The link between chronic spontaneous urticaria and metabolic syndrome

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Key words
cardiovascular risk; chronic urticaria; chronic spontaneous urticaria; metabolic syndrome; obesity

Summary
Metabolic syndrome (MS) is a cluster of risk factors for cardiovascular disease and is considered a chronic low-level systemic inflammatory condition. Recent preliminary findings have shown an increased prevalence of MS among patients with chronic urticaria (CU) as compared to controls, with a particularly higher prevalence detected in patients with uncontrolled CU. Chronic spontaneous urticaria (CSU) appears to share some pathomechanisms with MS, including a pro-inflammatory state, increased oxidative stress, alterations in adipokine profile and activation of the coagulation system. Further studies are needed to assess the association of MS and its components with CU/CSU and to obtain more precise information regarding epidemiological aspects, clinical significance and implications. The aim of this review is to present the most relevant literature data on the link between CU/CSU and MS.

Introduction

Chronic spontaneous urticaria

Chronic urticaria (CU) is characterized by recurrent wheals, angioedema, or both for at least six weeks. CU can be distinguished into two main groups depending on whether the lesions occur spontaneously [chronic spontaneous urticaria (CSU)] or are induced by specific physical-environmental stimuli [chronic inducible urticaria (CIndU)] (1).

Various aetiological factors and mechanisms have been implicated in the development of CSU, but a specific cause is unidentifiable in most cases. Disease pathogenesis remains incompletely understood, although an autoimmune basis is increasingly being recognized based on the presence of functional histamine-releasing autoantibodies in a subset of patients (2,3). The autologous serum skin test (ASST) is a simple screening tool able to detect autoreactivity related to the presence of circulating histamine-releasing factors of any type, and not only of functional autoantibodies (1). Current evidence supports the possible contribution of other pathomechanisms, including the dysregulation of intracellular signalling pathways in basophils and mast cells, an abnormal innate immunity response, and the simultaneous activation of inflammatory response and coagulation system (2-4). With regard to the last aspect in more detail, significantly increased circulating levels of inflammatory markers [such as C-reactive protein (CRP) and interleukin (IL)-6], fibrin degradation products and D-dimer have been associated with the active phase of CSU, in correlation with disease severity (5). The activation of coagulation in CSU is likely to take place through the involvement of eosinophils and tissue factor pathway with thrombin generation and increased vascular permeability (6). An elevated oxidative stress level was demonstrated in patients with CSU (7-9) in parallel with systemic inflammation (10).
Nevertheless, the various mechanisms proposed so far individually cannot explain all the cases of CSU. CSU can be considered a heterogeneous multifactorial condition resulting from a complex interplay between the different pathogenic pathways and/or consisting of various subgroups driven by different pathomechanisms.

Metabolic syndrome

Metabolic syndrome (MS) is estimated to affect approximately 20-25% of the adult population and is a cluster of risk factors for cardiovascular disease, including atherogenic dyslipidaemia, glucose intolerance, arterial hypertension and central obesity. In particular, this syndrome has been found to cause a 5-fold increase in the risk of type 2 diabetes mellitus and 2-fold increase in the risk of cardiovascular disease over the next 5 to 10 years (11). Among the various definitions of MS, the most widely accepted and used are those developed by the World Health Organization (WHO), the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATPIII), the American Association for Clinical Endocrinology (AACE) and the International Diabetes Federation (IDF) (12,13). Insulin resistance is a required criterion for diagnosis in the WHO definition. According to the NCEP-ATP III 2001 definition, MS can be diagnosed in the presence of three or more of the following criteria: waist circumference ≥ 102 cm in men or ≥ 88 cm in women; triglyceride level ≥ 150 mg/dl; high-density lipoprotein (HDL) cholesterol level < 40 mg/dl in men or < 50 mg/dl in women; blood pressure ≥ 130/85 mmHg; and fasting plasma glucose level ≥ 100 mg/dl (14).

In addition, the syndrome encompasses a systemic prothrombotic and pro-inflammatory state as relevant features with endothelial dysfunction and hypercoagulability (12), and can be considered a chronic low-level systemic inflammatory condition. Elevated circulating cytokines and acute-phase reactants, and abnormalities in clotting and antifibrinolytic factors have been found, such as high levels of IL-1, IL-6, tumor necrosis factor (TNF)-alpha, CRP, fibrinogen, tissue factor, factor VII, and plasminogen activator inhibitor (PAI)-1. Adipose tissue plays a crucial role in conditioning the prothrombotic risk, as well as systemic inflammation, through an altered secretion of adipokines that enhance and sustain the inflammatory response and the hepatic production of CRP (12,15).

The role of oxidative stress in MS components, as well as in the onset of MS-related cardiovascular complications, has been remarked (16). A linear increase in the concentration of the thrombotic marker D-dimer was detected in MS, in correlation with chronic inflammation, oxidative stress and altered hemorheology (17).

Methods

Considering the above-mentioned premises outlining possible shared inflammatory pathways between CSU/CU and MS, we reviewed the available literature on the association and interaction between such conditions. PubMed searches were conducted using the keywords “chronic urticaria” or “chronic spontaneous urticaria”, and “metabolic syndrome” and single MS components. The search was also extended to cover other relevant topics, such as “adipokines” and “cardiovascular risk”.

Articles concerning heterogeneous patient populations without proper selection of CU or CSU patients (e.g. subjects with unspecified urticaria or dermatitis / urticaria) were excluded.

Association with MS or MS components

The link between CU and MS has been highlighted by a cross-sectional study carried out on 131 Korean patients with CU (18). MS, diagnosed using the NCEP-ATP III definition, was present in 29.8% of patients and 17.8% of subjects in the control group, giving rise to a statistically significant difference. Comparison of each component of MS between patients and controls showed a statistically higher frequency of central obesity, hypertriglyceridemia and hyperglycemia in CU patients. Compared with CU patients without MS, those with MS were found to be significantly older and more often males, to have more frequent negative ASST results, less frequent angioedema and higher urticaria activity score. Therefore, the presence of MS was more strictly associated with nonautoimmune reactive form and correlated with disease severity but not with angioedema. Logistic regression analysis revealed that the presence of MS was an independent predictor of uncontrolled CU defined by the absence of symptom control after 3 months of treatment. Moreover, patients with CU and MS had higher serum levels of eosinophil cationic protein, TNF-alpha, and complement factors C3 and C4.

An investigation on multiple epidemiological features of CSU was conducted using the Health Search IMS Longitudinal Patient Database (HSD), that contains electronic medical records of patients aged ≥15 years with at least 1 year of medical history registered by 700 selected Italian general practitioners (19). In this population-based study, the risk of CSU was shown to be significantly increased (adjusted hazard ratio, 1.40; 95% confidence interval, 1.17-1.67) in the presence of obesity (ICD-9-CM code 278.0 or body mass index ≥ 30).

Rogala et al. (20) described the association between impaired glucose tolerance and recurrent angioedema without wheals. The authors noted that fasting plasma glucose levels, random blood glucose levels and oral glucose tolerance testing values were significantly higher in patients with angioedema alone as compared to CSU patients.
A relationship between CU and serum lipids and fatty acids was previously suggested by Kobayashi (21), who hypothesized the role of omega-6 and omega-3 series of polyunsaturated fatty acids and lipid peroxidation as mediators in CU. The association between hyperlipidemia and CU has recently been evaluated by a case-control study using a population-based dataset in Taiwan, and involving 9,798 adults with CU and 9,798 sex- and age-matched controls (22). These subjects were examined for whether they had received a prior diagnosis of hyperlipidemia (pure hypercholesterolemia; pure hypertriglyceridemia; mixed hyperlipidemia; hyperchylomicronemia; other and unspecified hyperlipidemia). Compared to patients without CU, CU patients independently had a 1.65-fold (95% confidence interval, 1.55-1.76; p < 0.001) increased risk of having a prior diagnosis of hyperlipidemia, after adjusting for relevant covariates. The analysis of patients with atopic dermatitis matched by sex, age group and index year disclosed that atopic dermatitis was not associated with a previous hyperlipidemia diagnosis, ruling out a relationship of this diagnosis with inflammatory skin diseases in general.

A prospective study in a cohort of 228 consecutive adults with moderate to severe CU revealed that blood hypertension was associated with extended duration of CU and influenced disease remission (23). In particular, persistence of CU after 5 years was still detected in 74% and 54% of CU patients with and without hypertension, respectively.

The association between CU and hypertension was examined by a retrospective cohort study of 2,460 patients with CU and 9,840 age-, sex-, and index year-matched control patients, using the National Health Insurance of Taiwan database (24). The median follow-up periods were 7.13 years and 7.20 years for the CU cohort and for the control group, respectively. Patients with CU were found to have a 1.37-fold (95% confidence interval, 1.22-1.53) greater risk of developing subsequent hypertension than the non-CU cohort after adjusting for sex, age, comorbidities, and nonsedating antihistamine use.

Role of adipokines

The association between CU and MS as a whole or individual components is very interesting, and might support the existence of shared factors and/or mediators. Systemic inflammation is a phenomenon common for MS and CU acting as a possible link between the two conditions.

In this context, the role of obesity appears to be particularly relevant. In recent years, visceral adipose tissue, previously thought to be an inert tissue, has been shown to be an active secretory organ and a source of adipokines crucially involved in immunity and inflammation (25,26). As a consequence, a connection between obesity and autoimmunity has been hypothesized and appears to be corroborated by several findings. Obesity may in fact contribute to the onset and progression of various autoimmune conditions. A systematic review disclosed that obesity significantly increases the risk of rheumatoid arthritis, multiple sclerosis, psoriasis and psoriatic arthritis, and worsens the course of rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis and psoriatic arthritis (26).

Adipokines have been linked to the pathogenesis of MS and its comorbidities through their effects on vascular function and inflammation. Human mast cells may be also a direct target of adipokine activity (27,28).

Systemic inflammation generated during obesity is characterized by an oversecretion of inflammatory markers such as CRP, IL-6, IL-1beta, TNF-alpha, leptin and visfatin, with a simultaneous hyposecretion of anti-inflammatory and anti-atherogenic substances (12,15,29).

Trinh et al. recently described an imbalance in pro- and anti-inflammatory adipokines in CU. They assessed serum levels of adiponectin, leptin, lipocalin-2 (LCN2), IL-10, IL-6, and TNF-alpha in 191 CU patients and 89 healthy controls (30). In CU patients compared to controls, mean levels of serum LCN2, TNF-alpha, IL-6, and IL-10 were significantly higher, and adiponectin levels were significantly lower.

Adiponectin is one of the most abundant peptide hormones derived from adipose tissue and has anti-inflammatory and anti-oxidative properties. Adiponectin acts as a key regulator of innate immune system and progression of inflammation and metabolic disorders. This protein downregulates the expression and release of a number of pro-inflammatory immune mediators, plays a major role in glucose and lipid metabolism and prevents development of vascular changes. Hypoadiponectinemia is associated with a prothrombotic state, atherosclerosis, obesity, and MS (31-33).

LCN2, also known as neutrophil gelatinase-associated lipocalin (NGAL), is a secreted glycoprotein that belongs to the lipocalin family of proteins that transport small hydrophobic ligands, such as steroid hormones, lipids and retinoids, and has recently been characterized as a member of the adipokines superfamily (34). This adipokine plays a role in innate immunity and acute phase response to infection, and has been reported to have roles in the induction of apoptosis in hematopoietic cells, modulation of oxidative stress and inflammation, and metabolic homeostasis. LCN2 has been investigated as a diagnostic and prognostic biomarker in numerous pathological conditions, such as cancer, tissue injury, inflammation and autoimmunity (34,35). Recently, LCN2 has also been proposed as a possible biomarker for CU. In the study performed by Trinh et al. (30), elevated levels of LCN2 in CU patients were inversely correlated with urticarial activity score, while LCN2 was significantly increased in patients with responsive CU compared to those with CU resistant to antihistamines.
Assessment of cardiovascular risk

Several immune-mediated inflammatory disorders, including rheumatoid arthritis, systemic lupus erythematosus, psoriatic disease and intestinal bowel diseases, have been associated with an elevated cardiovascular burden (25,36-39). The pathophysiological basis of such an increased risk is not completely understood, but MS and obesity in particular, with a dysregulated secretion of pro-inflammatory adipokines, could be major contributing features. Low-grade inflammation, that occurs in both CSU and MS, plays an important role in atherosclerosis. In a nationwide Danish cohort using prospectively collected administrative data, the assessment of cardiovascular risk was performed in 2,215 patients with CU and 977 with CIIndU (40). Patients were adults who received a first time diagnosis between 1997 and 2012, and were matched with healthy controls according to a 1:30 ratio. After adjustment for potential confounding factors, there were not significantly higher risks of myocardial infarction, ischaemic stroke, cardiovascular death, or major adverse cardiovascular events in the total population of patients with CU compared to controls. Similarly, no increased risk in any of the above-mentioned cardiovascular outcomes was seen in patients with CIindU, as well as in those with CSU. Moreover, in patients with long-lasting moderate-severe CSU compared to healthy subjects, Grzanka et al. did not find any increase of circulating levels of matrix GLA protein, a biomarker of arterial calcification that is known to be overexpressed in patients with atherosclerosis (41).

Conclusions

Preliminary evidence from the limited data currently available seems to support the association between CU/CSU and MS. The presence of MS was shown to be associated with nonauto-reactive forms and to act as an independent predictor of severe and uncontrolled disease, suggesting the possible involvement of the low-grade inflammatory status related to MS in perpetuating and exacerbating the inflammatory processes underlying CSU pathogenesis. CSU appears to share some pathobiological pathways with MS, including a pro-inflammatory state, increased oxidative stress, alterations in adipokine profile and activation of the coagulation system.

The role of obesity appears to be of particular interest. It has been reported that the serum levels of mast cell-derived tryptase and the number of adipose tissue mast cells are increased in obese patients and high fat diet-fed mice, respectively (42,43). Mast cells in adipose tissue have been proposed to contribute to the pathophysiology of obesity and diabetes and related systemic inflammation (44). MS and some components in particular (e.g. obesity) might also affect the response to the pharmacotherapy of CSU. Further research is needed to assess the association with MS and the practical implications in terms of prognosis and treatment response among CSU patients. The influence of drugs used to manage MS components on CSU severity and course should also be defined. While CU has been associated with MS components in recent reports, there appears to be no increased prevalence of cardiovascular disease among CU patients, possibly because of the relatively short disease duration, that is unable to confer a relevant arteriosclerotic risk following sustained low-level inflammation, unlike other chronic long-standing skin conditions, such as psoriasis (40).

Conflict of interest

During the last three years, G.A. Vena has been a speaker and/or an advisory board member for Novartis Farma and Pfizer, and N. Cassano has been a scientific consultant for Leo Pharma, Novartis Farma, and Pfizer.

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