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Original Article

Chronic idiopathic urticaria, gastrointestinal symptoms and *Helicobacter pylori* infection

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Abstract Chronic idiopathic urticaria (CIU) is one of the most persistent and distressing skin diseases and the only treatment available is symptomatic in the form of H_1 blockers and systemic steroids in severe cases. Chronic infections have always been implicated in the causation of chronic urticaria. The presence of associated gastrointestinal symptoms in a sizable percentage of patients of chronic urticaria as well as the chronic and asymptomatic nature of *Helicobacter pylori* infection make the possibility of an association between chronic urticaria and *H. pylori* infection a biologically plausible one.

In the present study sixty patients of chronic idiopathic urticaria were evaluated along with an equal number of age and sex matched controls for presence of *H. pylori* infection by means of an ELISA-based serological test. All seropositive patients were then given eradication treatment for *H. pylori* infection and monitored for any improvement in signs and symptoms. The overall *H. pylori* seropositivity was found to be 60% in cases as compared with only 31.6% in control group. Furthermore, there was an overall response rate of 58% in those patients who were treated by *H. pylori* eradication therapy.

Key words
Chronic idiopathic urticaria, *Helicobacter pylori*.

Introduction

Chronic urticaria is one of the most persistent skin disorders and around 40% of the patients with a history of chronic urticaria of more than 6 months duration will be expected to have persistent symptoms even after 20 years of onset.[1] The condition is also a very distressing one to treat and the only treatment option available is to put these patients on long-term H_1-antihistaminic therapy and even systemic steroids in severe cases. Various causes implicated for the condition are foods and drugs, inhalant allergens, systemic diseases like connective tissue disorders and endocrine disorders, autoimmunity and chronic infections of bacterial, viral, protozoal or helminthic origins. All these causes, however, account for only a minority of cases[1,2] and the condition remains idiopathic in majority even after extensive investigations.[1,2]

Gastrointestinal symptoms in the form of nausea, vomiting and abdominal pain are present in around 40% of patients of chronic idiopathic urticaria[3] (CIU) and the term "Chronic Gastrointestinal Urticaria" has been coined to describe this condition.[4] *Helicobacter pylori* is a multiflagellated

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Gram-negative bacillus found endemically in human stomach all over the world. *H. pylori* has been equivocally linked with many skin diseases like rosacea,[5] psoriasis[6] and also chronic urticaria.[7,8] Some of these studies have reported a dramatic cure of chronic urticaria following *H. pylori* eradication therapy.

Patients and methods

Sixty patients in whom a diagnosis of CIU was established after thorough clinical assessment and relevant investigations were selected for study and were designated as cases. The patients were then grouped according to their age, duration of urticaria and presence/absence of associated gastrointestinal symptoms. Patients with pure physical urticaria or recurrent urticaria and patients with a history of intake of any anti-*H. pylori* drug in preceding three months were excluded from the study.

As the control population sixty healthy individuals matched with cases according to age and sex were selected. History of intake of any anti-*H. pylori* drug in preceding three months was used as an exclusion criterion in this group also.

Both the cases as well as controls were then investigated for the presence of *H. pylori* infection by means of an ELISA-based serological test. The seropositivity rates were then compared between the two groups and any correlation of the seropositivity rate with the duration of urticaria or with presence of associated gastrointestinal symptoms was also noted.

In the next step, all patients who had tested positive for *H. pylori* infection were given eradication treatment for the same using a combination of omeprazole, clarithromycin and amoxycillin for a period of one week. At the end of eradication therapy, an attempt was made to stop the antihistaminic drugs and only those patients showing persistent antihistaminic dependence were put on the smallest dose of H_1 blocker drugs possible. The patients were thus monitored for any improvement in signs and symptoms at the end of eradication therapy as well as for the next six months of follow up. The variables noted down were any improvement in the severity and/or frequency of urticarial attacks and also in antihistaminic dependence. During the follow-up period H_1 blockers were continued in the smallest dose possible and only in those patients who had persistent urticarial symptoms. Patients going into complete remission after eradication therapy were not given any further treatment.

Results

The age of our patients ranged from a minimum of 8 years to a maximum of 60 years with a mean of 28.3 years. Majority of the patients (n=28) belonged to the 3rd and 4th decades of life. There were a total of 38 females and 22 males both in the study as well as control groups.

The duration of urticarial symptoms ranged from a minimum of 2 months to a maximum of 12 years with a mean of 15.3 months. 28% of patients had a duration of urticaria of >2 years. A history of associated gastrointestinal symptoms was found in 13 patients constituting 21.7% of the whole group.

Table 1 *H. pylori* seropositivity values in cases and controls.

Age group	*H. pylori seropositive (Cases)*	*H. pylori seropositive (Controls)*
0-20 years	11 (50%)	3 (13.6%)
21-40 years	18 (64.3%)	10 (35.7%)
41-60 years	7 (70%)	6 (60%)
Total	36 (60%)	19 (31.6%)

Table 2 Correlation of *H. pylori* seropositivity with presence of gastrointestinal symptoms.

Group	*H. pylori*-positive	*H. pylori*-Negative
Positive H/O GI symptoms (n=13)	12 (92%)	1 (8%)
Negative H/O GI symptoms (n=47)	24 (51%)	23 (49%)

H. pylori seropositivity in cases and controls

On testing the patients for the presence of *H. pylori* infection by means of ELISA based serological test, an overall seropositivity of 60% was found in cases compared with an overall value of 31.6% for the control group. The age wise seropositivity values in cases and controls are given in **Table 1**.

After statistical analysis of the results using the odds ratio and Z-test of proportions, the difference in seropositivity between cases and controls was found to be statistically significant ($p<0.01$). Comparison of individual age groups also revealed a statistically significant difference in the seropositivity values except in the 41-60 years age-group where a high value was found in both the study as well as control population.

Correlation of H. pylori seropositivity with presence/absence of associated gastrointestinal symptoms

The seropositivity values were also correlated with the presence/absence of associated gastrointestinal symptoms and it was observed that out of 13 patients with a positive history of such symptoms, 12 were seropositive for *H.pylori* infection which meant a seropositivity value of 92%. On the other hand, of the 47 patients with no history of any associated gastrointestinal symptoms, *H.pylori* antibodies were demonstrated in only 24 giving a seropositivity value of 51% (**Table 2**). The difference was found to be statistically significant ($p<.05$).

II. Response to eradication therapy

Out of 36 patients who tested positive for *H. pylori* infection, 5 were lost to follow-up. The rest of 31 patients were given eradication therapy for *H. pylori* infection as described above. At the end of eradication therapy we had 13 patients (42%) in complete remission who required no further treatment. In five other patients (16%) the severity of urticarial symptoms had decreased appreciably and their antihistaminic dependence was markedly reduced. During the six months of follow-up all those patients who had gone into complete remission remained so while the five other patients who had attained a partial remission were also able to stop their antihistaminic treatment permanently. Thus at the end of follow-up period we had 18 patients (58%) in complete remission.

Correlation of response rate with history of associated gastrointestinal symptoms

Out of a total of 11 *H. pylori* positive patients with ‘chronic gastrointestinal urticaria’ 8 patients responded completely to eradication therapy. Thus the overall

response rate was calculated to be 73% in these patients. In the other subset of patients with no history of associated gastrointestinal symptoms and a positive *H. pylori* serology, there were ten responders out of a total of twenty (50%).

Discussion

Chronic idiopathic urticaria still remains one of the most difficult skin diseases to treat being of chronic and idiopathic nature. Treatments ranging from simple H_1 antihistaminics to procedures like plasmapheresis, desensitization procedures etc. have been tried but all with limited success. Elucidating the cause and treating the same still remains the best possible option.

While different infections have been implicated in the causation of chronic urticaria in the past, the concept of *H. pylori* infection as a possible causative factor is a relative new one.[7] What makes this association worthy of investigation is the chronic and asymptomatic nature of *H. pylori* infection and its highly endemic nature. How *H. pylori* can cause chronic urticaria is not known with certainty but some recent studies have reported a high titer of IgG and IgA antibodies to 19-kDa *H. pylori* associated lipoprotein in chronic urticaria patients.[9]

In our case control study majority of patients belonged to the third and fourth decades of life with 28 of the 60 cases (46.7%) belonging to this age group. This observation has been made by all the famous studies that have been conducted on this subject previously.[1,2,3] Thirty-seven of our sixty cases were females giving a male: female ratio of approx. 1:2. This is also in total conformity with the observations made in the above-mentioned studies. Thirteen patients in our study population had a positive history of associated gastrointestinal symptoms; this percentage (21.7%) is less than that reported by Juhlin[3] and Champion *et al.*[1] in their studies. However this difference can be easily explained by the exclusion of those patients from the study that had a history of intake of any anti-*H.pylori* drug in preceding three months.

With our case-control study, we have demonstrated a possible role of *H. pylori* infection, at least in a subset of CIU patients. While we have not seen a very high or universal presence of *H. pylori* infection in these patients as shown by Bohmeyer *et al.*[7] we have found the seroprevalence in cases to be definitely higher than in the control group.

And secondly, what we have demonstrated is that mere presence of *H. pylori* infection does not implicate it in the etiology of chronic idiopathic urticaria. In some of the patients *H. pylori* infection is just a coincidental one as shown by the negative response to *H. pylori* eradication therapy in this group. This will also explain the lower remission rate that we have achieved in our patients as compared to that reported by Bohmeyer *et al.*[7] and di Campli *et al.*[8]

Another interesting finding in our study relates to the possible association of gastrointestinal symptoms in chronic urticaria and its *H. pylori* etiology. While many previous studies have refuted such an association,[4] what we have seen is that the presence of associated gastrointestinal symptoms significantly increases the

chances of *H. pylori* being the incriminating factor and thus the chances of a positive response to *H. pylori* eradication therapy.

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