

Coexistence of Angioedema Alone with Impaired Glucose Tolerance

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Key Words

Angioedema · Glucose · Diabetes · Urticaria

Abstract

Background: Most patients with chronic spontaneous urticaria (CSU) exhibit recurrent angioedema. As of yet, the pathogenesis of angioedema in CSU is largely unclear, especially when angioedema occurs in patients who do not develop wheals. Over the past years, we and others have repeatedly observed that patients with recurrent angioedema alone exhibit impaired glucose tolerance. **Aim:** To assess blood glucose levels and glucose tolerance in these patients and to compare the results to those of CSU patients who do not develop angioedema. **Methods:** A total of 29 patients with angioedema alone (15 women, mean age 43.2 ± 12.8 years) and 33 CSU patients (17 women, mean age 41.9 ± 17 years) were investigated and compared for clinical features and laboratory values, including fasting and random blood glucose levels, and glycated hemoglobin (HbA1c%). All patients were subjected to oral glucose tolerance testing (OGTT). **Results:** Fasting plasma glucose levels, random blood glucose levels and OGTT glucose levels were significantly higher in patients with angioedema alone as compared to CSU patients. Glucose tolerance was impaired in 17 of 29 patients with angioedema alone (58.6%) and only in 2 of 33 CSU patients (6.1%). Patients were found to have an

increased risk of high glucose (OR 1.74) and HbA1c (OR 1.83) blood levels and of developing a high BMI (OR 1.97). **Conclusion:** Recurrent angioedema in patients who do not develop wheals appears to be associated with impaired glucose tolerance and elevated blood glucose levels. We recommend blood glucose measurements in patients with recurrent angioedema alone.

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Introduction

According to the current EAACI/GA²LEN/EDF/WAO guidelines for urticaria, chronic spontaneous urticaria (CSU) is defined as the reoccurrence of spontaneous wheals, angioedema or both [1]. Up to 90% of CSU patients exhibit wheals and many of them also develop recurrent angioedema. About 10% of CSU patients do not show wheals and exclusively develop angioedema. To date little is known about this subtype of CSU, but the guidelines recommend using the same diagnostic and therapeutic approaches in all CSU subtypes [1, 2].

Importantly, recurrent angioedema in CSU patients is mast cell mediator-mediated and needs to be distinguished from bradykinin-mediated angioedema. Subtypes of bradykinin-mediated angioedema can be either hereditary or acquired (e.g. ACE inhibitor-induced or

due to acquired C1-inhibitor deficiency), and patients with bradykinin-mediated angioedema typically do not develop wheals [3–8].

Recently, CSU patients were reported to exhibit metabolic syndrome with increased body mass index (BMI) values [9, 10]. Therefore, we began to test our CSU patients for blood glucose levels and found them to be frequently elevated, especially in CSU patients with angioedema alone. This prompted us to check and compare patients with different CSU subtypes for differences in blood glucose levels and related clinical features and lab values, as well as for differences in the outcome of oral glucose tolerance testing (OGTT).

Materials and Methods

Patients

Consecutive CSU patients with angioedema alone ($n = 29$) and without angioedema ($n = 33$), referred to and treated by our clinics between February and May 2013, were included in this study. All patients provided written informed consent, and the study was approved by the Ethical Committee of the Medical University of Silesia. All CSU patients with angioedema alone (15 women, mean age 43.2 ± 12.8 years, age range 24–71; group A) and CSU patients without angioedema (17 women, mean age 41.9 ± 17 years, age range 21–74; group B) included in the study met all the inclusion criteria (recurrent spontaneous angioedema for more than 6 months and no wheals, or recurrent spontaneous wheals for more than 6 months and no angioedema) and none of the exclusion criteria (hereditary angioedema, excluded by C1 inhibitor and C4 measurements; ACE inhibitor-induced angioedema; recurrent angioedema due to type I allergy, excluded by allergy testing; patients diagnosed with autoimmune, Cushing and Addison diseases). In addition, we included 28 healthy control subjects (15 women, mean age 41.7 ± 12.4 , age range 18–45, group C) without CSU and diabetes but with a BMI comparable with the other studied patients. Patients with angioedema alone did not respond to H1 antihistamine drugs.

Clinical Investigation

All patients were investigated for their blood pressure, personal and family history of diabetes, and their BMI. Quality of life (QoL) was assessed by use of the dermatology life quality index (DLQI), a commonly used instrument for measuring skin disease-specific QoL impairment. DLQI scores of 0–1, 2–5, 6–10, 11–20 and 21–30 reflect no, mild, moderate, very large and extremely large QoL impairment, respectively [11].

Laboratory Investigations

Patients were investigated for their erythrocytes sedimentation rates and complete blood counts (Penta 120S, Horiba ABX SAS, Montpellier, France), for serum levels of total IgE (Atopy Euroline, Euroimmune, Lubeck, Germany), fasting and random glucose, glycated hemoglobin (HbA1c%), total cholesterol, high- and low-density lipoprotein (HDL and LDL), triglycerides and uric acid serum levels (all Integra 400 Plus, ECLIA, Roche Diagnostics,

Warsaw, Poland), as well as thyroid-stimulating hormone (TSH) serum and thyroid antibody levels (Cobas e411, ECLIA, Roche Diagnostics). For OGTT, blood glucose levels were measured 2 h after the consumption of 75 g of glucose dissolved in a glass of water, at least 8 h since the last meal.

Statistical Analyses

Data are presented as means and standard deviations unless indicated otherwise. Comparisons between groups of patients were done by nonparametric ANOVA testing, and a p value <0.05 was considered to show statistical significance. Adjusted odds ratio (OR) with 95% confidence intervals were used to assess the risk of a particular clinical condition.

Results

CSU patients with and without angioedema showed similar rates of obesity and diabetes, and both CSU subpopulations exhibited similar levels of markedly impaired QoL (table 1). In contrast, CSU patients with angioedema alone were found to have significantly higher mean glucose plasma levels in blood samples obtained either after fasting or randomly, as compared to CSU patients without angioedema (table 2). Sixty-six percent of CSU patients with angioedema alone, but only 9% of CSU patients without it, showed higher than normal fasting glucose levels (table 2). Also, glucose tolerance was impaired in 17 out of 29 CSU patients with angioedema alone (58.6%) and only in 2 out of 33 CSU patients without it (6.1%).

Assessment of the risk analyses showed that CSU patients with angioedema alone have an increased risk of high glucose (OR 1.74) and HbA1c (OR 1.83; table 3). Additionally, CSU patients with angioedema alone had significantly higher fasting glucose levels, HbA1c% and often impaired OGTT than the healthy controls despite a comparable BMI. There were no significant differences in the above analyzed parameters between healthy controls and CSU patients without angioedema.

Discussion

Our findings demonstrate that recurrent angioedema in some CSU patients who do not develop wheals is associated with elevated blood glucose levels and impaired glucose tolerance. The reasons for this remain unclear. It may be that impaired glucose tolerance and high glucose levels contribute to the development of recurrent angioedema. Alternatively, recurrent angioedema may result in the development of impaired glucose tolerance and higher glucose levels. Our findings may also be explained

Table 1. Clinical features and QoL impairment of patients with angioedema alone, with CSU without angioedema, and healthy controls

	Group A (n = 29)	Group B (n = 33)	Group C (n = 28)	p
Women/men	15/14	17/16	15/13	n.s.
Age in years	43.2±12.8	41.9±17.8	41.7± 12.4	n.s.
BMI >30	13 (44.8)	17 (51.5)	15 (53.6)	n.s.
BMI ¹ , kg/m ²	25.2±3.2	26.4±5.2	24.9±6.4	n.s.
Personal history of diabetes	6 (20.7)	5 (15.2)	–	n.s.
Family history of diabetes	2 (6.8)	1 (3.5)	2 (7.1)	n.s.
Systolic blood pressure, mm Hg ²	149±20*	139±23	132±48	<0.05*
Diastolic blood pressure, mm Hg ³	85±15	78±12	69±14	n.s.
QoL impairment: DLQI score	23.7±8.6	19.8±6.1	–	n.s.

Data are presented as n (%) or mean ± SD. * Significant differences between group A and other groups, for p < 0.05. Group A = CSU patients with angioedema but not wheals; group B = CSU patients without angioedema but with wheals; group C = healthy controls; n.s. = not significant.

¹ Normal range: 18.5–25. ² Normal: <140 mm Hg. ³ Normal: <80 mm Hg.

Table 2. Patients with angioedema alone exhibit high glucose plasma levels and impaired glucose tolerance

	Group A (n = 29)	Group B (n = 33)	Group C (n = 28)	p
Fasting plasma glucose, mmol/l ¹	7.1±1.4*	4±0.6	4±1.1	<0.01*
Patients with increased fasting glucose	19 (65.5)*	3 (9.1)	4 (14.3)	<0.001*
Random plasma glucose, mmol/l	8.8±2.3*	7.3±1.5	7.0±2.3	<0.05*
Patients with increased random plasma glucose	20 (69)*	4 (12.1)	3 (10.7)	<0.01*
OGGT plasma glucose, mmol/l ²	9.7 ±2.9*	7.5 ±1.9	6.9 ±2.4	<0.01*
Patients with increased OGTT plasma glucose	17 (58.6)*	2 (6.1)	2 (7.2)	<0.001*
HbA1c% ³	6.9±2.9*	6.1±2.0	5.9±2.0	<0.05*
Total cholesterol, mg/dl ⁴	199±45	196±41	182± 55	n.s.
HDL cholesterol, mg/dl ⁵	60±12	59±12	56±21	n.s.
LDL cholesterol, mg/dl ⁶	122±18	131±28	138±31	n.s.
Triglycerides, mg/dl ⁷	189±147*	135±104	142±96	<0.05*
Uric acid, µmol/l ⁸	238±36	251±43	232±78	n.s.
TSH, µIU/ml ⁹	1.7±0.6	1.6±0.5	1.2±0.4	n.s.
Total IgE, IU/l ¹⁰	76±53	89±64	70±34	n.s.

Data are presented as n (%) or mean ± SD. * Significant differences between group A and other groups, for p < 0.05. Group A = CSU patients with angioedema but not wheals; group B = CSU patients without angioedema but with wheals; group C = healthy controls; n.s. = not significant.

¹ Normal range: 3.88–5.5 mmol/l. ² Normal: <7.8 mmol/l. ³ Normal: <7%. ⁴ Normal: <190 mg/dl. ⁵ Normal: >65 mg/dl. ⁶ Normal: <70 mg/dl. ⁷ Normal: <150 mg/dl. ⁸ Normal range: 142–240 µmol/l. ⁹ Normal range: 0.27–4.2 µIU/ml. ¹⁰ Normal: <100 IU/ml.

by shared pathogenic mechanisms of both conditions. For example, adiponectin and other adipokines, such as RBP-4 retinol-binding protein, vaspin, omentin, chemerin, FGF21-21-fibroblast growth factor, A-FABP-adipocyte fatty acid-binding protein and DPP4-dipeptidyl peptidase, are known to contribute to the development of impaired glucose tolerance, high glucose levels and diabetes. Some of these adipose tissue-derived mediators [4, 12–

14] are known to have proinflammatory effects. They can increase the permeability of skin after capillaries by damaging the endothelium and initiating the activation of the intrinsic coagulation pathway [16, 17].

On one hand, our results show that patients with various CSU subtypes exhibit important differences, some of which can be important for the diagnostic workup and management of these subtypes. This suggests that further

Table 3. Patients with angioedema alone have an increased risk of developing increased high fasting glucose blood levels and HbA1c%

	OR	95% CI
BMI, kg/m ²	1.01	0.47–1.23
HbA1c%	1.83	1.33–1.98
Fasting plasma glucose	1.74	1.14–1.89
Diabetes in family	1.04	0.78–1.22
Total cholesterol	0.93	0.67–1.07
Triglycerides	0.95	0.45–1.55
TSH	0.89	0.67–1.1
IgE	0.97	0.72–1.08
Female	0.98	0.68–1.29
Systolic blood pressure	0.89	0.78–1.11
Diastolic blood pressure	1.12	0.98–1.45

studies are needed to better characterize the subtypes of CSU, especially with angioedema alone, as this could help to develop subtype-specific approaches that may improve the treatment of CSU patients. On the other hand, our results confirm that CSU is a debilitating disorder with substantial QoL impairment in patients with different subtypes.

Our study has several strengths and limitations. The number of patients in the two CSU subtypes studied was low and all of them were treated by a single center. Therefore, these results should be confirmed by a larger number of patients. Also, our study did not include CSU patients with wheals and with angioedema, arguably the most frequent subtype of CSU. The reason for this was our hypothesis that CSU patients with angioedema alone show distinct abnormalities in glucose metabolism. To test this hypothesis we wanted to compare CSU patients with angioedema alone with a CSU control group that does not exhibit recurrent angioedema, and with healthy

controls. Further trials should include CSU patients with wheals and angioedema in order to test if patients with this subtype share the glucose metabolism profiles of CSU patients with or without angioedema. The strongest point of our study is that we applied rigorous inclusion and exclusion criteria to make sure that the recurrent angioedema patients we studied were CSU patients and not patients with bradykinin-mediated angioedema or other forms of recurrent angioedema, as has been described in other studies [18–21].

Our findings point to a problem with glucose tolerance in CSU patients with angioedema alone. The vast majority of these patients show impaired glucose tolerance and high glucose plasma levels. The analysis of their lipid profile revealed significantly higher levels of triglycerides and elevated blood pressure. Screening of CSU patients with angioedema alone for elevated blood glucose levels may help to reduce their risk of developing metabolic syndrome, and blood glucose-lowering treatment may improve their recurrent angioedema. Further studies are warranted to substantiate these speculations. In conclusion, CSU patients with angioedema and without wheals have a significant predisposition to impaired glucose tolerance. For now, we recommend screening such patients for increased blood glucose levels.

Acknowledgements

We would like to thank Mr. Bartosz Rogala for his linguistic assistance, which helped to shape the final form of this work.

Disclosure Statement

All authors have confirmed no conflicts of interest.

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