

## Helicobacter Pylori Infection and Its Potential Role in Childhood Eczema

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### Abstract

**Objective:** To determine whether *Helicobacter pylori* is associated with childhood eczema.

**Design:** Case-control study.

**Settings:** Al Azhar University Hospitals in Cairo, Egypt. Local hospital in Hafer Al Batin, Saudi Arabia.

**Participants:** A total of 170 patients with Atopic dermatitis (Eczema) who were 2 months to 7 years old and had fulfilled the American Academy of Dermatology Criteria for Atopic dermatitis (AD), and a total of 80 healthy controls with no history of Atopy were matched by country of origin, age, sex, family size, socio- demographic variables and ethnicity to the 170 atopic cases.

**Main Outcome Measure:** *Helicobacter pylori* infection determined by *H pylori* stool antigen testing and serologic anti-*H. pylori* IgG antibodies.

**Results:** Of the 170 patients presenting with atopic dermatitis, 6 cases (3.5%) tested positive serologic anti-*H. pylori* IgG antibodies and 12 cases (7.0%) tested positive *H pylori* Stool antigen; Of the 80 healthy controls, 12 cases (15.0%), 6 cases (7.5%) and 2 case (2.5%) were tested positive by serology, stool antigen and both Serology/Stool antigen tests respectively. (For serology testing, Odds Ratio = 0.2073, 95% CI = 0.0748 - 0.5749, Z statistics = 3.024, P value = 0.0025).

**Conclusion:** *H pylori* infection is associated with childhood eczema in genetically predisposed atopic children. Significant inverse correlation between atopic dermatitis and positive *H pylori* serologic testing was reported.

**Keywords:** *Helicobacter pylori*; Atopic eczema; Atopic dermatitis; Helminthes

### Introduction

Atopic dermatitis (AD) also known as atopic eczema or eczema [1] is a type of dermatitis, an inflammatory, relapsing, non-contagious and itchy skin disorder [2]. It is often chronic in nature. In children under one year of age much of the body may be affected. As they get older the back of the knees and front of the elbows are the most common area for the rash. In adults the hands and feet are the most affected [3]. The cause is believed to involve a number of factors including; genetics, environmental exposures, and difficulties in permeability of the skin. The diagnosis is based on the signs and symptoms. Other diseases that need to be excluded are contact dermatitis, psoriasis and seborrheic dermatitis [3]. The ISAAC (International Study of Asthma and Allergies in Childhood) revealed that AD affects children all over the world, although the disease prevalence varies substantially among countries [4]. The prevalence of AD is also increasing, especially in developing countries [5]. It affects more than 10% of children in the United States and is more common in younger children. Most people outgrow it [3]. It has been given names like "prurigoBesnier," "neurodermatitis," "endogenous eczema," "flexural eczema," "infantile

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eczema,” and “prurigodiathesique” [6]. Since the beginning of the twentieth century, many mucosal inflammatory disorders have become more common; atopic eczema (AE) is a classic example of such disease. It now affects 15–30% of children and 2–10% of adults in developed countries. In the United States it has nearly tripled in the past thirty to forty years [7]. Prevalence continues to vary and has changed in different regions of the world. Nigeria, the United Kingdom and New Zealand had been areas of the highest prevalence. The prevalence of AD seems to have reached a plateau around 20% in countries with the highest prevalence, suggesting that AD may not be on a continued rise but that a finite number of individuals may be susceptible to the condition. Risk factors associated with increased prevalence include higher socioeconomic status, higher level of family education, smaller family size and urban environment [8]. Research indicates that food allergy and atopic sensitization to environmental allergens may not be directly causal of the condition and that a non-atopic form of the condition exists. About 60% of patients will experience remission. The number of patients who will progress through the atopic march to develop asthma and allergic rhinitis depends on the underlying features of their condition [8]. The increasing prevalence of allergic disorders could be explained if they were prevented by microbial colonization in early childhood [9]. The so called hygiene hypothesis suggests that the allergy protective effect may be mediated by microbial agents associated with the presence of older siblings. In other words, infections may have a protective effect on the development of allergic disorders [9].

*H. pylori*, has been demonstrated worldwide and in individuals of all ages. It is estimated that 50 percent of the world’s population is affected. Infection is more frequent and acquired at an earlier age in developing countries compared with industrialized nations [10]. Once acquired, infection persists and may or may not produce gastro-duodenal disease. In developing nations, where the majority of children are infected before the age of 10, the prevalence in adults peaks at more than 80 percent before age 50 [10,11]. In developed countries, such as the United States, evidence of infection in children is unusual but becomes more common during adulthood [11]. *H. pylori* is a spiral shaped, microaerophilic, gram negative bacterium, the organism can be biochemically characterized as catalase, oxidase, and urease positive. The organism’s urease, motility, and ability to adhere to gastric epithelium are factors that allow it to survive and proliferate in the gastric milieu [12]. Disruption of urease activity, bacterial motility, or attachment prevents *H. pylori* colonization [13]. *H. pylori* then attaches to gastric epithelial cells by means of specific receptor-mediated adhesion [13,14]. Although attachment is dependent upon binding of bacterial surface adhesins to specific epithelial cell receptors, host factors can modulate this process. As an example, certain individuals may express specific surface receptors or greater numbers of receptors, making them more susceptible to *H. pylori* attachment and colonization [15]. As *H. pylori* is a gram-negative bacteria; therefore, *H. pylori*-derived LPS is considered a direct stimulator of Toll-like Receptor (TLR4)-mediated innate immunity. Previous immuno-histochemical studies revealed that the expression of TLR4 in *H. pylori* gastritis was higher than that in uninfected gastric mucosa [16]. Recent studies have demonstrated that TLR signals can influence intestinal homeostasis [17]. Mucosal cells and consequent activation of signaling cascades can enhance the production of pro-inflammatory cytokines and antimicrobial peptides, as well as the maintenance of the epithelial barrier function. Hence, parasitic infection can maintain the epithelial barrier function and epithelial cell proliferation through TLR signaling pathways [18].

### Methods

Approval of this study was received from the administrations of the Hospitals in which the study was conducted in. The routine consents for Laboratory diagnosis were implemented for all cases according to Hospital regulations, and the study protocol conforms to the ethical Guidelines of the 1975 Declaration of Helsinki. Children were recruited through primary care physician offices and Clinics and Nor-khan General Hospital (Hafer Al Batin, Saudi Arabia) as well as Al Azhar University Hospitals Cairo, Egypt. All participants between 2 months to 7 years were investigated for *H. pylori* using two laboratory tests.

Exclusion criteria included cases of hematologic disorders, metabolic disorders; food allergy, Celiac Disease, collagen vascular diseases, severe illness or children on antibiotics for four weeks ago or on antisecretory /steroid therapy for two weeks ago were all excluded from this study. All cases were relatively matched with the eligible control group for age, sex, race, maternal age, family size, education, and other socio-demographic variables to rule out any possible confounders.

Inclusion Criteria included cases with presumed atopic dermatitis from 2 months to 7 years old, they should have their diagnosis based on the criteria summarized in Box 1 and according to the American Academy of Dermatology [19].

Features to be considered in the diagnosis of atopic dermatitis. **ESSENTIAL FEATURES**-Must be present: \*Pruritus \*Eczema (acute, subacute, chronic), Typical morphology and age-specific patterns, Chronic or relapsing history.

**Patterns include:** 1. Facial, neck, and extensor involvement in infants and children, 2. Current or previous flexural lesions in any age group, 3. Sparing of the groin and axillary regions. **IMPORTANT FEATURES.** Seen in most cases, adding support to the diagnosis: \*Early age of onset \*Atopy (Personal and/or family history, Immunoglobulin E reactivity) \*Xerosis

### Detection of *H. pylori* infection

The case and control groups were investigated for *H. pylori* using a stool antigen test. This one-step test is a chromatographic Immune assay for the qualitative detection of *H. pylori* infections (Alcon Laboratories Inc.). It is a relatively simple, reliable, more applicable, and noninvasive test of *H. pylori* infections in children. *Helicobacter pylori* fecal antigen has shown a high degree of sensitivity, specificity, and positive and negative predictive values [20].

### Anti-*H. pylori* antibodies test

Individuals infected with *H. pylori* develop antibodies that significantly correlate with the histologically confirmed cases. It is noteworthy that the geographic distributions of eligible participating children add more strength to the design of the study. There is a good correlation between ELISA antibody test and rapid urease test, which afford confirmatory diagnosis of *H. pylori* infection [21,22]. In this study, serum samples were assessed through ELISA for the presence of anti-*H. pylori* IgG antibodies against high molecular weight cell-associated protein (HM-CAP) of *H. pylori* using the HM-CAP ELISA kit (EZ-EM Inc. Westbury, NY, USA) as described previously [23]. All analyses were performed using SPSS (SPSS Inc.). The demographic characteristics of cases and controls were compared using the Fisher exact test, and odds Ratio.

### Results

Among the 250 enrolled participants, there was homogeneous distribution in both groups (atopic cases and non-atopic control) regarding to age, sex, race, family size, insurance status, and maternal education. In atopic cases, there were 100 girls (58.8%) and 70 boys (41.2%). Compared to control, the enrolled girls and boys were 60% and 40% respectively. The mean age was (3.7 ± 1.1) and (3.5 ± 1.9) years for case and control groups respectively. Age distribution of atopic cases showed 76 cases (44.7%) in the age group (2 months to 2 years) and 94 cases (55.3%) in age group (2 to 7 years); In control 36 (45.0%) in the age group (2 months to 2 years) and 44 (55.0%) in the age group (2 to 7 years) as in Table 1. Of the total 170 Atopic cases, 6 cases (3.5%) tested positive serologic ELISA assay and 12 cases (7.0%) tested positive *H. pylori* Stool antigen. In control, there were 12 cases (15.0%), 6 cases (7.5%) and 2 cases (2.5%) tested positive by serologic ELISA, Stool antigen test and both tests respectively Table 2. For serologic testing, Odds Ratio (OR) = 0.2073, 95% Confidence Interval (CI) = 0.0748-0.5749. Z statistics = 3.024, P value = 0.0025 i.e. Significant inverse correlation between atopic dermatitis and positive *H. pylori* serologic testing. For *H. pylori* stool antigen testing, OR = 0.9367, 95% CI = 0.3384 to 2.5929, Z statistics = 0.126, P value = 0.8998, No significant correlation between atopic dermatitis and positive *H. pylori* stool antigen Table 3.

Eligible cases were enrolled from outpatient clinics of Al-Azhar University Hospitals (Cairo, Egypt) and from Nor-Khan General Hospital (Saudi Arabia). Informed consents were obtained from Parents or Guardians according to hospital regulations. Printed records were collected to verify inclusion criteria, medications given, clinical review, family and past histories. Cases with presumed atopic dermatitis from 2 months to 7 years old should have their diagnosis based on the criteria summarized in Box 1 and according to the American Academy of Dermatology. There was homogeneous distribution in both groups (atopic cases and non-atopic control) regarding to age, sex, race, family size, insurance status, and maternal education.

Participants.No.,(%)		
Characteristic*	Atopic cases (N = 170)	Control (N = 80)
Age		
2 Months-2 yrs.	76 (44.7%)	36 (45.0%)
2 Yrs-7 yrs.	94 (55.3%)	44 (55.0%)
Mean Age, yrs.	(3.7 ± 1.1)	(3.5 ± 1.9)
Female	100 (58.8%)	48 (60.0%)
Male	70 (41.2%)	32 (40.0%)
Child Nationality		
Egyptian	64 (37.6%)	32 (40.0%)
Saudian	58 (34.1%)	28 (35.0%)
Others	48 (28.2%)	20 (25.0%)

\*Socioeconomic status is based on parental occupation. Education was nearly balanced among participant's parents, particularly when considering the average level nature of the hospital community.

**Table 1:** Demographic characteristics of 250 participants including case group (Atopic patients) and Control group.

Test	Atopic Cases (N = 170)	Control (N = 80)
+ELISA	6 (3.5%)	12 (15.0%)
+H pylori stool antigen	12 (7.0%)	6 (7.5%)
+Both	--	2 (2.5%)
Total	18	20

**Table 2:** Laboratory testing of *Helicobacter pylori* (*H pylori*) in Atopic Cases versus Control.

Parameter	ELISA Test	H pylori stool antigen Test
Odds ratio	0.2073	0.9367
95% CI:	0.0748 to 0.5749	0.3384 to 2.5929
z statistic	3.024	0.126
Significance level	P = 0.0025	P = 0.8998

**Table 3:** Statistical Comparison between ELISA and H pylori stool antigen testing for the studied groups.

## Discussion

The results of this study suggest that the relationship between childhood eczema and *H pylori* infection is a complex one, at least in this clinical sample of children referred for *H pylori* testing. The genetic diversity of *H. pylori* and the variations in human host response to the microorganism underlie the complex host-pathogen relationship that determines the natural history of infection. Since the relationship between infections and eczema is not a simple one, it is not surprising that some studies confirmed the inverse association between atopy/allergic diseases and *H pylori* infection. Other studies claimed that the association is causal and directly proportional. According to the *hygiene hypothesis* [24] when children are brought up exposed to allergens in the environment at a young age, their immune system is more likely to tolerate them, while children brought up in a modern "sanitary" environment are less likely to be exposed to those allergens at a young age, and when they are finally exposed, develop allergies. There is some support for this hypothesis with respect to AD.

A meta-analysis reported a favorable effect of exposure to dogs and pets on the risk of AD in infants or children, whereas no association emerged with exposure to cats [24]. To our knowledge, our study is the first to clearly evaluate the potential role of *H pylori* infection in Childhood atopic dermatitis in developing countries. Moreover, the study may disclose the apparent ambiguity related to the contradiction between some clinical studies that confirmed an inverse association between *H. pylori* and atopy, and other studies that reported an antagonistic result [25]. A recent study have indicated that differences in gut microbiota do precede development of atopy [26] and early postnatal or even pre-natal factors, such as an alteration of the gut micro flora, play an important role in eczema development [27]. The more recent research conducted by Zhou., *et al.* demonstrated the role of lactobacilli in treating *H pylori*-related diseases, and the results indicated that viable lactobacilli prevented the development of *H pylori* Sydney strain 1 (SS1) lipo polysaccharide (LPS)-activated Toll-like receptor (TLR4) pathways in SGC-7901 cells, leading to the inhibitory effects of lactobacilli on IL-8 production stimulated by *H pylori* SS1 LPSs [28]. Schmidt., *et al.* demonstrated that TLR4 is involved in the development of contact allergy to nickel in humans and was attributed to activation of the pro inflammatory intracellular signal transduction cascades [29]. Other data implicate site-specific human TLR4 inhibition as a potential strategy for therapeutic intervention in contact hypersensitivity that would not affect vital immune responses [29]. Toll-like receptors have also been shown to be an important link between innate and adaptive immunity through their presence in dendritic cells. The TLRs 3 and 4 are present on the surface of monocyte derived dendritic cells. TLRs have also been shown to be expressed on immune cells like T cells [30]. It is reported that low level LPS signaling through TLR4 is necessary to induce Th2 responses. The mechanism by which LPS signaling results in Th2 sensitization involves the activation of antigen-containing dendritic cells. In contrast to low levels, high levels of LPS with antigen resulted in Th1 responses. These studies suggested that the level of LPS exposure can determine the type of inflammatory response generated [31]. Other results demonstrated the crucial and innate role of TLR4 in promoting the activation of CD4+ and  $\gamma\delta$  T cells, which contributes to the initiation of autoimmune inflammation [32]. Other studies clearly reported that *H pylori* seropositivity was highly prevalent in rural Tanzania and Seropositive persons showed a Th2-dominant immune response to *H pylori* infection, which may be due to effects of concurrent infection with parasites and/or bacterial infections [33]. Taken together, it is evident that Toll-like receptor signaling pathway activation mediated the *H pylori* immunologic aspect of pathogenesis. Our results reported a significant inverse relation between atopic dermatitis and positive Serology for *H pylori* infection with its implication of definite enhancement of TLR4 signaling cascade central to production of pro-inflammatory cytokines that ultimately direct the activation of Th2  $\rightarrow$  B cell  $\rightarrow$  IGE atopic response instead of Th2  $\rightarrow$  B cell  $\rightarrow$  Ig response, normally encountered in non-atopic population. LPS, also termed endotoxin, represents the main surface antigen (O-antigen) for Gram-negative bacteria. It was released when the bacteria underwent lysis [34]. Accordingly, LPS concentration is directly proportional to the degree of *H pylori* cell lysis. Thus, induction of TLR-Th2-B cell atopic pathway is evidently caused by the persistent low level of bacterial cell death. This probably could elucidate the slowly progressive release of pro-inflammatory cytokines and antimicrobial peptides as well as the maintenance of the epithelial barrier function and epithelial cell proliferation characteristic of TLR signaling pathways. This pattern of adaptive immunologic pathway expressed in gut milieu could not mount an anti-*H pylori* IgG antibodies. On the contrary, the non-significant association of atopic dermatitis with *H pylori* stool antigen test may be explained by the observation that high levels of LPS implicated high antigen load with the resultant Th1 responses (cell mediated non atopic response). As the high levels of LPS indicate instant rapid *H pylori* lysis, this means that *H pylori* is readily attacked by an antimicrobial factor in the gut, which may be another micro biota flora, helminthes or its product, or even antibiotics. This may uncover and explain the conclusions of the following studies:

- 1 The role of Lactobacillus reuteri in reducing atopic eczema in childhood [35].
- 2 Epidemiological studies reported a protective role for Helminthes against AD [36].
- 3 Helicobacter, the germ that causes stomach ulcers can also trigger eczema [37].
- 4 Corrado., *et al* demonstrated a positive association between *H pylori* infection and food allergies in thirty children who were suffering digestive symptoms [38].
- 5 Galadari., *et al* reported that the incidence of *H pylori* in 20 atopic dermatitis patients was considerably higher than that of control subjects [39].

During pregnancy, the cytokine inflammatory-response profile of the fetus is diverted away from cell-mediated immunity (T-helper 1) toward humeral immunity (i.e) Th2 type. Hence, the Th2 type is typically the general immune response in early infancy. The risk of allergic disease could will be the result of a lack or delay in the eventual shift of the predominant Th2 type of response to more of a balance between Th1- and Th2-type responses [40]. Administration of probiotic bacteria during the time, in which a natural population of lactic-acid-producing intestinal bacteria is developing, could theoretically influence immune development toward more balance of Th1 and Th2 inflammatory responses [41]. The intestinal bacterial flora of atopic children has been demonstrated to differ from that of non-atopic children [42,43] which has served as rationale for the administration of probiotics to infants at risk of atopic diseases, particularly for those who are formula fed.

### In short

The apparent inverse relation between atopic dermatitis and *H pylori* seropositivity could be expected in atopic infants as atopic infants divert the Th2 type (B cell -->IgG) response of *H pylori* to Th2 type (B cell -->IGE) response. As the infant grows up, eventual shift of the predominant Th2 type of response to more of a balance between Th1- and Th2-type responses. The insignificant relation between atopic dermatitis and *H pylori* stool antigen testing (*H pylori* colonization) could be explained as follows; *H pylori* colonization does not necessarily invoke inflammatory immune responses as evidenced by the well documented asymptomatic and subclinical cases of *H pylori* infections. Moreover, colonization is instantly opposed and antagonized by multiple factors including; competitive inhibition by another gut microbiota or Helminthes or its products, host factors (genetic susceptibility, diet) environmental, geographic variation, and wide usage of antibiotics. All these factors imply disproportionate correlation between colonization and the atopic immunologic response to *H pylori* infection.

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