



## A Systematic Review of Findings on Comorbidities of Chronic Urticaria (Asthma, Atopic Dermatitis, and Allergic Rhinitis)

### Abstract

The relationship between the occurrence of chronic urticaria (CU) and asthma, atopic dermatitis (AD), and allergic rhinitis (AR) has remained unclear over the years. Our aim was to provide an update on knowledge from observational studies determining the prevalence of asthma, AR and AD in patients with CU from PubMed, EMBASE, Clinicaltrials.org, and Cochrane Library databases. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used in the identification of literature for analysis. The quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) which revealed that the selected articles are of good quality. A total of 12 studies met the criteria and were included in this review. Two of the publications were prospective, six retrospective, and four were cross-sectional studies. Except for one article, all the studies reported data on the occurrence of asthma, AR, and AD. AR was the most prevalent co-morbidity with its frequencies ranging between 16.5%-48%, followed by asthma that occurred in 4.7%-25.8% of patients, and finally, AD was the least reported condition among CU patients (1%-22.5%), particularly among the elderly. Nonetheless, 50% of the selected articles were based on archived data or analysis of medical records which are likely to be biased. Therefore, there is a need for additional longitudinal studies to explore the role of age in the occurrence of AD, AR, and asthma among CU patients.

### Results

#### Study Characteristics

The electronic search yielded n=867 studies, including n=597 from PubMed, n=174 EMBASE, n=1 Clinicaltrials.org, and n=95 Cochrane Library. An additional n=4 records were identified through the hand search. After elimination of n=321 duplicates, another n=429 were excluded based on abstract and title screening. In addition, of the n=113 full-text publications which were assessed for eligibility, n=101 were removed for not reporting on AR, AD, or asthma. Therefore, a total of n=12 studies were included in the systematic review. The selected studies were carried out in various countries across the world, including two in the United States<sup>1, 2</sup>, three in Thailand<sup>3, 4</sup>, two in Germany<sup>5, 6</sup>, two in Korea<sup>7, 8</sup>, one in Israel<sup>9</sup>, one in Taiwan<sup>10</sup>, and another one involved patients in Denmark, Norway, and Sweden<sup>11</sup>. Two of the publications were prospective<sup>11, 6</sup>, six retrospective<sup>2 3 4 7 10 12</sup>, while four were cross-sectional studies.<sup>1, 5, 8, 9</sup>

Whereas six of the investigations focused on describing the baseline features of AWARE patients with CU or CSU<sup>11, 6, 7, 2, 1, 12</sup>, another five concentrated on the prevalence of the comorbidities (AR, AD, and asthma) of CU<sup>5, 3, 12, 8, 4, 9</sup>, and one explored the correlation between dry eye disease (DED) and asthma.<sup>10</sup> In total, the number of patients in each of the study ranged between 93 to 74,335, while in four studies which involved controls<sup>8, 9, 5, 10</sup> the number vacillated between 4,053-1,318,043. In a majority of the studies (66.7%), identification of CU was done primarily through doctor diagnosis<sup>3, 1, 12, 4, 7, 6, 11, 9</sup>, in 25% of the studies by ICD 9/10 codes<sup>10, 2, 8</sup>, and 8% used a combination of DLQ1 questionnaire, interviews personal interviews, and physical examination<sup>5</sup>. Owing to the significant heterogeneities available in the investigations, in terms of methodology, design, and location, pooled analyses were not carried out.

Except for one study<sup>7</sup>, all the remaining reported data on the occurrence of asthma, AR, and AD. AR was the most prevalent co-morbidity with its frequencies ranging between 16.5%-48%; followed by asthma that occurred in 4.7%-25.8% of cases; and finally, AD was reported among CU patients (1%-22.5%). Nonetheless, the remaining retrospective study<sup>7</sup> that explored the clinical feature and prevalence of CU among geriatric patients reported no data on AR and asthma but found significantly high AD (37.8%).

### Prevalence of Allergic Rhinitis in CU Patients

As stated earlier, AR was reported as the most prevalent co-morbidity among CU patients. For example, n=158 AWARE adult patients in a prospective study<sup>11</sup> were engaged to investigate the baseline data for CU and it was found that 16.5% of the respondents had AR. In similar prospective research<sup>6</sup> it was reported that 18.2% of the n=1539 AWARE patients in Germany were diagnosed with AR. In four retrospective analyses<sup>2, 4, 12, 3</sup> it was reported of AR prevalence of 48%, 20.4%, 20%, and 17%, respectively. The mean ages of the respondents in these studies were between 36.4 and 43.5, and the majority of the patients were female (>69%). Another retrospective research<sup>10</sup>, unlike the investigations mentioned above, matched the prevalence of AED among asthmatic patients versus non-asthmatic controls. The information on AED acquired by registered ICD-9 codes illustrated a significantly increased risk for AR (mOR, 1.52, 95% CI 1.45-1.59; P<0.0001).

In a cross-sectional investigation<sup>9</sup> between 2002 and 2008, a total of n=11,271 adult CU patients with a mean age of 47.4 years were evaluated over the study period and compared with n=67,216 controls. The objective of the study was to assess the correlation between metabolic syndrome and CU. AR was a predictive measure for CU as shown by an odd ratio (OR) 2.03, 95% CI (1.89 – 2.18; P<0.00). One more cross-sectional analysis<sup>8</sup> of adult Korean National Health Insurance recipients, including n=74,335 CU/CSU patients and n=1,281,043 controls, with data on obtained by ICD-9 codes, showed that the occurrence of AR was nearly 4.68 times higher in CU/CSU patients than in the controls. A similar study<sup>5</sup> compared the occurrence of AD, AR, and asthma in n=189 CU patients versus n=4,003 individuals with no CU in Germany. The diagnosis of CU was confirmed through the combination of DLQ1 questionnaire, interview, and physical exam. The findings reported 41.9% of the CU patients had AR, and the lifetime occurrence rates of CU depending on the population cohort under investigation. Finally, in another quantitative research<sup>1</sup> a large insurance database in the United States was analyzed, claims in line with the diagnosis of CSU/CIU were pulled out, approximating an annual prevalence of 0.08%, with 48% of the confirmed cases presenting with AR.

### Prevalence of Atopic Dermatitis in CU Patients

Primary surveys of adults and seniors illustrated significantly increasing trends in the occurrence of indications and any detection of AD history; nonetheless, none of the twelve investigations focused on children alone. Only ten of the studies provided data on the relationship between AD and CU, with the findings suggesting that AD is common in elderly patients. Medical records of n=837 elderly patients in Korea were analyzed<sup>7</sup> to describe the clinical features and prevalence of CU. The retrospective investigation reported that the geriatric patients with CU are at increased risk of developing AD compared to their younger counterparts. The incidence of AD was equivalent to 21.7% in patients <60 years versus 37.8% in those >60 years (p=0.022); one more study<sup>3</sup> reported the same results: only 1% of AD in CU patients. Notably, skin diseases are common in individuals with AD, which heightens the risk of bacterial colonization, particularly *Staphylococcus aureus*, as the AD degrades ceramide, thus facilitating the penetration of the skin barrier and induction of immunoglobulin E (IgE) sensitization. However, the findings of another study<sup>2</sup> suggest that AD was common among adults aged between 40-49 years. Investigations that compared the prevalence of AD among CU and non-CU controls reported increased risk for AD in CU patients than in control

cohorts.<sup>10, 9</sup> In particular, it was observed<sup>10</sup> that there existed an association between AD with DED mainly in asthmatic female patients. However, two researches<sup>8,12</sup> found no relationship between AD and CSU, but the latter reported a link between family history of AD and CU.

### Prevalence of Asthma in CU Patients

All the studies likened asthma with CU except one<sup>7</sup> which reported no significant difference in the occurrence of asthma among both young and elderly CU patients in Korea. Four studies found prevalence rates >15%.<sup>1,5,11,2</sup> Whereas another four investigations<sup>6,3,4,12</sup> reported an incidence rate of less than 15%. The studies that matched the occurrence of allergic triad among CU versus non-CU controls found that asthma was 1.11, 1.62, and 4.63% more common in CU than in patients with no CU respectively.<sup>10, 9, 8</sup> The wide disparity of the occurrence rates can be attributed to the methodological differences used in the investigations.

### Discussion

The systematic review has examined the occurrence of AR, AD, and asthma co-morbidities and the baseline characteristics among CU patients. Even though CU is experienced in clinical practice and has a substantial impact on the QoL of patients, there is a dearth in the literature on the link between the aforementioned variables. A positive correlation between the occurrence of the chronic urticaria and allergic triad, namely: AD, AR, and asthma was noticed, and the relationship was stronger for female than male participants irrespective of the geographic setting, study design, and diagnostic measures. A prospective study<sup>11</sup> was conducted among adults in three Scandinavian nations and it was found that 19.5%, 16.5%, and 6.3% of the CU patients had asthma, AR, and AD respectively, while representative prospective population survey in Germany<sup>6</sup> reported a period prevalence of 12%, 18.2%, and 6.8%. A retrospective analysis conducted in Taiwan found the allergic triad (AR, AD, asthma) were 1.52, 1.94, and 1.11 times more prevalent in CU adult patients compared to those without CU.<sup>10</sup> Another study<sup>1</sup> approximated a 12-month period CU prevalence of 0.08%, with the majority of the CU patients (48%) suffering from AR. Similar findings were posted in a retrospective investigation<sup>2</sup>. The variability in the approximate data is possibly owing to the disparities in methodologies used to gather the sample group and to describe CU: recall bias<sup>7, 2, 6, 4, 3, 10</sup> and the espousal of claims database<sup>10, 1, 8</sup> may have biased the findings. The latter is in line with reports of a systematic review<sup>13</sup> in Italy, which suggest that insurance or claims of administrative databanks produced for billing reasons may not include clinical information, thereby resulting in under or over-coding.

The empirical outcomes were inconsistent regarding the link between AD and CU, particularly with the consideration of age. It was suggested<sup>7</sup> that AR may be common among geriatric patients with CU. This finding is in congruence with the results of another study<sup>14</sup> which illustrated that CU due to infections was prevalent in elderly patients owing to the low immunity that predisposes their body to bacterial pathogens that cause skin disease. Besides, considering the relatively young age of the populations investigated (mean age 40±6 years), these participants were highly likely to present fewer co-morbidities than older patients (>60 years).

### Conclusion

The objective of the systematic review was to explore the prevalence of co-morbidities, particularly allergic rhinitis, asthma, and atopic dermatitis among patients with chronic urticaria. The meta-analysis of the twelve articles that met the selection criteria suggested that the allergic triad were the key co-morbidities of CU in patients aged beyond 18 years. However, geriatric patients with CU were more likely to report atopic dermatitis than those below sixty years, because of the increased likelihood to acquire bacterial infections and the use of multiple drugs that can cause allergic side effects.