Original Article

Comorbidities in Patients with Chronic Urticaria; linical and Epidemiological Review Study

Javad Ghaffari[1] **Abbas Dabbaghzadeh[2*]** Negar Ghaffari[3]

1. Professor of allergy and clinical immunology, Department of Pediatrics, Faculty of Medicine, Molecular and Cell Biology Research Center, Mazandaran University of Medical Sciences, Sari, Iran
2. Assistant Professor of Allergy and Clinical Immunology, Department of Pediatrics, Faculty of Medicine, Pediatric Infectious Diseases Research Center, Mazandaran University of Medical Sciences, Sari, Iran
3. Medical student, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

*__Correspondence to__: Abbas Dabbaghzadeh
siamakdabbaghzade@yahoo.com

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Abstract

***Background and purpose*:** Urticaria is a pruritic cutaneous disease characterized by weal and flare. Acute and chronic urticaria affects the quality of life. Some abnormalities are associate or comorbid with urticaria. The purpose of this study was to examine comorbid conditions in patients with urticaria.

***Materials and Methods*:** We searched in many databases including Google Scholar, PubMed, Scopus, and Embase. Keywords were comorbid and urticarial. All full articles and the English language were included. We evaluated 500 articles that reported association or relation as comorbidity between urticarial and disorders in primary screening to be 250, 100, 80, and 70 articles in Google Scholar, PubMed, Scopus, and Embase, respectively.

***Results*:** Prevalence of psychiatric problem (according to SCID-1) was 60% in chronic idiopathic urticaria. Thyroid autoantibodies (anti-thyroglobulin and anti-peroxidase) were found to be positive about 5 to 15% of CU. Food allergy, allergic rhinitis, atopic dermatitis, and asthma were significantly higher in CSU. Eradication of H. pylori infection was a tendency to more rapid improvement of chronic urticaria.

***Conclusion*:** Psychiatric disturbances, such as depression or anxiety and autoimmune thyroid disorders, were documented to be more common in chronic urticaria which should be considered as comorbidity.

Key Words: Chronic Urticaria; Comorbid; Psychology; Treatment; Thyroid

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1. Introduction

Urticaria or hives is a pruritic cutaneous disorder with central edema (wheal) and peripheral erythema (flare) (1). The prevalence of urticaria is 10-30% in general population (1, 2). Urticaria disorder is more common in female than male (3). Urticaria especially chronic urticarial (CU) has significant effects on quality of life (4, 5). The exact etiologies of urticaria are unknown, but genetic and environmental factors contribute to it (6). Chronic urticaria (more than 6 weeks) is less common than acute urticarial. CU could be spontaneous (CSU) with no obvious eriology or inducible with a clear etiology. Etiology of CU is often idiopathic in 80-90%. Of these patients, 40-50% have autoimmune pathophysiology. Some patients with chronic urticaria have inflammation and coagulation pathophysiology. Finally, 40-50% are really pure idiopathic (1,2,7). Genetic factors are extensive and environmental triggers, such as aeroallergens (indoor and outdoor) which can induce urticaria, so that in the north of Iran, mite was more common positive in chronic urticaria patients (7-10). Variable disorders can be associated with urticarial. Helicobacter pylori and rarely malignancies are possible induce urticaria (11,12). Acute urticaria is often created due to infections, drug, food, and insect (1, 2). Diagnosis of urticaria is often clinical based on exact history and physical examination. In special conditions, laboratory tests might be necessary for diagnosis. In acute urticaria, there is usually no need for laboratory examination as it is usually self-limited (1, 2, 13). The first line treatment of urticaria is antihistamines (AH). Of course, avoidance of obvious risk factor is more important. Most of the cases improve with AH with few or no complications. Second-generation antihistamines are preferred which have no or less sedating. The second line is increasing double dose of AH. The third line drugs are anti leukotrienes and/or Omalizumab (150 or 300 mg every 4 weeks) (1, 2, 14-18). Definition of co-morbid is related to or denoting a medical condition that co-occurs with another. In comorbidity, there may be dependency between two conditions, but there is usually not any dependency between them. However, comorbid is associated with more complex clinical health (19). Urticaria disorder as another allergic disorder may be associated with other conditions that affect it. When a patient with CSU is not responsive to standard treatment, we should be investigating for underlying diseases. There is association between autoimmune and psychological disorders with urticarial (20, 21). The aim of this study was to evaluate comorbid conditions in patients with CSU.

2. Materials and Methods

The current study was a narrative review. We searched in many database including Google Scholar, PubMed, Scopus, and Embase. Key words were comorbidity disorders, comorbidity diseases, association, relation, chronic spontaneous urticarial, chronic idiopathic urticarial, and chronic urticaria. All original and review full articles in English language were included. The search was in the time range of 2005 to 2020. Hence, 500 articles that reported association or relation as comorbidity between urticarial and disorders in primary screening were evaluated (250, 100, 80, and 70 articles in Google Scholar, PubMed, Scopus and Embase, respectively). Many research articles were excluded in primary and

secondary evaluations due to their abstracts, non-English languages, not evaluating relation or comorbidity, and no access to their full texts. Inclusion criteria were association or relation or comorbidity of disorders with any chronic urticarial. Exclusion criteria were abstract articles, non-English languages and acute urticaria. Finally, 62 articles were evaluated.

3. Results

Psychiatric disturbances, such as depression and anxiety can create chronic urticaria (Table-1).

Table 1. Psychological problems in chronic urticaria

Disorder	Number, ages(y)	Severity of PTSD	Prevalence (%)	References
Post-traumatic stress disorder(PTSD) in CIU[a] without allergy	100, >18	Mild Moderate Moderate to severe Severe	42 20 13 6	22
PTSD in CIU[a] with allergy	100, >18	Mild Moderate Moderate to severe	57 12 10	22
PTSD in CU[b]	5,	Treatment of PTSD	All Improved of CU (clinical and QOL	23
DHEA-S in CIU[a] with negative ASST	32, adults	Active of CIU resolution of CIU	Lower Higher	24
DHEA-S in healthy	40, adults	-	Higher	24
DHEA-S in psychological distresses	Adults	-	Lower	24
DHEA-S in CU and psychologic/ooooooal symptoms	Adults	-	Lower than healthy group	25
Depression, trait anxiety and phobia	54,Children	27 with CIU 27 with healthy	70% affected 30% affected	26
PTSD in CIU and control	104, >18 years	89=CIU 15=control	69% 43%	27
Quality of life	196,	100=CU 96= healthy	Lower Higher	28
Depression, anxiety and somatoform disorders	196	100=CU 96= healthy	Higher Lower	
Mental disorders in CSU	100	Anxiety Depression Somatoform	30% 17% 17%	29
psychiatric problem in CIU	-	Before CIU After CIU	7% 52%	30
psychiatric problem in CIU	208,adults	CIU=75 Control=133	P<0.05	31
Psychiatric disorders	Children		70.4%	32
Psychiatric disorders		CU	31.6%	33

[a]CIU= chronic idiopathic urticarial, [b]CU= chronic urticarial, QOL= quality of life, DHEA-S= dehydroepiandrosterone sulphate

In a study, severity of urticaria was higher in patients with positive ASST than negative ASST (25). Hergüner et al. showed that there was no correlation between severity and duration of CIU with psychological functions (26). PTSD severity was lower in married CIU and severity of PTSD symptoms was associated with urticaria severity (27). Emotional distress was more common in CSU with mental disorders than without mental diseases (29). Yang et al. reported that

insomnia is the most important risk factor for inducing CIU (31). Hypothyroidism is more common than hyperthyroidism in CU, although most CU cases experience euthyroidism (3,6).

Rheumatoid arthritis (RA) with positive 2.1% Rheumatoid factor and type I diabetes mellitus were also observed to be more common in CU. Antinuclear antibodies were significantly more common in CU than normal people. Type I diabetes mellitus, Sjogren syndrome, celiac disease, and SLE was significantly more common in women with CU than normal women (3).

In a systematic review in children less than 12 years old with CSU, a positive ASST (36.8%), detectable antinuclear antigen (10.4%), seroprevalence of Helicobacter pylori (21.1%), and low 25-OH vitamin D level (69.1%) were documented. These studies did not have control groups (32).

Food allergy, allergic rhinitis, atopic dermatitis and asthma were significantly higher in CSU (34). Allergic rhinitis, drug allergy and asthma were found to be the most common comorbid disorders in patients with CU and or CIU. The reason for this relation is inflammation due to an IgE-mediated immune response to specific allergens (35-37).

Malignancies may be association with CU, but there are not enough studies confirming it. One study did not report association between cancer and CU (10), and two other studies showed association between CU and cancer (38,39).

CSU is common in SLE patients, and they often co-exist, especially in female. CSU is a risk factor for developing SLE. SLE has more severity and bad prognosis when coexisting with CSU. Pathogenesis of both diseases is inflammation, autoimmunity, complement and coagulation (3,40). Thyroid abnormality is more common in CU (Table 2).

Table 2. Thyroid abnormality in chronic urticaria

Test	Urticarial	Prevalence (%)	References
Thyroid antibodies (anti-thyroglobulin and anti-peroxidase)	CU	5-15%	3,6,41
thyroid biological anomalies	CSU in children less than 12	6.4%	32
Autoimmune thyroid diseases	CSU	4.3-57.4%	20
Anti-thyroid antibodies	CSU, all cases	10-42.5%	42
Autoimmune thyroid diseases	CSU, adult women	4.3-57.4%	42
SLE	CSU	-	3,40

Immunological alteration in CSU and autoimmune thyroid disease are increasing IL-6, decreasing number and function of lymphocytes, and increasing IL-17 lymphocytes. ASST can be an initial test for the detection of underling autoimmune mechanism (42). The CD63 basophil activation test is more helpful for detection of underling autoimmunity (43). Anti-TPO and TSH should be evaluated in patients with urticarial and Levothyroxine therapy of chronic urticarial, which is beneficial in

the treatment of thyroid dysfunction (44). In a case-control study, there was found a significant association between CSU and thyroid autoimmunity (45). A few studies report an association between CSU and hypertension, and CSU may be a risk factor for inducing hypertension (46,47).

4. *Discussion*

CU, and for example CSU, is overall more common in women than in men. Exact etiology is not clear, and that, why CU is more common in female, perhaps one reason is autoimmunity pathogenesis. Autoimmunity is contributed in 40-45% of CSU, and basically, autoimmune disorders are more common in female (35, 48,49). Also, CSU may be severe and longer in females probably due to sex hormones, but it is not exactly clear (24, 50). Autoimmune pathophysiology may also be the common reason for both thyroid autoimmunity and CU, so that both entities may coexist in a patient. Researchers confirmed autoimmunity in CU with demonstration of IgG autoantibodies anti-IgE and IgG anti-FcεRI targeted at basophils and mast cells. Therefore, there is possible comorbidity of autoimmune disorders with CU. Some research showed significant improvement (both partial and/or total) in CU with levothyroxine treatment of thyroid autoimmunity disorder (6,41,51,52) which can support relation and association between CU and thyroid autoimmune disease. In Pan`s study, there was found a significant increase in positive thyroglobulin antibody (TgAb), thyroid microsome antibody (TmAb), and thyroid peroxidase antibody (TPOAb) in patients with urticarial compared to normal people. They suggest thyroid autoimmunity may be associated with urticarial (51). In our study, there was documented a significant increase in both anti-TPO and thyroglobulin antibody (anti-Tg), and antibodies in CU than normal general population (6). In patients with positive antibodies with normal thyroid function (euthyroid) who do not respond to routine antihistamines, treatment with levothyroxine is suggested (6). Hypo or hyperthyroidism has a specific treatment. Autoimmunity has a significant role in pathogenesis about half of CIU.

Kolkhir et al. in a systematic review described a close relationship between autoimmune thyroid disease and CSU (20). Thyroid dysfunction (more common in adults than children) is more common in CSU patients and hypothyroidism and Hashimoto`s thyroiditis are more common than hyperthyroidism and graves` disease. Pathogenesis of CSU in patients with autoimmune thyroid disorder may also develop autoantibody IgG (strong evidence) and IgE (weak evidence) against thyroid antigens, especially TPO, then it can end in the formation of immune-complex association complement activation and mast cell degranulation. Why thyroid disorder is more common in CSU than normal people is not clear. ***There*** is strong evidence that CSU is improved with levothyroxine or other thyroid drugs treatment in patients with positive thyroid autoantibodies. CSU in hyperthyroid and eu-thyroid patients have better response to treatment than hypothyroid patients (strong evidence) (20). Psychiatric disturbances, such as depression and anxiety, can create urticarial (22-31). All urticaria patients, especially CU, are affected by psychiatric behavior which creates more depression and anxiety. Psychiatric diseases are more common in people who have experienced stressful life events (26).

Usually severity of disease is a risk factor for outcomes. Severity of urticarial might have effect on creating psychiatric disorders (26-29), which is not confirmed by other studies (53, 54). Because most studies showed reciprocal effects of CIU and psychiatric disorders, comorbidity is very high between them (22-31). Posttraumatic stress disorder (PTSD) symptom severity from past trauma can cause the exacerbation of CIU (22). CIU can also induce psychiatric abnormality, such as stress. Skin disorders, such as urticaria and psychiatric diseases, frequently occur together. Pathogenesis of this interaction is the secretion of local neuroimmunoendocrine due to stress (22). Histamine is the major wake-promoting neurotransmitter in the central nervous system which is increased in PTSD while increasing urticarial. Lower serum levels of dehydroepiandrosterone sulfate (DHEA-S) during active stage of urticarial cause more psychologic distress (23-25). There was also found an association between CU and psychological problems, because DHEA-S decreased in both (24,25). Severity of mental disorder has a direct relationship with QOL in CSU (28,29). The diagnosis and therapy of mental disorders and emotional distress improved QOL and CSU symptoms (26, 28, 29).

Several studies revealed comorbidity of mental disorders in CSU from 35-60%. The reasons for these wide range (35-60%) include; sample size, geographic area, genetic, age, way of collecting data (direct interview by psychiatrist, questionnaires; SCL90R, HADS, SCID-1, and etc.) (30,55). Among mental disorders, anxiety depression and somatoform diseases were more common in CSU patients (21,53,54). PTSD treatment improved clinical manifestations and quality of life of urticarial, which was a reason to confirm comorbidity of PTSD with CU (23-25).

Because all our reviewed articles reported association between CSU and/or CIU with psychological disorders, the psychological status should be considered routinely in children and adult with CU (22-31).

The atopic diseases (rhino conjunctivitis and eczema) were also found to strongly overrepresented among CU patients (56). Food allergy, allergic rhinitis, atopic dermatitis, and asthma were significantly higher in CSU (34). Allergic rhinitis, drug allergy and asthma were the most common comorbid disorders in patients with CU and or CIU (35-37). HBV and HCV were documented to be not common in CSU, and routine examination was cost/benefit for them. If there is clinical suspension or abnormal liver function test and/or urticarial vasculitis, HBV and HCV should be considered (57).

In the study of Ghazanfar et al., rheumatoid arthritis was numerically much higher represented than SLE, thyroiditis, and vitiligo in CU (56). In a review study by Shakouri et al., half of the studies reported improved CU after treatment of H. pylori, but the other half did not show improved CU after H.pylori management (58). In another review study, there was found a significant association between H. pylori treatment and CU improvement, which did not depend on the eradication of H. pylori (59). Eradication of H. pylori infection was a tendency to more rapid improvement of CU (60), but in a clinical study in Iraq, H. pylori infection was not associated with CU. Of course, the sample size of the study was small (number of CU cases=49) (61). One case of CU was reported to have improved after the underlying H. pylori infection was treated (62). Despite there were some studies that revealed the

improvement of CU and/or CIU or CIU with treatment of H. pylori, these were not found high evidence of base medicine.

However, there was observed association and comorbidity between psychological dysfunction, such as stress and anxiety, atopic condition, and autoimmune disorders, such as thyroid dysfunction with CU or CIU and/or CSU. Each patient with CU should be evaluated for psychological problems and autoimmune thyroid diseases. CU patients often need counselling with a psychiatrist.

5. *Conclusion*

Psychiatric disturbances, such as depression or anxiety and autoimmune thyroid disorders, are more common in CU which should be considered as comorbidity of CU.

Conflicts of Interest

The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

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