Dermatology Practical & Conceptual

Characterization of Chronic Urticaria and Associated Conditions - A Web-Based Survey

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Key words: chronic urticaria, autoimmune urticaria, comorbidity, angioedema

Citation: Zysk W, Trzeciak M. Characterization of Chronic Urticaria and Associated Conditions - A Web-Based Survey. *Dermatol Pract Concept*. 2023;13(1):e2023056. DOI: https://doi.org/10.5826/dpc.1301a56

Accepted: May 28, 2022; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Chronic urticaria is a common disease, characterized by the development of wheals, angioedema, or both, which can be associated with several comorbidities. Most of the available studies have focused on specific common comorbidities and their association with CU, but have seldom reported the overall burden of comorbidities.

Objectives: This study aimed to investigate and analyze self-reported comorbidities in Polish patients with CU.

Methods: An anonymous online survey consisting of 20 questions was conducted on members of an Urticaria group on the social media platform Facebook. A total of 102 people took part in this survey. The results were analyzed in Microsoft Excel 2016.

Results: In the group, 95.1% were females and 4.9% males, with a mean age of 33.8 years. The most common diagnosed type of urticaria was spontaneous (52.9%). Angioedema accompanied urticaria in 68.6% of the respondents, mainly those with delayed pressure urticaria (86.4%). 85.3% of respondents reported comorbidities, most often atopic diseases and allergies (49%), chronic inflammation and infections (36.3%), thyroid (36.3%) and psychiatric disorders (25.5%). Moreover, in 30.4% of patients, at least one autoimmune disease was noted. As compared to the patients without autoimmune urticaria, many more with autoimmune urticaria had a coexisting autoimmune disease (50% vs. 23.7%). Family history of autoimmune diseases was positive in 42.2%, and the familial history of urticaria and atopy was positive in 7.8% and 25.5%, respectively.

Conclusions: The knowledge of comorbidities of chronic urticaria may support clinicians to manage and treat patients with this common condition.

Introduction

Chronic urticaria (CU), affecting 0.5%–1% of the general population, is defined by the repeated occurrence of itchy hives, angioedema, or both, for 6 weeks or more. According to current guidelines, CU can be divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) with several subgroups. Both CU types can occur concomitantly in the same patient [1]. CU develops more frequently in adults, in the third to fifth decade of life, and females are affected at least twice as often as males [2].

Several studies reported that patients with CU frequently exhibit comorbidities. The association of CU with psychiatric disorders, including depression, anxiety and behavioral problems, atopic disorders, autoimmune disorders, hypertension, osteoporosis, and infections, has been reported previously [3-7]. Most of these studies have focused on specific common comorbidities and their association with CU, but have seldom reported the overall burden of comorbidities.

Objectives

This study aimed to investigate and analyze self-reported comorbidities in Polish patients with CU.

Material and Methods

The study was based on an anonymously filled online survey prepared by the authors. Individuals with CU and parents of children with CU were recruited for participation in the study through closed membership CU support groups found on social media platforms (Facebook). Individuals interested in participating in the survey were directed through an introduction and implicit consent into Google Forms.

The questionnaire consisted of 20 questions: 7 single-choice and 13 multiple-choice. Single-choice questions concerned basic demographic information, presence of angioedema, age of the first episode of CU, and frequency of CU symptoms. Multiple-choice questions concerned information about diagnosed types of CU, localization of angioedema, family history of urticaria and atopy, family history of autoimmune diseases, the coexistence of connective tissue, thyroid gland, digestive system, inflammatory diseases, metabolic and cardiovascular diseases, skin diseases, allergic diseases, mental disorders, neoplasm diseases, and others that individuals could add in a designated place.

Data about family history of atopy was defined as the presence of asthma, eczema, allergic rhinitis, or rhinoconjunctivitis, whereas autoimmune diseases were defined as Hashimoto's thyroiditis, systemic lupus erythematosus, pernicious anemia, vitiligo, Graves' disease, rheumatoid arthritis, celiac disease, alopecia areata, sclerosis multiplex, scleroderma, diabetes mellitus type 1, Crohn' disease and ulcerative colitis.

A total of 102 people (97 women and 5 men) took part in this survey. The average age of patients was 33.8 years (range, 9-57 years). The results were analyzed in Microsoft Excel 2016 and presented on a percentage scale.

The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/833/2021).

Results

The majority of CU patients were 19–39 years old (59.8%), followed by patients aged ≥40 years old (33.3%), while a small proportion, 6.9% of patients were ≤18 years old. The vast majority of the respondents (80.4%) lived in cities, the remaining 19.6% lived in villages. More than half of the respondents (63.7%) reported higher education, 17.6% secondary, and 3.9% vocational. Nearly 16% of respondents were studying.

The mean age at disease onset was 27.5 years (range, 3–55 years). Among all patients, the most frequent type of CU was CSU, diagnosed in 78.4%. Autoimmune urticaria, which is a subtype of CSU, was diagnosed in 25.5%. Among all patients with CU, 59.8% were diagnosed with CSU only, 21.6% were diagnosed with isolated CIndU only and the remaining 18.6% had a combination of both types. The most common subtypes of CIndU were delayed pressure urticaria (21.6%), symptomatic dermographism (14.7%), and cholinergic urticaria (8.8%; fig 1).

Angioedema symptoms were reported by 70 patients (68.6%) and occurred mainly in patients with delayed pressure urticaria (86.4%; fig 2). Of the 70 patients who experienced symptoms of angioedema, the most frequently reported locations for angioedema were non-facial body areas (82.9%), most commonly the hands (68.6%), feet (57.1%), over joints (35.7%), and trunk (5.7%). 17.1% of patients reported experiencing swelling symptoms over the whole body. On the face, angioedema occurred in 68.6% of patients: the areas around the eyes were affected in 67.1% of cases, the lips in 65.7%, the oral mucosa in 12.9%, and the tongue in 11.4%.

In more than half of the cases (59.8%), hives appear every day, in 16.7% several times a week, in 8.8% several times a month, in 10.8% several times a year, and in 3.9% less frequently.

We examined the prevalence of reported comorbid diseases by CU patients, grouping them into 10 disease categories. The data presented in Table 1 summarize the comorbidity profile of CU patients. Of 102 CU patients, 85.3% had one or more concomitant diseases. Almost 50% of patients had at least one atopic disease or allergy and it was the most

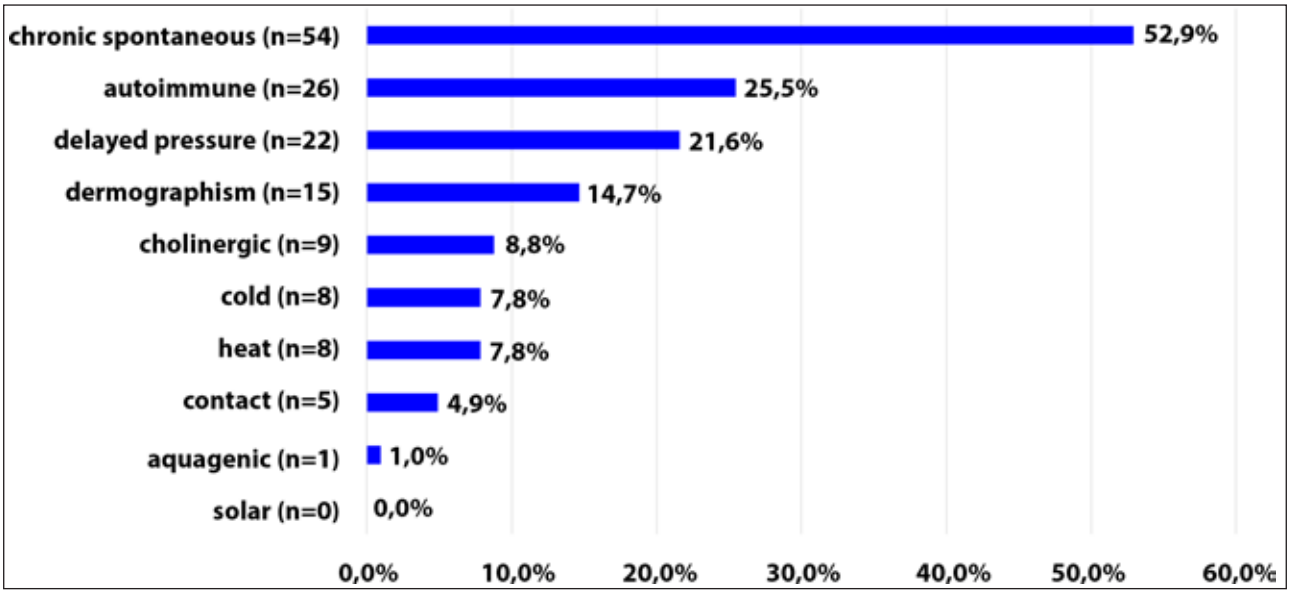

Figure 1. Percentage of patients with chronic urticaria (CU), divided by subtype (n=102).

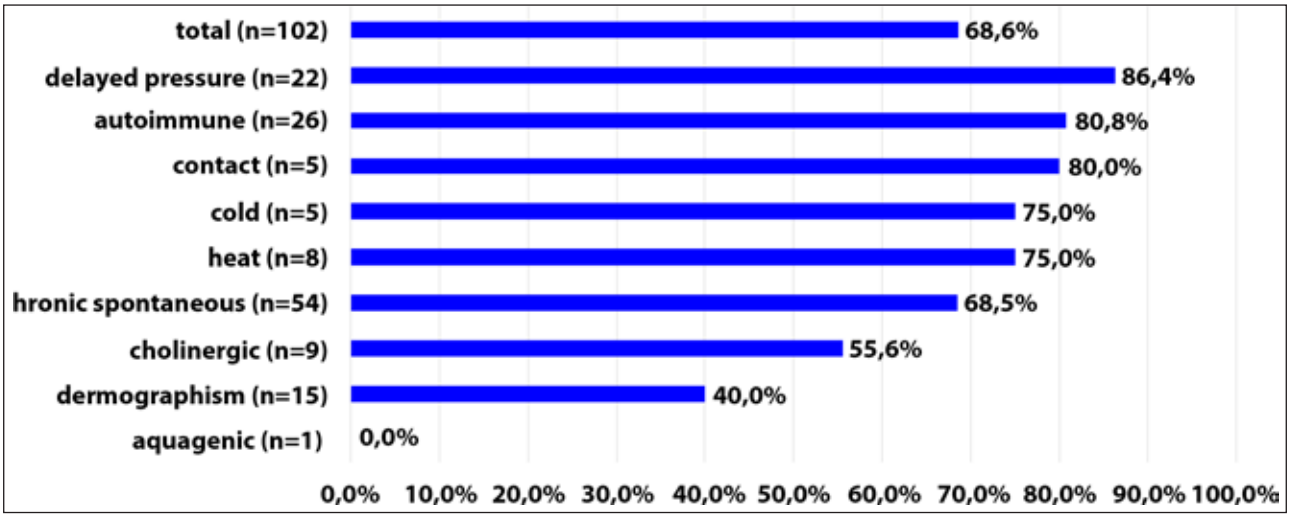

Figure 2. Percentage of patients with concomitant angioedema, divided by subtype of chronic urticaria (CU).

commonly reported group of comorbidities, followed by chronic inflammation and infections (36.3%), thyroid disorders (36.3%), psychiatric disorders (36.3%), skin diseases (18.6%), gastrointestinal diseases (18.6%), cardiometabolic diseases (10.8%), rheumatic diseases (6.9%), malignancies (2.0%), and others included migraine, endometriosis, pernicious anemia and epilepsy.

Among all comorbidities reported by patients, we determined autoimmune diseases. Of 102 CU patients, 31 (30.4%) had one or more comorbid autoimmune diseases (Table 2). The most prevalent were autoimmune thyroid diseases (24.5%, mostly HT in 22.5%). Other common autoimmune comorbidities included systemic lupus erythematosus (2.9%) and rheumatoid arthritis (2.9%). Of the 31 CU patients with a comorbid autoimmune disease, 74.2% had one, most often HT, 22.6% had 2, and 3.2% had 3 (Table 2). As compared to the patients without autoimmune urticaria, many more with autoimmune urticaria had a coexisting autoimmune disease (50% vs. 23.7%).

Interestingly, in 43 patients (42.2%) with CU there was a familial history of autoimmune disease, in 26 patients (25.5%) familial history of atopy, and in 8 patients (7.8%) familial history of chronic urticaria.

Discussion

In line with the findings of previous studies, CSU occurs with a higher frequency than CIndU, with comorbid CIndU likely in a fifth of the cases, despite heterogeneity in the regional distribution of CU and its phenotypes [8]. Symptomatic dermographism has previously been reported to be the most common of the physical urticarias [9]. We observed that delayed pressure urticaria was the most commonly diagnosed CIndU subtype.

Table 1. The Comorbidity Profile of Chronic Urticaria Patients.

Diseases		Prevalence in all CU patients (n=102)	
Atopy and allergies	Drug allergy	21,6%	49,0%
	Allergic rhinitis	20,6%	
	Food allergy	17,6%	
	Asthma	15,7%	
	Inhaled allergy	12,7%	
	Atopic dermatitis	10,8%	
	Rhino-conjunctivitis	6,9%	
	Insect venom allergy	6,9%	
Chronic inflammation and infectious	Sinusitis	17,6%	36,3%
	Gastritis	10,8%	
	Urinary tract infection	7,8%	
	Helicobacter pylori	6,9%	
	Periodontitis	5,9%	
	Otitis media	2,0%	
	Hepatitis B	1,0%	
	Autoimmune hepatitis	1,0%	
Thyroid disorders	Hashimoto's disease	22,5%	36,3%
	Hypothyroidism	17,6%	
	Hyperthyroidism	2,9%	
	Graves' disease	2,0%	
	Goiter	1,0%	
Psychiatric disorders	Depression	16,7%	25,5%
	Anxiety disorders	14,7%	
Skin diseases	Allergic contact dermatitis	9,8%	18,6%
	Psoriasis	4,9%	
	Vitiligo	2,0%	
	Seborrheic dermatitis	1,0%	
	Alopecia areata	1,0%	
Gastrointestinal diseases	GERD	10,8%	18,6%
	IBS	8,8%	
	Peptic ulcer	2,9%	
	Celiac disease	1,0%	
Cardiometabolic diseases	Arterial hypertension	8,8%	10,8%
	Ischemic stroke	2,0%	
	Diabetes mellitus type 2	1,0%	
Connective tissue diseases	SLE	2,9%	6,9%
	RA	2,9%	
	MCTD	1,0%	
	Polymyositis	1,0%	
Neoplasm	Melanoma	1,0%	2,0%
	Carcinoid tumor	1,0%	
Others	Migraine	12,7%	19,6%
	Endometriosis	5,9%	
	Pernicious anemia	2,0%	
	epilepsy	1,0%	

CU = chronic urticaria; GERD = gastroesophageal reflux disease; IBS = irritable bowel syndrome; MCTD = mixed connective tissue disorder; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

Table 2. The Number and Combination of Autoimmune Diseases in Chronic Urticaria Patients.

AID, No.	Prevalence in all CU patients with AID (n=31)	Prevalence in all CU patients (n=102)
Hashimoto's disease, 23	74,2%	22,5%
SLE, 3	9,7%	2,9%
RA, 3	9,7%	2,9%
Vitiligo, 2	6,5%	2,0%
Graves' disease, 2	6,5%	2,0%
Pernicious anemia, 2	6,5%	2,0%
Autoimmune hepatitis, 1	3,2%	1,0%
Celiac disease, 1	3,2%	1,0%
Alopecia areata, 1	3,2%	1,0%
MCTD, 1	3,2%	1,0%
Polymyositis, 1	3,2%	1,0%
Number of AID in CU		
One, 23	74,2%	22,5%
Two, 7	22,6%	6,9%
Three, 1	3,2%	1,0%
Combination of CU of two or more autoimmune diseases		
HT + pernicious anemia, 2	6,5%	2,0%
HT + celiac disease, 1	3,2%	1,0%
HT + vitiligo, 1	3,2%	1,0%
HT + RA, 1	3,2%	1,0%
HT + SLE, 1	3,2%	1,0%
HT + SLE + RA, 1	3,2%	1,0%
alopecia areata + SLE, 1	3,2%	1,0%

AID = autoimmune diseases; CU = chronic urticaria; HT = Hashimoto's disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

The available data suggest that 33–67% of all patients with CU have concomitant angioedema [10]. We obtained very similar results. Angioedema usually affects the skin on the face, mainly the lips and eyelids [11]. In contrast, our results showed that non-facial body areas were the most frequent locations for angioedema, which may be related to the relatively high percentage of patients with delayed pressure urticaria in our study, which is characterized by erythematous swelling of the skin 4 to 6 hours after the application of pressure. The swelling of the hands and feet provoked by pressure may be difficult to tell apart from swelling caused by angioedema [12].

Most publications do not provide information on the frequency of episodes of CU. The data mainly relate to the duration of the disease, which is estimated at generally 1-5 years [10]. The frequency of urticaria symptoms in this study was estimated as: 59.8% daily, 16.7% several times a week, 8.8% several times a month, and 14.7% irregularly.

Many researchers analyzed mainly allergic diseases accompanying urticaria. Shalom et al. [13] reported that the most common were allergic rhinitis (19.9%) and asthma (10.8%). Zuberbier et al. [14] also concluded that atopy, mainly allergic rhinitis (41.9%), and atopic dermatitis (18.9%) were the most common. A Korean study also highlighted the high burden of allergic rhinitis, drug allergies, and asthma [15]. In the Scandinavian AWARE study, a follow up-study of patients with CU refractory to antihistamine treatment, the most common comorbidities were atopic diseases including asthma, allergic rhinitis, food allergies, and atopic dermatitis. [16]. Our results are similar to these past findings. Type-I auto-allergic CSU is quite common and possibly more likely associated with atopic comorbidities than type- IIb auto-immune driven CSU, which seemingly be the reason for the high frequency of atopic comorbidities observed in the overall CU population [17].

On the other hand, the large registry study from Germany demonstrated hypertensive diseases (43.5%), lipoprotein metabolism disorders (32.1%), and affective disorders (26.0%) as the most frequently reported comorbidities of

special interest [18]. This is in contrast to our findings where coexisting hypertension was reported by only 8.8% of patients. A retrospective Danish cohort study that examined the prevalence of cardiovascular diseases did not find any increased risk of these in CU patients compared to the general population [19]. However, an extended duration of CSU is more likely in patients with arterial hypertension [5]. In the Taiwan study, among the four categories of comorbidities that were examined, inflammatory diseases (9.78%) were the most prevalent, followed by psychiatric disorders (8.53%), rheumatic diseases (2.48%), and thyroid disorders (1.78%) [20].

Other studies have found that psychiatric comorbidities were the most commonly recognized in CU patients, ranging up to 60%. Anxiety, depression, and somatoform disorders have been reported to be the most prevalent mental disorders in CU patients [21]. In our study, almost 26% of patients reported psychiatric disorders, most often depression.

Many authors emphasize the possible role of parasitic infestations and inflammation in chronic urticaria [22]. In our analysis, none of the respondents reported parasitic infestations. Whereas among inflammatory diseases, the most common were sinusitis (17.6%), gastritis (10.8%), and urinary tract infection (7.8%). Authors from Taiwan found peptic ulcer was the most prevalent inflammatory disease (4.83%), followed by hepatitis B/hepatitis C (1.64%) and periodontitis (2.82%) [20].

The association between CU and neoplasm diseases is still controversial. One population-based study reported no association between CU and cancer [23]. A study from Taiwan demonstrated an increased risk of hematological malignant tumors, especially non-Hodgkin lymphoma, in patients with CU [24]. A Korean study showed an increased risk of non-hematological tumors, especially stomach, thyroid, and liver cancers in the case of CU, and thyroid, liver, and prostate cancers in the case of CSU [15]. In our study, two patients reported the presence of melanoma and carcinoid tumor.

A systematic review of the literature on autoimmune comorbidities in patients with CU showed that the most common autoimmune comorbidities were autoimmune thyroid diseases and vitiligo [25]. Our results are similar, except that the next most common diseases after autoimmune thyroid diseases (24.5%) were rheumatoid arthritis (2.9%) and systemic lupus erythematosus (2.9%).

Thyroid dysfunctions, especially autoimmunity, have been most commonly found among CU patients, with the reported prevalence ranging up to more than 50% depending on the inclusion criteria. Association studies using the presence of anti-thyroid antibodies as the criteria usually obtained higher frequencies [26]. In this study, we defined the presence of thyroid disorders based on self-reports by patients. We found the prevalence of thyroid diseases among CU patients was about 36.3%. Hashimoto's thyroiditis was the most prevalent thyroid disease (22.5%), followed by hypothyroidism (17.6%), hyperthyroidism (2.9%), and Graves' disease (2.0%).

The relationship of CU with autoimmune thyroid diseases has been underlined for many years and a large number of studies have been conducted worldwide [27]. It is worth noting that most of the studies have analyzed the relationship between CSU and thyroid autoimmunity. Little is known about whether CIndU is also linked to thyroid autoimmunity. Our data showed that 26,3% of patients with isolated CSU had autoimmune thyroid disease, while with isolated CIndU only 13,6%.

The guidelines of the EAACI/GA2LEN/EDF/WAO recommend that physicians assess CU patients for family history of urticaria and atopy [1]. In our study, family history of urticaria and atopy was negative in the majority of patients, 92.2 % in urticaria and 74.5% in atopy. On the other hand, autoimmune disorders were common in family members.

Our study has some limitations. First, respondents were recruited through Facebook groups and there is a potential sample selection bias. Our study population cannot be representative of all chronic urticaria patients as the participation of men has been unrepresentative. We did not use any instrument for assessing urticaria severity therefore we do not know the severity of the disease in the respondents. However, patients participating in urticaria groups typically have more severe and uncontrolled symptoms of the disease. In addition, women participate more actively in social networks and are looking for more information about the diseases they suffer from. Another limitation is the fact that middle-aged patients are more likely to participate actively in social networks and online survey studies thus the obtained data may not be representative of all age groups. Most of our study population were patients between the ages of 19 and 39. Taking into account all of this, our data have over-represented young women and those who have more severe chronic urticaria.

As mentioned above, young women and patients with severe diseases seek more information about the disease they suffer from and are more active on social media. Such a profile of patients participating in our study may affect the percentage of comorbidities which is relatively high compared to other reported publications.

Finally, the high registration percentage of delayed pressure urticaria in our study may be a result of the percentage of angioedema. Regarding the fact that it can be difficult for patients to distinguish between swelling caused by pressure from swelling caused by angioedema they often confuse the two entities or report them in the same way.

Conclusions

In conclusion, CU significantly influences the quality of patients' lives, which may be negatively affected by the association with a wide range of comorbidities. Our study found that the most common comorbidities in CU include atopic and allergic diseases, chronic inflammations, thyroid, and psychiatric disorders. This pattern of comorbidities seems to be specific to CU. Our data suggest that patients with autoimmune urticaria are more likely to have autoimmune comorbidities than patients without this subtype of CSU. This may be explained by the known co-occurrence of multiple autoimmune phenomena and autoimmune diseases. Therefore, autoimmune comorbidities in patients with chronic urticaria may suggest the presence of an autoimmunological subtype of CSU, which is usually more severe and has a significantly worse response to omalizumab treatment [28]. Knowledge of the comorbidities of CU may support clinicians in appropriately managing and treating this condition.

Acknowledgments

We would like to express our gratitude to the patients who complete our survey.

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