Brief Report

Clinico-Epidemiologic Profile and Response to Levocetirizine in Chronic Spontaneous Urticaria: A Retrospective Cohort Study from a Tertiary Care Center in North India

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Abstract

Background: Comprehensive long-term follow-up data regarding chronic spontaneous urticaria (CSU) among general populations, especially from the Indian subcontinent is scanty. **Aim and Objectives:** The aim of the study were to analyze the clinico-epidemiological profile, comorbidities of CSU patients, and factors affecting patient response to various doses of levocetirizine. **Materials and Methods:** In this retrospective cohort study, complete history regarding demographic profile, clinical examination, investigations, treatment given, and follow-up details of all CSU patients attending urticaria clinic between 2010 and 2019 were analyzed. These were considered variables to determine the factors playing a role in response to various doses of levocetirizine. **Results:** Totally, 1104 files of CSU were analyzed. The male-to-female ratio was 1:1.5 with a mean age of 33.03 ± 14.33 years. Thyroid dysfunction and atopy were seen in 142 (12.8%) and 184 (16.7%) patients, respectively. Vitamin D deficiency and high serum immunoglobulin E (IgE) levels were seen in 461 (41.7%) and 340 (30.7%) patients, respectively. Immunosuppressives were required at some point in 196 (17.7%) patients. Patients with higher levels of serum IgE and D-dimer ($P < 0.05$) were found to require frequent updosing of levocetirizine, while age, sex, duration of illness, presence of angioedema, co-morbidities, identifiable precipitating factors, presence of diurnal variation, family history, and vitamin D deficiency were found to not have an effect on levocetirizine dosing. **Conclusion:** Ours is a large single-center study exemplifying the biomarkers including baseline serum IgE and D-dimer levels, which could identify a CSU patient who could warrant a higher dose of antihistamine/antihistamine refractory urticaria.

Keywords: *Angioedema, antihistamines, chronic spontaneous urticaria, D-dimer, immunosuppressives*

Introduction

Chronic urticaria (CU) is a mast cell-mediated condition characterized by the occurrence of urticaria and/or angioedema for a duration of 6 weeks or more. The prevalence of CU has been reported to be 0.1–3% worldwide, though its exact prevalence in India remains unknown. The diverse presentation of urticaria ranging from occasional localized wheals to recurrent widespread lesions with angioedema and consequent patient discomfort, emphasizes the importance of identifying various clinical patterns and understanding the need for effective management of urticaria. Despite being a common dermatosis, not many studies are available, especially pertaining to the Indian population.

Materials and Methods

This was a UCARE (single center), retrospective cohort, study analyzing data from case files of CU patients attending the urticaria clinic in our institute between 2010 and 2019. Only patients with a clinical diagnosis of chronic spontaneous urticaria (CSU), were included and studied. Those who were lost to follow-up within 10 weeks, pediatric cases, inducible urticaria, and files with missing/incomplete data were excluded from the analysis. All patients were treated as per European Academy of Allergy and Clinical Immunology (EAACI) guidelines with second-generation antihistamines (AH2) mainly levocetirizine as it's cost-effective.

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Results

Totally, 1906 patients of CU attended the urticaria clinic during a 10-year period. After applying inclusion and exclusion criteria, 1104 files of CSU patients were eligible.

The clinico-epidemiological profile of patients has been summarized in Table 1. The male-to-female ratio was 1:1.5; age at presentation varied widely from 18 to 79 years with an average of 33.03 ± 14.33 years. The duration of illness varied between 3 months and 35 years, with a median duration of 2 years at presentation. Diurnal variation was reported by 200 (18.1%) patients.

Factors that exacerbated already-present urticaria varied widely from patient to patient and were identified in only 224 (20.3%) patients. Food was the most common exacerbating factor including pickles, dairy products, eggs, meat, citrus fruits, and tomato ketchup among many others. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics including the penicillin group, sulfonamides and tetracyclines, anti-tubercular drugs, and antiepileptics were the most frequent culprits of drugs that exacerbated urticaria.

Table 1: Clinico-epidemiological profile of patients

	Number of patients (percentage)
Total patients	1104 (100%)
Number of males	428 (38.8%)
Number of females	676 (61.2%)
Mean age of presentation (years)	33.03±14.33
Median duration (years)	3.46±4.55 (median: 2 years)
Presentation	
Wheals only	717 (64.9%)
Wheals and angioedema	329 (29.8%)
Angioedema only	23 (2.1%)
Wheals and symptomatic dermographism	33 (3.1%)
Diurnal variation	200 (18.1%)
Comorbidities	
Atopy	184 (16.7%)
Thyroid disease	142 (12.8%)
Diabetes	65 (5.8%)
Hypertension	54 (4.8%)
Dental caries	42 (3.8%)
Autoimmune disease	28 (2.5%)
Metabolic syndrome	43 (3.8%)
Patient identified precipitating factor present in	224 (20.3%)
Family history present in	100 (9.1%)
Elevated serum IgE seen in	340 (30.7%)
Low serum vitamin D levels in	461 (41.7%)
Elevated D-dimers	276 (25%)
Treatment given (and controlled on)	
Levocetirizine	425 (38.4%)
Other antihistamines only	259 (23.5%)
Levocetirizine + other antihistamines	200 (18.2%)
Immunosuppressives	196 (17.7%)
Omalizumab	24 (2.2%)

Thyroid dysfunction in the form of hyperthyroidism, hypothyroidism, and/or raised IgG anti-thyroid peroxidase (TPO) antibodies were found in 142 (12.8%) patients. One hundred eighty-four (16.7%) patients were atopic, and 28 (2.5%) had an underlying autoimmune condition including systemic lupus erythematosus, rheumatoid arthritis, psoriasis, vitiligo, and type-I diabetes. Diabetes mellitus, hypertension, and metabolic syndrome were seen in 65 (5.8%), 54 (4.8%), and 43 (3.8%) patients, respectively. Serum vitamin D levels were found to be inadequate (less than 30 ng/dL) in 461 (41.7%) of patients who were supplemented with oral vitamin D. Serum immunoglobulin E (IgE) levels >100 IU/mL were found in 340 (30.7%) of CSU patients.

All patients received varying doses of AH2 as per EAACI guidelines. Underlying associated conditions and infections were treated as well. The preferred AH2 was levocetirizine, which was the only treatment given in 425 (38.4%) patients, while it was combined with other antihistamines in 200 (18.1%) patients. Other antihistamines including desloratadine, loratadine, cetirizine, fexofenadine, hydroxyzine, and mast-cell stabilizer-montelukast were prescribed alone or in combination at varying doses in 259 (23.4%) patients. Immunosuppressives were required at some point in addition to AH2 in 196 (17.7%) patients in view of CSU being refractory to 4 times the updosing of AH2 designated as Chronic refractory urticaria (CRU). In CRU, steroid-sparing agents frequently used was cyclosporine (3–5 mg/kg/day), azathioprine (2–2.5 mg/kg/day), phototherapy, and methotrexate (0.2–0.5 mg/kg/week) in 74 (6.7%), 48 (4.3%), 50 (4.5%), and 24 (2.17%) patients, respectively. Omalizumab (300 mg/month) was opted for by only 24 (2.2%) CSU patients due to its unaffordability.

All clinico-epidemiological factors as well as baseline laboratory investigations were considered variables to determine the factors playing a role in response to AH2 therapy. Patients well controlled on treatment were defined as having 90% or more improvement in UAS7 scores from baseline by the end of 10 weeks while on treatment. Responders were grouped into four groups based on daily dose of levocetirizine (5 mg, 10 mg, 15 mg, and 20 mg). Patients with higher serum D-dimer levels [Figure 1] and Ig E levels [Figure 2] were found to require higher doses of levocetirizine for response ($P < 0.05$). Age, sex, duration of illness, duration, and frequency of wheals, presence of angioedema, identifiable co-morbidities, identifiable precipitating factors, presence of diurnal variation, family history, and vitamin D deficiency did not have an effect on the dosing schedule of levocetirizine [Table 2].

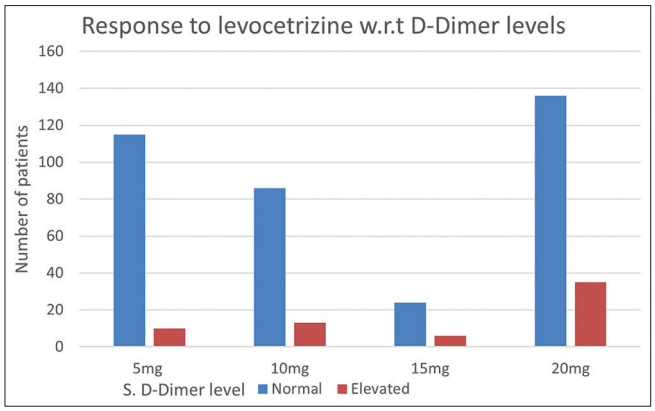

Figure 1: Clustered column chart showing the relationship between serum D-dimer levels and response to levocetirizine

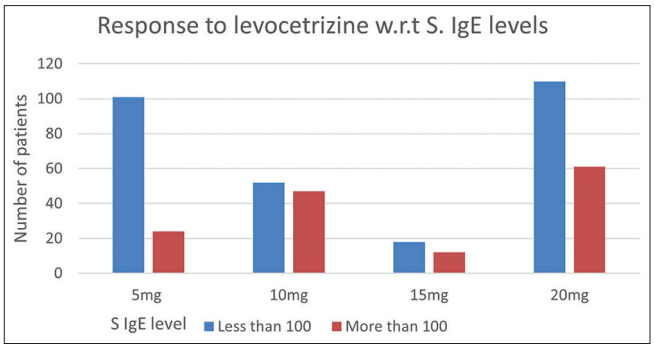

Figure 2: Clustered column chart showing the relationship between serum immunoglobin E levels and response to levocetirizine

Discussion

CSU is a common dermatological condition that can be debilitating and have a profound negative impact on patients' quality of life, including work productivity loss, interference with sleep patterns and daily activities, and high levels of anxiety and psychological stress.

CSU depicts a higher female incidence with an overall male: female ratio varying from 1:2 to 1:4 in contrast with our study, wherein the ratio was 1:1.5.[1] The higher female preponderance is attributable to the possible autoimmune etiology of CSU, and the higher incidence of various autoimmune diseases among women. Our patients seemed to have a lower mean age at presentation (33.03 ± 14.33 years) as compared to previous studies (40–45 years).[2-4] Angioedema without wheals was seen in very few of our patients (2.1%) as compared to 10–20% reported in previous studies.[5]

Food, drugs, and emotional stress are other known exacerbating factors of CU, as noted among our patients as well. The role of food in CSU is widely debated, and while some authors attribute a role to pseudoallergens, others have not found any such association. NSAIDs and antibiotics, not NSAIDs and ACE inhibitors, were more common exacerbating factors in our patients owing to their younger age.[5,6]

In accordance with previous studies, 16.7% of our patients had a history of atopic disease in the form of allergic rhinitis, asthma, atopic dermatitis, etc., These atopic diseases share a series of processes that result in inflammation due to an IgE-mediated immune response to specific allergens, and such IgE-mediated reactions may result in CSU.[7]

Thyroid disease has long been recognized as one of the most common autoimmune diseases associated with CSU.[1] Interestingly, a recent study showed that patients with a combination of elevated anti-TPO and low IgE levels showed low response rates to AH2.[8] Although the mechanism of association between thyroid disease and CSU is elusive, it is thought to be due to their shared autoimmune nature and chronic inflammatory state.[9] The same mechanism is extended to the association of CSU with other autoimmune disorders, including Sytemic lupus erythematosus (SLE), RA, inflammatory myositis, Sjogren syndrome, inflammatory bowel disease, and Kawasaki syndrome, though a shared genetic redisposition has also been suggested.[7]

Table 2: Factors determining requirement of higher doses (20 mg/day) of levocetirizine (multinomial regression)

Variable	*P*	Odds ratio (CI)
Sex	0.303	0.716 (0.379–1.353)
Age	0.781	0.997 (0.976–1.018)
TDI	0.451	0.971 (0.899–1.048)
Elevated serum IgE	0.004	0.385 (0.199–0.742)
Elevated D-dimer	0.005	0.239 (0.089–0.647)
Vitamin D deficiency	0.390	0.764 (0.413–1.412)
Anti-TPO positivity	0.140	0.138 (0.010–1.918)

CI=Confidence interval, IgE=Immunoglobulin E, TPO=Thyroid peroxidase, TDI=Total duration of illness

Inadequate levels of vitamin D were seen in 41.7% of our patients. Tsai *et al.*, in a meta-analysis, concluded that vitamin D deficiency was seen significantly in adult patients with CU but not in those with acute urticaria or in the pediatric age group.[10] Though there are variable results in studies assessing urticaria severity in response to vitamin D supplementation, the majority of supplementation trials showed a significant reduction in clinical urticarial score on intervention with vitamin D.[11]

The majority (80%) of our patients responded to antihistamines alone. Since a significant proportion of patients belong to lower socio-economic strata, cost is an important deciding factor when prescribing antihistamines, especially for a long duration of time, making levocetirizine a popular option. Among 425 (38.4% overall) patients who had disease control with monotherapy with levocetirizine, 29.4% responded to the standard 5 mg dose. These findings are similar to those observed by Sharma *et al.*, who concluded that sequential up-dosing of levocetirizine shows progressive improvement in symptoms, though 46% of patients still

required other therapies.[12] Our analysis further revealed an association between elevated levels of serum IgE as well as D-dimer with a higher dose requirement of levocetirizine. Fok *et al*. concluded that high UAS7 scores, elevated D-dimer and CRP levels were predictive markers of non-response to standard doses of second-generation H1 antihistamines.[13] Serum IgE has been proposed to be associated with longer disease duration, as well as disease severity previously.[14] Other studies have revealed that patients with severe disease show activation of tissue factor pathway of coagulation cascade resulting in elevated levels of D-dimer and has been used as an indicator for severe disease.[15] Baseline levels of IgE and D-dimer may thus be useful to counsel patients regarding disease course and prognosis and may warrant a higher initial dose of antihistamine based on clinical scenario.

Among patients requiring immunosuppressives, cyclosporine, azathioprine, and phototherapy were preferred in contrast to Western countries, where omalizumab is preferred. Only 2.2% of our patients not responding to antihistamines could afford omalizumab. Azathioprine and methotrexate were also more frequently used in our experience, either when patients are non-responsive/intolerant to cyclosporine or due to cost issues. A recent review summarized the use of steroid-sparing agents in CSU and concluded that cyclosporine is a recommended useful alternative in the absence of omalizumab, with a good safety profile while other agents have only limited evidence.[16] Narrow band ultraviolet B(NBUVB), Broadband ultraviolet B (BBUVB) and psoralen plus ultraviolet A (PUVA) have all been used with variable response rates, though NBUVB is preferred.[17]

Limitations

As ours is a tertiary care center, it is inevitable that patients with more severe and refractory diseases are more represented in our data, while milder cases are successfully treated by peripheral practitioners. The study design is retrospective; some variation due to errors in data entry and loss of records is unavoidable. Furthermore, the use of serum IgE and D-dimer as markers for treatment response is limited by the cost incurred.

Conclusion

Ours is a large single-center retrospective study, which analyzed clinico-epidemiological data of CSU and response to levocetirizine in patients hailing from northern India. Higher baseline serum IgE and D-dimer levels are likely predictive biomarkers, suggesting higher doses of levocetirizine or refractory to levocetirizine in patients with CSU.

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Conflicts of interest

There are no conflicts of interest.

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