Original paper

Evaluation of antihistamine-refractory chronic urticaria patients who used biological agent treatment in terms of cardiovascular risk

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Abstract

Introduction: The idea that chronic inflammatory processes may play a role in the etiopathogenesis of both treatment – refractory chronic spontaneous urticaria and cardiovascular diseases is an important research topic.

Aim: Within the scope of this research, we aimed to elucidate a new perspective on the follow-up of chronic urticaria patients by evaluating the 10-year cardiovascular risk and metabolic syndrome in resistant chronic spontaneous urticaria patients who were unresponsive to maximum antihistamine treatment.

Material and methods: A total of 170 individuals who applied to our institution's Health Science University, Tepecik Education and Research Hospital, allergy and immunology outpatient clinic have been analysed in this retrospective case-control study. Metabolic syndrome was calculated according to the National Cholesterol Education Program –- Adult Treatment Panel III, and the cardiovascular risk was calculated according to the Framingham Heart Study of the National Heart, Lung and Blood Institute.

Results: The study included 85 patients diagnosed with chronic spontaneous urticaria (CSU) alongside 85 control subjects. Comparative analysis between the CSU patient group and the control group revealed substantial differences in terms of gender distribution, smoking habits, metabolic syndrome prevalence, waist circumference measurements, body mass index (BMI), hypertension incidence, and levels of C-reactive protein (CRP) ($p < 0.05$). However, factors such as patient age, fasting blood glucose, diabetes status, triglyceride (TAG), high density lipoprotein (HDL), low density lipoprotein (LDL), and the percentage risk of cardiovascular events over 10 years were not found to influence CSU ($p > 0.05$).

Conclusions: Regarding the outcomes of this study, the presence of hypertension, obesity, waist circumference and C-reactive protein values associated with metabolic syndrome should be followed for antihistamine-refractory CSU. Early diagnosis and treatment of metabolic syndrome and its components in these patients may play a role in preventing potential complications. No significant increase in the 10-year cardiovascular risk was observed.

Key words: cardiovascular risk, chronic spontaneous urticaria, metabolic syndrome.

Introduction

Although urticaria, a heterogeneous disease, has different subtypes according to its clinical appearance, the common skin reactions observed are itchy erythematous, oedematous urticarial skin lesions, and/or angioedema. Approximately 9% of people experience an urticaria attack at least once in their lifetime [1]. Chronic urticaria (CU), characterized by urticarial lesions lasting longer than 6 weeks, is thought to develop in 0.1–1% of these cases. Spontaneous urticaria, the most common type of urticaria which occurs without any external stimulus, is called chronic spontaneous urticaria (CSU). It is thought that various underlying factors, such as intolerance reactions to food and drugs, infections, and auto-reactive mechanisms, play a role in the formation of CSU. There are spontaneous and inducible types of chronic urticaria [2]. Chronic spontaneous urticaria is the occurrence of erythematous-oedematous papules, angioedema, or both, occurring spontaneously for more than 6 weeks for a known or unknown reason. Chronic urticaria lesions are typically oedematous pink or red bumps of varying sizes and shapes, often itchy. Some patients may describe pain and burning (especially in angioedema and cutaneous vasculitis). Lesions usually regress within 24–48 h but may persist in other body areas. They should be evaluated for vasculitis when they persist for longer than 24–48 h.

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Symptoms such as joint pain, nausea, and difficulty breathing may also develop [3].

Metabolic syndrome (MS) is estimated to affect approximately 20–25% of the adult population. It represents 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 2-fold increase in the risk of cardiovascular disease in the next 5 to 10 years [4]. Abnormalities of elevated circulating cytokines (interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF-α)), are observed in metabolic syndrome. Adipose tissue plays a crucial role in conditioning systemic inflammation and prothrombotic risk, which increases the inflammatory response and hepatic C-reactive protein (CRP) production. The role of oxidative stress in components of metabolic syndrome and the onset of cardiovascular complication associated with metabolic syndrome has been published in several studies. Previous literature indicated that obesity significantly increases the risk of rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, systemic lupus erythematosus, inflammatory bowel disease and deterioration of these [5]. Adipokines have been associated with metabolic syndrome pathogenesis and comorbidities through their effects on vascular function and inflammation. Human mast cells may also be direct targets of adipokine activity. Inflammatory markers such as CRP, IL-6, IL-I, TNF-α and leptin have been associated with systemic inflammation during obesity indicating an imbalance of pro- and anti-inflammatory adipokines in chronic urticaria. Leptin, lipocalin-2 (LCN2), IL-10, IL-6 and TNF-α levels are elevated in chronic urticaria [6].

The underlying mechanism in both chronic urticaria and metabolic syndrome may indicate a persistent, mild inflammation. The idea that chronic inflammatory processes may play a role in the etiopathogenesis of these two conditions is an important research topic [7]. Within the scope of this research, we aimed to elucidate a new perspective on the follow-up of chronic urticaria patients by evaluating the 10-year cardiovascular risk and metabolic syndrome in resistant chronic spontaneous urticaria patients who were unresponsive to maximum antihistamine treatment.

In the treatment of CSU, management typically focuses on symptom control, employing a stepwise therapeutic approach. Antihistamines, which actively target the primary mediators of symptoms – the histamine (H1) receptors – constitute the foundational aspect of this treatment. These histamine receptors, such as serotonin and acetylcholine, exhibit anticholinergic activity and are capable of crossing the blood-brain barrier, which contributes to their sedative effects. The second generation antihistamines have been modified by the inclusion of hydrophilic groups into their structure, which hinders their ability to cross the blood-brain barrier, thus minimizing sedative effects and yielding new compounds.

Due to the reduced side effects, second generation antihistamines are more frequently preferred. They are recommended as the initial step in treatment; however, if there is no response, the next step involves escalating the dosage of antihistamines up to four times. If symptoms persist despite 2 to 4 weeks of treatment, it is accepted that urticaria is more resistant to treatment, at which point the third level of treatment is considered.

Omalizumab is a recombinant human monoclonal IgG antibody. It acts by inhibiting the binding of free IgE, thereby blocking the effects of allergens. Omalizumab, originally indicated for asthma therapy, is also used alongside conventional treatment for resistant chronic spontaneous urticaria.

Within the context of the ASTERIA study (a multicentre, double-blind, randomized, placebo-controlled arm), doses of 75 mg, 150 mg, 300 mg, and 600 mg of omalizumab were tried to determine the optimal dosage range for the treatment of CSU. A decision was made for a 300 mg dose to be administered subcutaneously once a month as the optimal dose. In the treatment of CSU, the side effects were found to be low and the tolerance level was deemed to be high.

Aim

In our research, individuals experiencing ongoing symptoms despite receiving the maximum dosage of second-generation antihistamines for 6–8 weeks were subsequently administered omalizumab, a biological agent. Presently, participants initiating this treatment are continuing it for varying durations, ranging from a minimum of 4 months to a maximum of 28 months.

Material and methods

A total of 170 individuals who applied to our institution's allergy and immunology outpatient clinic have been analysed in this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 2023-01-22 and informed consent has been obtained from all participants.

The participants were divided into patients with chronic spontaneous urticaria (n = 85) and a control group (n = 85). In the patient and control groups, metabolic syndrome was calculated according to the National Cholesterol Education Program – Adult Treatment Panel (NCEP/ATP) III and cardiovascular risk was calculated according to the Framingham Heart Study of the National Heart, Lung and Blood Institute [8].

Inclusion criteria

Patients aged 18–65 years who were diagnosed with chronic urticaria antihistamine-refractory chronic urticaria and then given biological agent treatment were included in the analysis.

Exclusion criteria

Patients aged ≤ 65 years who were diagnosed with acute urticaria complaints less than 2–6 weeks or chronic urticaria patients who did not receive biological agent treatment were excluded.

Statistical analysis

Patient data collected within the scope of the study were analysed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent sample *T*-test" was used for two groups, and the "Pearson χ^2 test" was used to compare categorical variables. Logistic regression was used to make the logistic functions predict the probability of disease. The results were considered statistically significant when the *p*-value was less than 0.05.

Results

A total of 170 individuals were divided into patients with chronic spontaneous urticaria ($n = 85$) and a control group ($n = 85$). There was a statistically significant difference in the frequency of smoking, metabolic syndrome, diabetes mellitus and hypertension between the patient and control groups ($p < 0.05$) (Table 1). Hypertension was more common (3.5 vs. 24.7). A significant difference was found between the health status and height of the study participants ($p < 0.05$). The mean height of the patients ($\bar{x} = 164.47$) was lower than the control group ($\bar{x} = 171.88$). While there was no significant difference between the mean weight of the participants, whether they were sick or healthy, the waist circumference value ($\bar{x} = 91.95$) of the patient group was higher ($p > 0.05$) than the control group ($\bar{x} = 82.19$). In addition, the calculation showed that the Body mass index (BMI) values of the patient group were significantly higher than the control group ($\bar{x} = 27.54$ versus $\bar{x} = 25.52$, $p > 0.05$). A significant difference was detected between the mean body surface area (BSA) of the participants and whether they were sick or healthy ($p < 0.05$). The mean body surface area of the patients ($\bar{x} = 1.81$) was lower than the control group ($\bar{x} = 1.89$). The blood pressure levels of the patient group ($\bar{x} = 94.02$) were lower than the control group ($\bar{x} = 99.12$) (Table 2).

In terms of laboratory parameters, a significant difference was observed between the study participants' CRP and Ig E values, whether they were sick or healthy ($p < 0.05$). The CRP value of the patients ($\bar{x} = 5.36$) is higher than the control group ($\bar{x} = 3.28$). The patients' mean IgE level ($\bar{x} = 390.4$) was much higher than the control group ($\bar{x} = 46.07$). Other laboratory parameters (vitamin D, thyroid stimulating hormone (TSH), LDL, and HDL) revealed no significance.

Gender-affected developing urticaria; women were 2.709 times more at risk than men (OR = 2.709, 95% CI: [1.412–5.197], $p = 0.003$). Additionally, smoking increased the risk 3.909 fold (OR = 3.909, 95% CI [1.911–7.997], $p < 0.001$), metabolic syndrome 2.681 fold (OR = 2.681, 95% CI [1.247–5.762], $p = 0.012$), waist circumference 1.057 fold (OR = 1.057, 95% CI [1.031–1.085],

Table 1. Examination of the patient and control groups in terms of categorical parameters

Parameter		Total ($n = 170$) *n* (%)	Control ($n = 85$) Mean ± SD	Patient group ($n = 85$) Mean ± SD	*P*-value
Gender	Male	61 (35.9)	40 (65.6)	21 (34.4)	0.002
	Female	109 (64.1)	45 (41.3)	64 (58.7)	
Smoking	Yes	51 (30)	14 (27.5)	37 (72.5)	< 0.001
	No	119 (70)	71 (59.7)	48 (40.3)	
Diabetes mellitus	Yes	8 (4.7)	0 (0)	8 (100)	0.004
	No	162 (95.3)	85 (52.5)	77 (47.5)	
	No	70 (82.4)	0 (0)	70 (100)	
Metabolic syndrome	Yes	38 (22.4)	12 (14.1)	26 (30.6)	0.010
	No	132 (77.6)	73 (85.9)	59 (69.4)	
Hypertension	Yes	24 (14.1)	3 (3.5)	21 (24.7)	< 0.001
	No	146 (85.9)	82 (96.5)	64 (75.3)	

All analyses were performed with the χ^2 test.

Table 2. Comparison of continuous variables between the two groups

Parameters	Control (n = 85) Mean ± SD	Patient group (n = 85) Mean ± SD	*P*-value
Age [y]	38.08 ±14.65	39.51 ±12.18	0.492*
Height [cm]	171.88 ±8.79	164.47 ±8.2	< 0.001*
Weight [kg]	75.45 ±13.12	73.38 ±14.86	0.245**
Waist circumference [cm]	82.19 ±12.41	91.95 ±14.01	0.006*
BMI [kg/m²]	25.52 ±3.95	27.54 ±5.4	< 0.001*
BSA [m²]	1.89 ±0.19	1.81 ±0.19	0.003**
CRP [mg/l]	3.28 ±3.05	5.36 ±4.5	0.001**
IgE [IU/ml]	46.07 ±54.91	390.4 ±554.95	< 0.001**
Vitamin D [ng/ml]	16.48 ±7.57	14.9 ±8.38	0.061**
TSH [IU/ml]	2.02 ±1.33	2.01 ±1.28	0.963**
FPG [mg/dl]	99.12 ±12.07	94.02 ±22.18	< 0.001**
LDL [mg/dl]	112.34 ±41.41	120.36 ±35.03	0.120**
TAG [mg/dl]	146.92 ±105.6	130.12 ±67.85	0.807**
HDL [mg/dl]	58.13 ±18.92	54.91 ±18.87	0.178**
Estimation of the 10-year CVR	2.46 ±4.01	3.45 ±4.54	0.096**

Table 3. Findings from the multiple logistic regression model on the association between chronic spontaneous urticaria and metabolic syndrome and 10-year cardiovascular risk components

Parameters	b	Sh (b)	Wald	*P*-value	Exp (b)
Gender	0.997	0.332	8.991	0.003	2.709
Smoking	1.363	0.365	13.936	0.000	3.909
Diabetes mellitus	21.302	14210.361	0.000	0.999	1783
Metabolic syndrome	0.986	0.390	6.379	0.012	2.681
Age [years]	0.008	0.011	0.478	0.490	1.008
Waist circumference [cm]	0.056	0.013	18.471	0.000	1.057
BMI [kg/m²]	0.091	0.034	7.148	0.008	1.096
BSA [m²]	–2.279	0.849	7.214	0.007	0.102
CRP [mg/l]	0.159	0.050	10.168	0.001	1.172
IgE [IU/l]	0.018	0.003	30.482	0.000	1.018
Vitamin D [ng/ml]	–0.025	0.020	1.645	0.200	0.975
TSH [UI/ml]	–0.007	0.118	0.004	0.952	0.993
FPG [mg/dl]	–0.020	0.011	3.124	0.077	0.980
LDL [mg/dl]	0.006	0.004	1.840	0.175	1.006
TAG [mg/dl]	–0.002	0.002	1.491	0.222	0.998
HDL [mg/dl]	–0.009	0.009	1.208	0.272	0.991
Estimation of the 10-year CVR	0.057	0.039	2.138	0.144	1.059
Hypertension	2.194	0.639	11.773	0.001	8.969

$p < 0.001$), BMI 1.096 fold (OR = 1.096, 95% CI [1.025–1.171], $p = 0.008$), CRP 1.172 fold (OR = 1.172, 95% CI [1.063–1.292], $p = 0.001$), and hypertension 8.969 fold (OR = 8.969, 95% CI [2.562–31.401], $p = 0.001$). On the contrary, some parameters presented relatively low effects, such as fasting plasma glucose (FPG) 1.018 fold, IgE 1.02 fold, and body surface area 0.102 fold. The regression analysis showed that diabetes did not affect the control and patient groups (Table 3).

Discussion

The terminology of chronic urticaria cases mainly constitutes physical urticaria (35%), idiopathic urticaria (35%) and autoimmune urticaria (25%). The group of patients with chronic idiopathic urticaria and those with unidentified resistant urticarial lesions is divided into two sub-groups: chronic autoimmune urticaria and chronic idiopathic urticaria. Angioedema is also accompanied in approximately 40% of patients with chronic autoimmune urticaria and chronic idiopathic urticaria [9]. Irinyi *et al.* reported that autoimmune disease history is frequently observed in patients with chronic urticaria. Additionally, thyroid autoantibodies frequently accompany this group of individuals, and antihistaminic treatment is less effective [10].

A metabolic syndrome is a group of risk factors for cardiovascular diseases that initiate insulin resistance and cause systemic disorders such as abdominal obesity, glucose intolerance, DM, dyslipidaemia, hypertension, vascular inflammation, and prothrombic conditions. The prevalence of metabolic syndrome in our country is 22%. Kozan *et al.* conducted research with the ATP-III criteria in 4259 adults and determined the frequency of metabolic syndrome to be 33.9% (28% in males and 39.6% in females) [11]. Gemalmaz *et al.* enrolled patients aged ≥ 20 years old and stated the frequency of metabolic syndrome as 38.1% and 41.4%, respectively, according to ATP-III and IDF criteria. In the same study, the frequency of metabolic syndrome according to ATP-III and IDF criteria was determined as 33.3% and 34.3% in men, 41.4% and 46.2% in women [12].

Ye *et al.* evaluated metabolic syndrome according to ATPIII criteria in 131 patients and 1285 controls. They indicated that 17.8% of the individuals in the control group were diagnosed with metabolic syndrome, while this ratio was 29.8% in patients with chronic urticaria ($p = 0.001$). This study also reported that components of metabolic syndrome (abdominal obesity, fasting plasma glucose, and triglyceride) were significantly higher in the chronic urticaria group [13]. Vena and Casano investigated the risk of chronic spontaneous urticaria in patients aged ≥ 15 years with at least 1 year of medical history in a population-based study and elaborated that chronic spontaneous urticaria was significantly increased (adjusted hazard ratio = 1.40; 95% confidence interval: 1.17–1.67) in the presence of obesity [14]. Shalom *et al.* conducted a large cross-sectional study of chronic urticaria patients ($n = 11,261$) and matched controls ($n = 67,216$) regarding the prevalence of metabolic syndrome, its components, and possible complications. They concluded that chronic urticaria was significantly associated with higher BMI and a higher prevalence of obesity, diabetes, hyperlipidaemia, hypertension, metabolic syndrome, chronic renal failure and gout. Additionally, they also detected a significant association between chronic urticaria and metabolic syndrome (OR = 1.12, 95% CI: 1.1–1.2, $p < 0.001$), obesity (OR = 1.2, 95% CI: 1.1–1.3, $p < 0.001$), diabetes (OR = 1.08, 95% CI: 1.01–1.15, $p = 0.001$), hyperlipidaemia (OR = 1.2, 95% CI: 1.1–1.2, $p < 0.001$) and hypertension (OR = 1.1, 95% CI: 1.1–1.2, $p < 0.001$) [15]. Rogal*a et al.* described the association between impaired glucose tolerance and recurrent angioedema without wheals. They concluded that fasting plasma glucose levels, random blood glucose levels, and oral glucose tolerance testing values were significantly higher in patients with angioedema alone than in chronic spontaneous urticaria patients [16]. Our study observed a statistically significant difference between the patient and control groups in metabolic syndrome, gender, smoking, waist circumference and body mass index. However we did not find an association between age, fasting blood glucose, diabetes, triglyceride, HDL, LDL and 10-year cardiovascular risk.

A change occurs in the lipid profile during inflammatory and auto-immune diseases. The relationship between chronic urticaria and serum lipids, omega-6 and omega-3 series of polyunsaturated fatty acids, and lipid peroxidation has been determined in an early study by Kobayashi *et al.* in chronic urticaria patients [17]. Chung *et al.* conducted a population-based case-control study on 9,798 patients and found that chronic urticaria independently had a 1.65-fold (95% confidence interval: 1.55–1.76; $p < 0.001$) increased risk of having a prior diagnosis of hyperlipidaemia [18]. In a recent study by Gupta *et al.,* chronic spontaneous urticaria was significantly associated with a higher prevalence of central obesity [7].

Nebiolo *et al.* investigated the association between hypertension and severe chronic spontaneous urticaria in 228 adults. They claimed that hypertension prolonged the duration of chronic spontaneous urticaria and deteriorated remission. Chronic spontaneous urticaria persisted in 74% and 54% of patients with and without hypertension [19]. Chang *et al.* performed a retrospective analysis on 2,460 chronic spontaneous urticaria patients and 9,840 healthy controls with a median follow-up of 7.13 years and 7.20 years, respectively and found that chronic spontaneous urticaria had a 1.37-fold risk of developing hypertension [20]. Similar to these outcomes, our study detected a statistically significant difference in hypertension between the patient and control groups.

The aforementioned studies revealed that the presence of metabolic syndrome association with non-autoreactive forms of chronic spontaneous urticaria acted as an independent predictor of severe and uncontrolled disease, suggesting the possible involvement of the low-grade inflammatory status in perpetuating and exacerbating the inflammatory processes underlying chronic spontaneous urticaria pathogenesis. Chronic spontaneous urticaria shares pathobiological pathways with metabolic syndrome, including a pro-inflammatory state, increased oxidative stress, alterations in adipokine

profile, and coagulation system activation [21]. We have achieved a statistically significant difference between the patient and control groups in CRP levels indicating an increased level of inflammation.

Urticaria is a disease characterized by temporary erythematous, oedematous plaques which resulted in vasodilatation and vascular permeability, which lead to vasodilatation and vascular permeability with the effect of various mediators, especially histamine, released from mast cells, in which mast cell degranulation plays a role [21]. Immune-mediated chronic inflammatory diseases such as psoriasis, rheumatoid arthritis, Crohn's disease and multiple sclerosis are more common than the general population in metabolic syndrome, thus stressing the role of chronic inflammation. Chronic inflammation causes atherogenesis and peripheral insulin resistance, indicating that the frequency of metabolic syndrome supports the idea of the increased rate of metabolic syndrome in chronic inflammatory diseases [22]. The disease duration was relatively short in our study population to observe atherosclerotic changes and their complications. Additionally, the relatively young age of our study population may have been effective in obtaining these results.

Conclusions

Regarding the outcomes of this study, the presence of hypertension, obesity, waist circumference and CRP values associated with metabolic syndrome should be followed for antihistamine-refractory chronic spontaneous urticaria. In our study, the pre-existing diagnoses of CSU at various clinics for some patients, combined with limited access to the exact onset dates of the urticaria, complicate the comparison between the 10-year cardiovascular disease risk (CVR) estimates and the initial urticaria durations. This situation highlights the challenge of accurately determining the onset and duration of the disease, which is critical for understanding the potential cardiovascular effects of CSU. Early diagnosis and treatment of metabolic syndrome and its components in these patients may play a role in preventing potential complications. No significant increase in the 10-year cardiovascular risk was observed.

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Ethical declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted by our institution. As this was a retrospective research no informed consent has been obtained from participants.

Conflict of interest

The authors declare no conflict of interest.

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