

Demographic and Comorbidity Associations in Chronic Spontaneous Urticaria: A Retrospective Analysis

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Abstract

Background: Chronic Spontaneous Urticaria (CSU) is a painful and often distressing dermatologic condition characterized by recurring wheals and intense pruritus that significantly impair patients' quality of life. Despite substantial research efforts, the exact etiology and pathophysiological mechanisms underlying CSU remain elusive. **Objective:** This study aimed to investigate demographic patterns in patients with CSU and identify key comorbidities, with a particular focus on Herpes Simplex Virus-2 (HSV-2) and Vitamin D deficiency. By highlighting these associations, we sought to deepen clinical understanding and encouraged future research to elucidate potential causal pathways. **Methods:** In this single-institution retrospective analysis conducted at Montgomery Allergy and Asthma, 195 patient charts were reviewed. Patients were included if they were aged 18 or older and had a documented clinical diagnosis of CSU. Demographic data—such as age, sex, and race—were recorded, as were comorbidities and specific laboratory findings (HSV-2 serology and 25-hydroxy Vitamin D). Deficiency of Vitamin D was defined as serum levels below 30 ng/mL. **Results:** Of the 195 patients, 35 (17.9%) were male and 160 (82.1%) were female. The racial distribution was 47.2% African American, 45.1% Caucasian, 6.2% Asian, and 1.5% Hispanic. Among 88 patients tested for HSV-2, 46 (52.27%) were positive, with a larger proportion being female (90.7%). Vitamin D levels were assessed in 116 patients, of whom 84 (72.41%) were deficient. We examined the comorbidity association between vitamin D deficiency and HSV-2 positive status as a possible causation relationship. The test yielded a $\chi^2 = 0.44$ and a $p = 0.50$ indicating that there is no statistically significant association between vitamin D deficiency and HSV-2 positivity in the cohort study. **Conclusion:** HSV-2 positivity and Vitamin D deficiency emerged as prominent findings in this patient cohort, however, the association of these two comorbidities was not

found. While causative relationships were not determined, this study underscores the need for broader, multicenter investigations to clarify immune and inflammatory processes potentially linking these comorbidities to CSU.

Keywords

Chronic Spontaneous Urticaria, Comorbidities, Demographics, Allergic Rhinitis, Vitamin D Deficiency

1. Introduction

Chronic Spontaneous Urticaria (CSU) is a debilitating skin disorder characterized by the recurrent appearance of pruritic, red, and elevated welts (wheals) that manifest without a clearly identifiable external trigger. These wheals not only cause physical discomfort but also disrupt patients' daily lives, affecting sleep, mental health, and overall quality of life [1]-[3]. Approximately 40% of patients with CSU also report having angioedema [4]. Women are affected twice as often as men and most patients are over 20 years of age. Although various investigations have expanded our understanding of CSU, the precise pathophysiology remains unclear. Proposed mechanisms encompass immune dysregulation, mast cell activation, and elements of autoimmunity, all of which underscore the complex interplay between environmental and genetic factors [5]-[7]. Given this complexity, additional insights into the demographic and comorbidity profiles of individuals with CSU may help clinicians better recognize potential risk factors, improve diagnostic approaches, and guide therapeutic strategies.

A systematic review of the literature will find the most common comorbidities associated with CSU were autoimmune thyroid diseases [8]. The prevalence of anti-thyroid disorders and CSU implies a pathogenic mechanism that includes autoantibodies, and immune complexes. The reported cases of CSU and accompanied thyroid diseases range from 40-50%. Other studies have found an association of CSU and various psychiatric diseases such as emotional distress, anxiety, and depression [9]. Despite the overwhelming evidence that CSU is associated with anti-thyroid disorders and psychiatric disorders, the underlying cause of the disorders is still unknown and approximately 50% of CSU cases remain idiopathic [10]. This study evaluates patient demographics and the prevalence of specific comorbidities—chiefly HSV-2 and Vitamin D deficiency—to shed light on the multi-faceted presentation of CSU. Ultimately, by identifying and discussing these associations, we aim to pave the way for further research that will refine our understanding of CSU and its underlying mechanisms.

2. Methods

2.1. Study Design

This retrospective study was conducted from November 2021 to October 2022 at

Montgomery Allergy and Asthma in Montgomery, Alabama, and included a total of 195 patients aged 18 years and older. To be included in the selection, patients had to be diagnosed clinically with Chronic Spontaneous Urticaria and were currently being treated for this disorder. The testing for comorbidities was both routine and based on their current symptoms. Researchers reviewed medical records for demographic data—including age, sex, and race—along with documentation of comorbid conditions and relevant serological testing. Each patient was assigned an anonymous unique study identifier to maintain confidentiality. The presence of HSV-2 was tested by an IgG Serological Blood test. Vitamin D was measured using the 25 Hydroxyvitamin D Blood Test and a value <30 ng/ml was considered deficient in Vitamin D.

2.2. Ethical Approval

This study was reviewed and approved by the Institutional Review Board (IRB) at Huntingdon College. All patients had agreed to the release of their medical records for this study. This methodology aligns with the Declaration of Helsinki, which outlines ethical principles for medical research involving human subjects.

3. Results

The study included a total of 195 patients diagnosed with CSU. Male patients accounted for 35 (17.9%) of the cohort, while female patients accounted for 160 (82.1%). When examined by race, 47.2% of the patients identified as African American, 45.1% as Caucasian, 6.2% as Asian, and 1.5% as Hispanic. This distribution aligns closely with local census data for Montgomery, Alabama, where 63.0% of the population is African American, 27.7% is Caucasian, 3.2% is Asian, and smaller proportions belong to other racial groups [11]. A list of the tested comorbidities and the number of afflicted patients is listed in **Table 1**. All statistical calculations were done using Microsoft Excel 365.

Table 1. Common comorbidities Associated with Chronic Spontaneous Urticaria in this cohort study.

Disease	# Afflicted
Allergic Rhinitis	142
Non-Allergic Rhinitis	105
Vitamin D Deficiency	84
GERD	58
Angioedema (with Urticaria)	55
HSV-2	46
Contact Dermatitis	38
Asthma	26
High IgE	26
Atopic Dermatitis	22

Among the 88 patients tested for HSV-2, 46 (52.27%) were positive, with women accounting for 90.7% of these cases. Additionally, Vitamin D levels were assessed in 116 patients, revealing that 84 (72.41%) were deficient.

3.1. HSV-2 and CSU Relationships

A significant portion of our CSU cohort tested positive for HSV-2, at a prevalence of 52.27% among those evaluated. This figure markedly exceeds the US national average of 11.9% [12]. Additionally, 90.7% of those who tested positive were women, echoing national trends that show a higher HSV-2 prevalence among females (25%) compared to males (17%) [12]. Due to the mucosal environment of the female reproductive track, a male-to-female transmission is easier. However, the higher percentage we observe here may be due to the greater likelihood that women get tested more for HSV-2.

While our findings do not confirm causality, existing research suggests that HSV-2 infection can intensify certain immune pathways [13]. Specifically, HSV-2 infection of human genital epithelial cells is linked to increased Toll-like receptor 9 (TLR9) expression through the SP1/JNK signaling pathway—a key modulator of inflammatory processes [14]. The correlation between HSV-2 and CSU observed here may reflect an overlapping mechanism of heightened immune and inflammatory activity, though additional studies are needed to define the exact nature of this relationship.

3.2. Vitamin D Deficiency as an Inflammatory Marker

Observed Among the 116 patients tested for Vitamin D, 84 (72.41%) were found to have deficient serum levels. These data are consistent with prior research showing that patients with Urticaria (acute and chronic) usually have lower Vitamin D levels compared to control groups [15]-[17]. This association suggests a possible connection between Vitamin D levels and inflammatory states associated with CSU, but it does not establish a direct causal relationship. We might expect Urticaria patients with positive HSV-2 test to have lower levels of Vitamin D. We tested this on our population. A total of 88 individuals were assessed for vitamin D deficiency and HSV-2 positivity. Of those who were vitamin D deficient, 23 (56.1%) tested positive for HSV-2, while among those who were not deficient, 23 (48.9%) were HSV-2 positive. The test yielded a χ^2 ($n = 88$) = 0.44 and a $p = 0.50$ indicating that there is no statistically significant association between Vitamin D deficiency and HSV-2 positivity in the cohort study. Vitamin D deficiency may be both a product of, and a contributor to, systemic inflammation, a hypothesis that warrants more in-depth evaluation through mechanistic and longitudinal studies.

3.3. Study Limitations

Despite providing valuable insights, this study has limitations that should be addressed in future research. First, the single-institution, retrospective design limits the generalizability of our findings. Larger, multicenter studies could offer broader

demographic representation and enhance statistical power, enabling more definitive conclusions about the associations observed. Moreover, while correlations were identified, causative relationships cannot be established without longitudinal or interventional approaches that can clarify temporal and mechanistic links between HSV-2, Vitamin D deficiency, and CSU.

4. Conclusions

This retrospective evaluation of 195 patients with Chronic Spontaneous Urticaria highlights noteworthy demographic distributions and high prevalence rates of HSV-2 and Vitamin D deficiency. Although these findings underscore potential immunological and inflammatory dimensions involved in CSU, definitive causal pathways remain uncertain. Further large-scale, prospective studies are warranted to elucidate the interplay between these comorbid conditions and CSU pathophysiology, potentially guiding more effective screening, management, and therapeutic interventions for this challenging disorder.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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