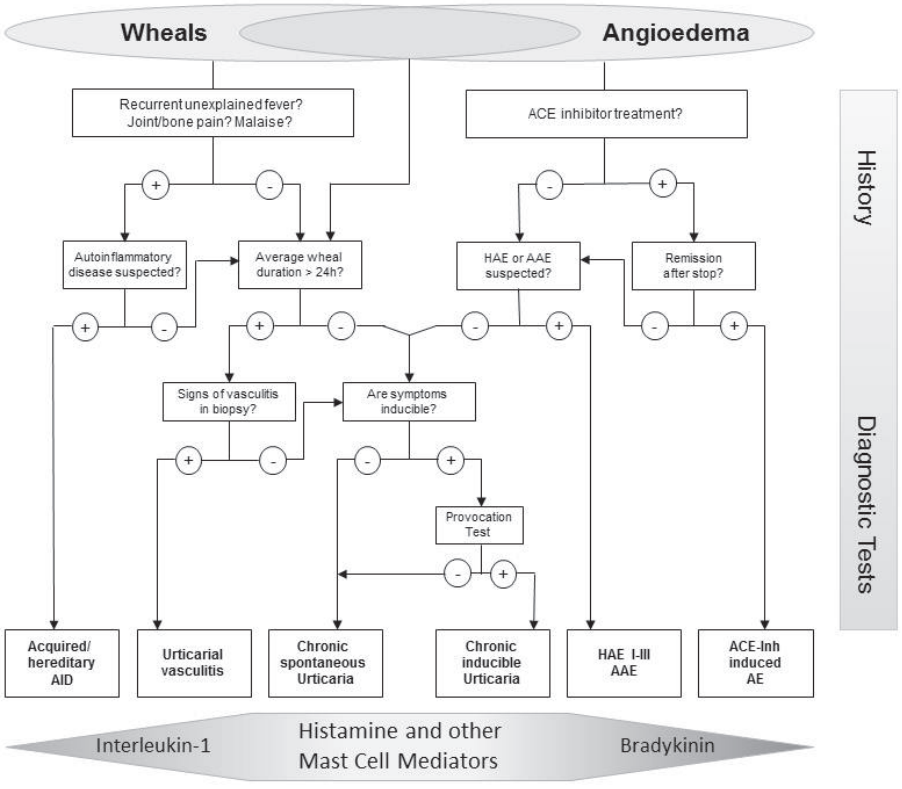


Fig. 2. Diagnostic algorithm for patients presenting with wheals only, wheals and angioedema, and angioedema only. Reproduced with permission from Dr Maurer and RightsLink.

information regarding treatment with ACE inihibitors and hereditary or acquired angioedema (HAE/AAE) is sought for. No. 2) is simply achieved by a blood sample for ESR, CRP and differential blood count. Lastly, the No. 3) "must" consists of measuring disease activity, impact on life quality and symptom control and this is achieved by using different validated questionnaires and physical tests. The lecturer reckons that these measurements are very important since they comprise the only available objective way to measure the effect of the treatment. The disease activity is measured in one or two questionnaires "*Urticaria activity score 7*" (UAS7) and "*Angioedema activity score*" (AAS) depending on the patients symptoms. In CindU, disease activity is measured by various physical tests (such as temperature test or light test), preferably as standardized as possible. Even for the measurement of the impact on the patient's quality of life there are validated questionnaires for urticaria and angioedema, CU-Q_2oL and AE-QoL. *Urticaria control test* (UCT) consists of 4 questions about the last 4 weeks and measure the symptom control. Lastly, for selected patients it can be attempted to identify the cause of CSU. Of the very few patients where a cause can be identified, autoreactivity, infection and intolerance dominate. Dr Maurer's opinion is that there are several advantages to test for autoreactivity with ASST or basofil release test: the patient will know the cause, the doctor can plan the treatment and associated autoimmune diseases can be identified earlier.

After lunch Professor *Carl-Fredrik Wahlgren* from Karolinska Institutet and University Hospital held a talk on "Hereditary angioedema- clinical manifestations and diagnosis". With a typical case Prof. Wahlgren illustrated some of the key characteristics of HAE: transient attacks of oedema in skin and mucosa which debuts before 20 years of age, an absence of urticaria and a presence of a trigger, and most (75–80%) have a relevant family history. The pathophysiology, which is a complex proteolytic cascade, was explained with a paedagogic short movie from *Youtube*. In short, prekallikrein is activated to plasmakallikrein by binding to endothelial cells where activating factors are present, such as factor XII (FXII). Plasmakallikrein then cleaves high-molecular weight-kininogen to liberate bradykinin, which is a peptide hormone that provokes the typical symptoms in HAE: oedema, pain and hypotension. In HAE patients too much bradykinin is released since there is a subnormal activity of C1-inhibitor (C1-INH). HAE is divided into 3 subtypes where type I has a reduced concentration of C1-INH, type II has a suboptimal activity of C1-INH and type III has a normal C1-INH but another mutation in a gene somewhere else in the proteolytic cascade, e.g. in the gene for FXII. Triggering factors for HAE include trauma (accidents, dentist procedures, etc), estrogen exposure (pregnancy, drugs), infections, physical or mental stress or ACE inhibitors. With a diagram Prof. Wahlgren showed us that nearly 50% of HAE patients have one or several attacks per month. It is most common to have symptoms from the skin, closely followed by the gastrointestinal canal but oedema can also arise in lips, tongue, larynx, and urogenital organs. Laryngeal angioedema is most dangerous and occur in about half of the patients during a life time. Unfortunately the laryngeal attacks are unpredictable and can rapidly progress to asphyxia. However, most often they are preceeded by oedema in the face and therefore such symptoms should always be promptly treated. To obtain the diagnosis the doctor can supplement the anamnesis with a blood sample for C4, C1-INH concentration and function and C1q. In selected cases an analysis of FXII could also be interesting but is usually only offered at special research laboratories.

Next, *Thomas Renné* at Karolinska Institutet told us about his research on the pathomechanism of HAE in his talk "Mechanisms of HAE – lessons from animal models". He introduced the term "*plasma contact system*" (PCS) which is the production of bradykinin from the binding of prekallikrein to endothelial cells as described above. The increased activation of PCS in HAE is either due to a decreased activity of C1-INH or an increased activity of FXII. Furthermore, the pathological activation of PCS in HAE also initiates the internal coagulation cascade and interacts with inflammatory- and renin/angiotensin systems. So far, so good, but Prof. Renné has asked himself, why do the symptoms only appear in certain pathological conditions? He hypothesizes that there must exist other precipitating factors beyond the overly sensitive PCS. A common feature of all known substances that can activate FXII is that they are negatively charged macromolecules. One such macromolecule is heparin. Heparin is a highly negatively charged polysaccharide that is found in mast cell granules. It is well known that mediators released by mast cells contribute to an increased vascular permeability and it has been shown that heparin from mast cells both initiate the production of bradykinin through FXII and causes fluid efflux from small capillaries in the skin of mice. The lecturer has also been able to show that in mice with a knock-out of the FXII- or B2-rec (that bradykinin binds to) gene, the heparin-induced fluid efflux is much decreased. Furthermore, when these knock-out mice are exposed to platelet-derived polyphosphate (PolyP), another macromolecule, the same result is obtained. PolyP is ubiquitous in nature and it is also present in mast cell granules. There is also a knock-out mouse for C1-INH (HAE type I) where challenge with IgE, heparin and PolyP induces an exaggerated production of bradykinin and a strongly increased oedema compared to *wildtype* mice. From these findings the lecturer concludes that FXII-initiated bradykinin production is

the main, or perhaps the only, mechanism for tissue oedema induction and that heparin and PolyP from mast cells activates the FXII-driven PCS.

The last talk in module two, "Management and treatment" of HAE was given by *Carl-Fredrik Wahlgren*. He told us that the management and treatment have improved greatly from a better understanding of the disease, new pharmacological treatments, the possibility of self-administered treatments and by the founding of patient organizations. The fundament of the treatment of HAE is to avoid triggers as much as possible. In addition there are different pharmacological treatments that include C1-INH i.v. (Berinert®, Cinryze®, Ruconest®), bradykinin B2R-antagonist s.c. (ikatibant/Firazyr®), androgens (e.g. oxandrolon), tranexamic acid (e.g. Cyklokapron®) and fresh frozen plasma (very rarely). Importantly, antihistamines, glucocorticosteroids and epinephrin have no effect on HAE! The treatment can be administered on demand, as short-term or long-term prophylaxis. On demand treatment with C1-INH or ikatibant is given for acute attacks that result in dysfunction, such as abdominal or laryngeal attacks. Short-term prophylaxis is given before the patient is exposed to known triggers, such as surgical interventions, and consists of C1-INH or androgens. Long-term prophylaxis can be achieved with C1-INH, androgens or tranexamic acid (seldom) and is given to severely afflicted patients. Despite the lack of head-to-head studies comparing different C1-INH the lecturer told us that there probably are differences between them. Berinert® has the quickest onset of effect but Ruconest® get the patients symptom free most rapidly. Moreover, Ruconest® is not extracted from human plasma like the other C1-INH but from rabbit plasma and consequently the patients need to be tested for rabbit allergy at regular intervals. Ikatibant (Firazyr®), a B2-receptor antagonist, is accepted for self-administration in adults and has a good safety and tolerability profile. Androgens increase the production of C1-INH and can be used both as short-term and long-term prophylaxis. Some patients have a good effect but unfortunately there are several unwanted side effects such as virilisation, breast and testicle atrophy, weight gain, hepatitis/cholestasis, dyslipoproteinemia etc. that require regular check-ups.

Allen Kaplan started module 3 with a lecture on "Management and therapy of urticaria". To recommend a treatment for urticaria its effectiveness must exceed the placebo effect that has been shown to be about 30%. The only medicines that have been proven to achieve this are antihistamines, cyclosporine, glucocorticosteroids and omalizumab. Antihistamines are effective in about 50% of the patients. They block the H_1-receptor and thereby inhibit vasodilation, vascular permeability and pruritus. However, since antihistamines and histamine bind to the H_1-receptor competitively the substance that is in the highest concentration locally "wins" and therefore a high dose of antihistamine is often required (up to 4 times the recommended dose) to achieve maximum effect. Regarding glucocortiosteroids there are no clinical studies on the treatment of urticaria but there is comprehensive clinical experience that has shown that >90% respond to systemic treatment. However, high doses are needed for symptom control which makes glucocorticosteroids unacceptable as a long-term treatment considering the side-effects. In the new guidelines, that the lecturer is a co-author to, glucocorticosteroids are only recommended as treatment for acute exacerbations. In contrast, there is relatively strong evidence for the efficacy of cyclosporine in the treatment of urticaria and it has been shown that cyclosporine inhibit histamine release from basophils. Of course cyclosporine has known side-effects that require regular check-ups of primarily creatinine, urea and blood-pressure. Allen Kaplan continued by telling us about the pilot and phase II–III trials he participated in regarding the treatment with omalizumab in chronic urticaria. In summary, omalizumab has been shown to have a good efficacy and a surprisingly rapid onset of action that Dr Kaplan thinks indicates that the drug has to have some other mechanism of action in addition to the already known, i.e. binding of free IgE and down-regulation of IgE-receptors on the mast cell surface. Perhaps there is an unspecific fast desensitization of mast cells when the concentration of IgE decreases? Or maybe the drug neutralizes yet unidentified autoallergens? The lecture ended with a discussion on how patients that do not respond to antihistamines, cyclosporine or omalizumab should be treated. There are a number of medicines that in smaller studies have been shown to have some effect, for example Dapsone, hydroxychloroquine, sulfasalazine, colchicine, methotraxate and IvIg and among these one can choose freely! However, the lecturer advises against from the use of H2-receptor antagonists and leukotriene antagonists.

Marcus Maurer ended this fantastic symposium with his lecture "Is there a role for anti-IgE treatment in chronic urticaria?". Although there are a number of treatments for urticaria the goal of the treatment should always stay the same – to get the patient free of symptoms. In the new treatment guidelines the first step in the treatment of urticaria is to start with second generation antihistamines in recommended dose. About 45% of the patients will then become symptom free. If symptoms remain, the dose should be increased up to 4 times and this will result in symptomatic control in another

20%. Thereafter treatment with one of omalizumab, cyclosporine and leukotriene receptor antagonist is recommended. The lecturer continued with telling us about the rationale for testing omalizumab as treatment of urticaria. Why was an anti-IgE treatment tested as therapy for CSU? CSU is not an allergy, relevant allergens are found in less than one percent of the patients. However, CSU-patients have an increased level of circulating IgE antibodies compared to healthy controls and CSU is also associated with the presence of IgG and IgE directed against thyreoperoxidase (TPO). Therefore the hypothesis was that CSU can be caused by an allergy to the patient's own proteins (autoallergy) that could be cured with omalizumab. The first proof-of-concept study was therefore conducted in a group of patients with IgE-anti-TPO and it showed that 70% of the patients became symptom-free from the treatment. Thereafter 3 phase III studies were conducted and the lecturer introduced two of them in detail. Both the studies "Asteria II" and "Glacial" were multi-national, multi-center, double blinded, randomized studies that included patients with CSU that were symptomatic despite adequate treatment with H_1-antihistamines in standard dose ("Asteria") or H_1-antihistamines in up to 4 times the standard dose, H2-antihistamines and/or leukotriene receptor antagonists ("Glacial"). In both studies omalizumab proved to be effective with a complete or almost complete response (UAS7≤6) in 65.8% and 52.4%. Unfortunately, in both studies the patients relapsed gradually over 2–3 months after the treatment was terminated. Many unselected patients have now been treated with omalizumab at the Dermatology clinic at Charité in Berlin and of the 30 first patients 83% had a complete response, 10% had a partial response and 7% had no effect. In 86% of the patients the treatment was effective already after the first injection and omalizumab also seems to be effective in about 71% of patients with CIndU. In conclusion, omalizumab is a safe and well-tolerated symptomatic treatment that is highly effective against urticaria even when it is resistant to other treatments.