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Original Article

Association of Chronic Urticaria with Hepatitis C Infection In Female Patients Visiting Tertiary Care Hospital in Pakistan

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ABSTRACT

Objective: To evaluate association of chronic urticaria with hepatitis C infection in female patients.
Study Design: comparative cross-sectional study.
Place and Duration of Study: Fauji Foundation Hospital Rawalpindi Pakistan, form Jan 2020 Jan 2021.
Methodology: One Hundred female patients (group 1) of age 60 years or less with chronic urticaria were enrolled in this study. Patients with chronic liver disease or signs of hepatic decompensation were excluded. Equal number of age and gender matched patients not having urticarial symptoms were selected as group 2. Anti-Hepatitis C Virus Antibody (HCV ab) was evaluated by Enzyme linked immunosorbent assay (ELISA). Disease severity was calculated by Urticaria activity score 7 (UAS 7). Association of HCV infection with chronic urticaria and its severity was analyzed by applying appropriate statistical tests.
Results: Anti HCV antibody positivity frequency was 14/100(14%) in group 1 and 4/100(4%) in group 2 (*p* value: 0.013; significant). Mean ages in group 1 and 2 were 39.88+1.38 and 38.79+1.35 years respectively (p value: 0.57; insignificant). Mean UAS 7 calculated in the HCV negative Urticaria cases was 6.73+2.94 while it was significantly higher in HCV positive group i.e. 8.78+6.459 (*p* value 0.01). Frequency of HCV positivity in patients with well controlled urticaria and mild urticaria was 6/59(10.0%) and 5/36(13.8%) respectively while in moderate urticaria was 3/5(60%) which was significantly higher (*p* value 0.04).
Conclusion: There is a significant association of chronic urticaria with anti HCV antibody positivity. HCV positive patients have more severe disease as compared to HCV negative patients.

Keywords: Anti HCV antibody, Chronic urticaria, Hepatitis C, Urticaria activity score.

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INTRODUCTION

Chronic urticaria is defined as episodes of recurrent wheals persisting for 6 weeks or longer1. Point prevalence of chronic urticaria in the Asian, European and North American population is.[1] 4%, 0.5% and 0.1% respectively revealing Asian population being most affected.[2] Etiology of chronic urticaria is multifactorial (drugs, food, infections, infestations, stress, systemic and autoimmune diseases).[3,4] In 50% of cases, the exact cause remains undiagnosed 3 posing great difficulty for the physician to treat patients effectively as a number of clinical, chemical and serological investigations are required.[3] Thorough workup of chronic urticaria is particularly difficult in the setting of COVID-19 pandemic when face-to-face consultations have reduced significantly and less patients are reaching for specialist care.[4] Therefore, there is a need to devise a set of screening tests, that may include HCV screening to rule out endemic infections notorious for causing chronic urticaria.

Hepatitis C infection is a blood borne disease, caused by HCV. Prevalence in Pakistan is 0.4 to 44% with a median of 5.3%.[5] One out of every 20 Pakistanis is infected with HCV implicating heavy disease burden and the number is growing.[5] Anti HCV antibody test by ELISA is the gold standard test (sensitivity upto 99%) for screening HCV infection.[6,7] HCV is associated with a number of cutaneous menifestations including pruritus, leukocytoclastic vasculitis, Raynaud's phenomenon, lichen planus, vitiligo, porphyria cutanea tarda and presumably, urticaria.[8] HCV is hypothesized to induce urticaria via a number of mechanisms: cross reactivity between endogenous and viral antigens; production of autoantibodies due to B cell response; generation of immune complexes; activation of complement system; activation and degranulation of mast cells.[9]

Regional studies done previously have shown high frequency of HCV infection in chronic urticaria patients. Whether this is because of high prevalence of HCV infection in our region or there is an association

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between the two cannot be established as comparative studies are not done previously. Moreover, urticaria severity has also not been assessed in HCV positive and negative patients. It was aimed to compare HCV positivity in chronic urticaria patients with an age and gender matched group. To best of our knowledge, this is the first comparative cross sectional study done in Pakistan in this field of interest. Results of this study would help clinicians tailor their diagnostic approach of chronic urticaria suitable for Pakistani population and resultantly be beneficial for the patients.

METHODOLOGY

This Hospital-based comparative cross-sectional study was carried out at the Outpatient Department of Dermatology, Fauji Foundation Hospital, Rawalpindi, Pakistan, from Jan 2020 Jan 2021). Non probability consecutive sampling was done. Permission for this study was obtained from Hospital Ethical Committee Ref No.476/RC/FFH/RWP. Purpose of the study was explained and informed written consent was taken from all the patients enrolled in the study. Sample size was calculated by using WHO sample size calculator. Reference prevalence/population proportion was 1.4% 2 with 95% confidence interval and 5% margin of error. Non probability consecutive sampling technique was used to collect data.

Inclusion Criteria: Group 1 included 100 female patients of age less than 60 years showing urticarial symptoms at least twice a week for more than 6 weeks. Group 2 were 100 female patients selected from dermatology OPD who were of age less than 60 years and did not give history of urticaria in previous five years.

Exclusion Criteria: Patients with chronic liver disease(CLD); who showed classical stigmata of CLD including caput medusa, splenomegaly, palmar erythema, dupuytren's contracture, leukonychia, gynaecomastia, spider naevi, palmar erythema and jaundice; Patients who showed signs of hepatic decompensation like encephalopathy, ascites, gastrointestinal bleeding and coagulopathy were excluded from the study.

Chronic urticaria was diagnosed on basis of detailed history and examination, with additional photographic evidence of wheals if available. The severity of disease in the group 1 was calculated by UAS-7 (urticarial activity score of past 7 days). A score ranging from 0 (no symptoms of the disease) to 3 (intense activity of the disease) for each of the symptoms: pruritus and wheals was calculated daily for 7 days (total score 0-42). Findings were documented on a predesigned proforma.

Interpretation of UAS7 was done by stratifying score into asymptomatic, well controlled, mild, moderate and severe urticaria respectively.[11] Interpretation of UAS7 is tabulated in Table-II

Blood samples of 5 milliliters were drawn from all the patients on OPD basis and were sent for analysis in the Hospital laboratory. Serum anti HCV antibody levels were evaluated by ELISA. Tests were carried out free of cost and funding for the study was done by Fauji Foundation Hospital

Data was analysed using IBM Statistical Package for Social Sciences (SPSS version 20 for Windows). Association of HCV infection and chronic urticaria in group 1 group 2 was analyzed by applying appropriate statistical tests. Qualitative data like anti HCV antibody positivity was analyzed by pearson chi square test and quantitative data like mean ages of group 1 group 2 was analyzed by independent t test whereas urticaria severity in hepatitis C positive and negative cases was analyzed by Likelihood ratio. Overall association was also assessed by chi square test. The *p* value of <0.05 was considered significant.

Table-I Urticaria Activity Score (UAS 7)

Score	Wheals	Itch
0	None	none
1	Mild (<20 wheals/24 hours)	mild
2	Moderate (20-50 wheals/24 hours)	moderate
3	Severe (>50 wheals/24 hours)	severe

Total score is 0 to 6 per day, 0 to 42 per week

Table-II Showing interpretation of Urticaria Activity Score (UAS 7)

Uas7	Urticaria	Interpretation
0	Asymptomatic (itch & hive free)	Full treatment response
1-6	Well controlled	Good response to treatment
7-15	Mild	Lower ressponse level
16-27	Moderate	Entry criteria for cinical trials
28-42	Severe	Poor response to treatment

RESULTS

Out of 200 patients, 18(9%) patients (14(14%) in group 1 and 4(4%) in group 2) had reactive anti HCV antibody test whereas 182(91%) patients; 86(86%) in group 1 and 96(96%) in group 2 were anti HCV antibody negative. The *p*-value calculated was 0.013 (significant). Results are tabulated in Table-III.

Table-III: Comparison of serum Anti HCV antibody test in groups 1 and 2.

Group	Serum Anti HCV ab		*p*-value
	Negative	Positive	
Group 1	86	14	0.013*
Group 2	96	4	
Total	182	18	

Table-IV: Mean values of UAS 7 in anti HCV positive and negative patients.

Cases	No. of cases (100)	Mean uas 7	*p* value
Anti hcv positive	14	8.78+6.46	0.01
Anti hcv negative	86	6.08+2.94	

The mean ages in case and control groups were 39.88+1.38 and 38.79+1.35 years respectively. Calculated *p* value = 0.57 (insignificant). This showed that there was no statistically significant difference between various age categories of cases and controls and they were adequately matched.

Mean UAS 7 calculated in the anti HCV antibody positive group was 8.78+6.46, whereas in negative group was slightly lower 6.08+2.94, p value was 0.01 (significant). This shows that hepatitis C infection implies increased disease severity. Results are tabulated in Table-IV

On comparing disease severity among group 1, frequency of Anti HCV antibody positivity in patients with well controlled urticaria and mild urticaria was 6/59(10.2%) and 5/36(13.8%) respectively while in moderate urticaria was 3/5(60%) which was significantly higher (*p* value 0.04). None lied in the two extremes i.e. asymptomatic and severe urticaria. Results are tabulated in Table-IV

Table-V Comparison of UAS 7 of patients in group 1

Group 1	Asymptomatic	Well controlled	Mild urticaria	Moderate urticaria	Severe urticaria	*p*-value
Positive	0	6(10.2%)	5(13.8%)	3(60%)	0	0.04*
Negative	0	53(89.8%)	31(86.1%)	2(40%)	0	
Total	0	59(59%)	36(36%)	5(5%)	0	

DISCUSSION

Frequency of HCV ab positivity in patients of chronic urticaria was significantly higher as compared to non urticaria group. Moreover, significantly higher number of HCV positive patients lied in the moderately controlled urticaria when compared within the urticaria group. These findings are comparable with a number of local and international studies. Zaib *et al* conducted a study in which three hundred patients of chronic urticaria were enrolled, frequency was calculated to be 19% that is comparable to our study.[12] Similar regional study was conducted in 2017 by Ahmed I *et al*, in which calculated frequency was 15% (15 out of 114 patients) that is also comparable to our results.[13] Perveen *et al* calculated frequency 16% which was also comparable to our study.[14] However, these studies did not compare urticaria group with an age and gender matched group therefore, our results showing association between chronic urticaria and hepatitis C infection cannot be compared with these studies.

In an international case control study conducted by Cribier *et al*, antibodies to HCV were found in 1 patient in cases and controls each showing similar prevalence of hepatitis C infection in cases and controls.[15] It was concluded that hepatitis C infection and chronic urticaria are not associated. Possible explanation of this discrepancy can be the fact that this study was conducted in the European population (where prevalence is less than that in asia). Moreover, this study was conducted 2 decades ago outdating its significance.

Another relatively recent review study was conducted in 2006 by Cribier BJ *et al* in which they studied various cutaneous manifestations of HCV infection in 321 patients, but none had urticaria15. They also discussed another case report showing a 5-year history of urticaria in a patient with active HCV infection16. Urticaria persisted even after treatment of HCV infection. On the other hand, they discussed a Japanese case control study conducted by Kanazawa et al showing a strong association of HCV infection and chronic urticaria (24% cases and 18% controls). Positive cases were further tested for PCR (polymerase chain reaction) and 22% came out to be positive. PCR positive patients had a longer duration of urticaria, had post urticaria pigmentation, had higher aminotransferase levels and lower mean platelet

counts. It was seen that patients who got treated with interferon treatment also showed improvement.[17] Therefore, it is a practical approach for clinicians to screen for HCV in urticaria patients who are living in high endemic areas.[18]

Previously no studies are done comparing urticaria severity in hepatitis C positive and negative cases. We compared mean UAS 7 values of HCV positive and negative patients. There was a statistically significant difference between the two groups suggesting that infection of hepatitis C virus is not only associated with chronic urticaria, its presence can be considered as an independent factor for increased disease severity and poor quality of life. The authors encourage clinicians to further study different genotypes of HCV and assess which ones are associated with a more severe disease.

LIMITATION OF STUDY

Only female patients could be enrolled in the study due to entitlement policy of the Hospital. Therefore, gender bias could not be avoided in our study. Due to limited resources, PCR was not done to see which genotype of HCV had association with a higher urticaria activity score.

CONCLUSION

There is a significant association of chronic urticaria with anti HCV antibody positivity. HCV positive patients have more severe disease as compared to HCV negative patients.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SWQ & FUR: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

BF & SK: Data acquisition, data analysis, approval of the final version to be published.

SJ: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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