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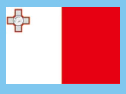

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MINIREVIEWS

# *Helicobacter pylori* and inflammatory skin diseases

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## Abstract

Throughout the history of mankind, infections have been the major cause of diseases. Over the last decades, not only the incidence of emerging infectious diseases have increased, but also tremendous strides have been made in understanding the biology of several pathogenic microorganisms. *Helicobacter pylori* (*H. pylori*) is a spiral-shaped, gram-negative bacterium, which infects over the half of the world's population. *H. pylori* has been implicated in the pathogenesis of a number of gastrointestinal disorders. However, new researches have demonstrated that *H. pylori* is also involved in the pathogenesis of various extragastric diseases. The difference in the clinical outcome of *H. pylori* infection may be explained, at least in part, by host response to the infection and *H. pylori* virulence factors. It is obvious that as developments in the research on *H. pylori* spring up, an understanding of the pathophysiology of *H. pylori* infection will continue to be identified. Here in this review, we summarize the current knowledge about *H. pylori* and its association with inflammatory skin diseases.

**Key words:** *Helicobacter pylori*; Etiopathogenesis; Skin diseases; Inflammatory



**Core tip:** *Helicobacter pylori* (*H. pylori*) is a worldwide bacterium found almost entirely in humans. Although the majority of infected individuals remain asymptomatic, *H. pylori* has been implicated in the etiology of several gastric and extragastric disorders. *H. pylori* is generally acquired during childhood and persists lifelong due to the failure of the immune response to eradicate the bacterium. *H. pylori* has mechanisms to evade the immune response and to establish local and low-grade systemic inflammation. A number of studies have revealed that Helicobacter pylori-induced chronic low-grade inflammation may contribute to the pathogenesis of several disorders, including inflammatory skin diseases.

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## HELICOBACTER PYLORI

*Helicobacter pylori* (*H. pylori*) is a gram-negative, spiral-shaped bacterium, which is thought to infect about half of the world's population. Barry Marshall and Robin Warren were the first researchers to isolate and culture this motile, S-shaped rod from human stomach, which was followed by demonstration of development of several upper gastrointestinal disorders, including chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer in the presence of Helicobacter pylori-induced gastric mucosal inflammation[1-4]. The prevalence of *H. pylori* varies significantly according to geographic region and country, those from developing countries are more prone to acquire *H. pylori* than subjects from highly developed industrialized countries[2]. One of the most successful human pathogen, *H. pylori*, exhibits a strict tropism for gastric epithelial lining, adhering specially to gastric epithelium, colonizing in the gastric mucosa, subsequently triggering the responsible inflammation for the resultant gastrointestinal diseases. Although there are a number of hypotheses to explain the precise underlying pathogenetic mechanism, one of the most appreciated one is that host immune response and *H. pylori* virulence factors interplay between each other in the development of these diseases[1,3-6].

Despite the worldwide high prevalence rate and the fact that *H. pylori* is most commonly acquired early in the childhood and if untreated, infection is lifelong, the majority of the individuals infected with *H. pylori* are asymptomatic[1,3-6]. Both the genetic characteristics of the host and genetic differences between strains of *H. pylori* determine the clinical outcome of the colonization[5,7]. *H. pylori* produces a number of virulence factors, including flagellins, which provide motility essential for evading from gastric peristalsis and immune challenge of the host, adhesins, conjugated proteins involved in the attachment of the organism to host cell surface. It has been long appreciated that key pathogenic pathways involved in *H. pylori* infection include chronic gastric inflammation and alternation of gastric physiology, including breakdown of protective gastric mucosal barrier. *H. pylori* produces different kinds of enzymes that are important in these pathogenetic effects[1,3-6]. The expressions of virulence-associated genes, cytotoxin-associated gene A (*cagA*) and vacuolating cytotoxin gene A (*vacA*), have been shown to be closely related with the diversity of clinical outcome of *H. pylori* infection. CagA protein, which is encoded by *cagA* gene, is associated with increased risk of developing atrophic gastritis, peptic ulcer and gastric cancer. The cytotoxin, vacA, causing severe vacuolation, has multiple effects on gastric epithelial cells: forms channels in membranes, alternates endosome/lysosome functions, increases transcellular permeability, induces apoptosis and promotes immune tolerance against *H pylori*[3,4,6,8].

An host-adapted pathogen, *H. pylori* has ability to mount an effective anti-immune response within the infected host, which results in a chronic lifelong infection. Although *H. pylori* employs elaborate strategies to evade the host's immune system, complete avoidance from immune activation is not possible. When some of *H. pylori* proteins cross the gastric mucosal barrier, both innate and acquired defence mechanisms are activated[8,9]. There has been considerable evidence suggesting that systemic immune response evoked by *H. pylori* participates in the development of diseases other than gastrointestinal in origin. Although there are many more questions to be answered, *H. pylori* has been implicated as the causal agent of several extragastric diseases, including neurodegenerative, cardiovascular, pulmonary, endocrinological, ocular, autoimmune and dermatological ones[9-12]. In this review, we aimed to present a summary concerning association of *H. pylori* with inflammatory skin diseases. We briefly have reported on the present state of basic knowledge and a concise analysis of clinical studies conducted to evaluate the relation of *H. pylori* with inflammatory skin diseases.

## PSORIASIS

Psoriasis is a common chronic inflammatory dermatosis characterized by erythematous, sharply demarcated papules and plaques covered by silvery white scales most commonly affecting scalp, lumbosacral region and extensor surfaces of elbows and knees in a symmetrical pattern. Psoriasis appears worldwide affecting both genders equally[13]. Psoriasis is an immune-mediated disorder. Although the immunopathogenesis of psoriasis has not been fully elucidated yet, it has been revealed that the main role in the immunological cascade of psoriasis is played by T cells. Interaction between inflammatory cytokines, dendritic cells, macrophages, and T-helper type 1 (Th1), Th17, regulatory T cell, Th22 cells contribute to the disease pathogenesis[14].

Genetic and environmental factors are involved in the etiology of psoriasis[15]. Environmental factors that have been claimed to contribute psoriasis include streptococcal tonsillitis[16], smoking[17], alcohol consumption[18], medications, stress, human immunodeficiency virus infection and trauma[15]. There is a growing body of evidence showing that superantigen-mediated T cell activation plays a critical role in the psoriasis pathogenesis. Superantigens are toxins produced by pathogenic bacteria and viruses. It has been suggested that *H. pylori* toxins, including the aforementioned ones can act as super-antigens, which mount inflammatory response dominated by activated T cells and monocytes. Indeed, superantigens have been presumed to directly trigger the inflammatory cascade, which is mediated by antigen-presenting cells, such as macrophages, dendritic cells and keratinocytes, thus contributing to development of psoriasis[19].

Several studies have been conducted to evaluate the role of *H. pylori* in the pathogenesis of psoriasis[20-26]. In one of the earlier studies about the possible relationship between *H. pylori* and psoriasis, Halasz[21] investigated

serum immunoglobulin G (IgG) antibody titers against *H. pylori* in 33 psoriatic patients and established a causative link of this pathogen with psoriasis. In 2003, Qayoom *et al*[22] also investigated *H. pylori* seropositivity in a group of psoriasis patients and compared it to a group of healthy subjects. Although the seropositivity of *H. pylori* among the patients and controls were lower than the expected prevalence range, meaning that lower than the general population's, since there was a statistically significant difference between the patient and control group and subjects with known upper gastrointestinal complaints were excluded from the study, they interpreted their study results as supporting a causal role of *H. pylori* in the pathogenesis of psoriasis[22].

Onsun *et al*[20] conducted a large-scale study to investigate the prevalence of *H. pylori* seropositivity in patients with psoriasis. Their study also aimed to figure out the relationship between disease severity and *H. pylori* infection, and to evaluate the impact of *H. pylori* infection on the response to psoriasis treatment. By means of assessing the *H. pylori* stool antigen in a total of 300 patients with psoriasis and 150 non-psoriatic healthy controls, it was found out that 184 psoriatic patients were infected with *H. pylori*. Fifty patients, which were selected from these *H. pylori* infected patients, randomized into two groups to receive acitretin with *H. pylori* eradication treatment or acitretin alone. In additon, they segregated 25 patients from the *H. pylori* infected patients, who received only *H. pylori* eradication treatment, not any systemic treatment for psoriasis. It was observed that disease severity index, Psoriasis Area Severity Index scores, were significantly higher in patients with *H. pylori* infection and *H. pylori* eradication treatment improved both the effectiveness of acitretin therapy and also the clinical outcome of the patients who did not receive acitretin[20].

In the literature, although there are also case reports describing the benefits of *H. pylori* eradication therapy in chronic psoriasis[27] and palmoplantar psoriasis[28,29], it is inevitable to detect studies showing that *H. pylori* infection is not associated with psoriasis[23,24,26]. In 2001, Fabrizi *et al*[23] performed [$^{13}$C] urea breath test ($^{13}$C-UBT) on 20 patients with psoriasis and a control group of 29 patients without any skin disorders, who were aged between 5 and 19 years, in order to investigate the presumed relationship between *H. pylori* and psoriasis. Results uncovered that the prevalence of *H. pylori* in children and teenagers with psoriasis was low and did not differ between the patient and control groups[23]. In a a case-control study including 61 patients with psoriasis and 61 healthy individuals, Azizzadeh *et al*[26] investigated seropositivity of *H. pylori* by measuring serum IgG antibody titers of *H. pylori* with enzyme-linked immunosorbent assay method. Accordingly, their study results revealed that there was no clear evidence to prove a causal relationship between psoriasis and *H. pylori* infection[26].

There have been several studies about the pathogenesis of psoriasis, which is regarded to be one of the most common and exceptional disease in dermatology practice. A lot of interest has been focused on the immune/inflammatory pathway in the pathogenesis of psoriasis.

Although the exact pathogenetic role of infectious agents remains to be determined and questions of paramount importance await to be answered, the superantigen theory has drawn growing interest in the immunopathogenesis of psoriasis[19]. It is obvious that there is a contradiction between the study results, which are about the causative role of *H. pylori* in the development of psoriasis[20-26] and further studies are needed to elucidate this possible role.

## LICHEN PLANUS

Lichen planus is a chronic, inflammatory, papulosquamous dermatosis that affects skin, scalp, nails and mucous membranes. Lichen planus is a distinctive disease, which is designated by well-known six "Ps" mnemonic, that stands for: pruritic, polygonal, planar, purple, papules and plaques. Although the etiology of lichen planus is still under discussion, it is believed that lichen planus is a T-cell mediated autoimmune disease, of which pathogenesis is centralized on abnormal immune response[30,31]. Up to date, several studies have been conducted to evaluate the relationship of *H. pylori* with lichen planus[24,32-37]. In one of the earlier studies, it was revealed that the prevalence of peptic ulcer was three-fold higher in patients with chronic/repeating lichen planus when compared with controls[32].

In a hospital based cross-sectional descriptive study, *H. pylori* stool antigen was assessed in 105 lichen planus patients and it was found out that stool antigen was positive in 77% of the patients[33]. Likewise, Moravvej *et al*[34] demonstrated higher $^{13}$C-UBT rates in patients with lichen planus when compared with the control group. These studies suggest that *H. pylori* has a role in the etiology of lichen planus. A possible mechanism of pathogenesis relies on in the induction of autoimmunity by infectious agents. Lichen planus is a multifactorial disease, in which certain infectious diseases have been proposed to be associated with autoimmune processes in susceptible individuals[32].

On the other hand, in the literature there are studies which do not establish any clear evidence of causality relationship between *H. pylori* and lichen planus. In one of them, $^{13}$C-UBT performed in 30 patients with cutaneous lichen planus, in 30 patients with oral lichen planus, and in 30 healthy individuals. Accordingly, no significant association was found between lichen planus and *H. pylori* infection[35]. Daudén *et al*[24] also investigated the prevalence of *H. pylori* infection in patients with psoriasis and lichen planus by performing $^{13}$C-UBT and their study did not prove any pathogenetic role of *H. pylori* in the development of psoriasis and lichen planus[24]. Moreover, there are studies particularly focusing on the relationship of *H. pylori* with oral lichen planus, which also do not support the pathogenetic

role[36,37]. As in psoriasis, the association of *H. pylori* with lichen planus seems to be mainly explained by induction of autoimmunity by infectious agents[32]. However, there are studies with conflicting results[24,32-37]. We suppose that further studies will demonstrate the presumed role of *H. pylori* in the pathogenesis of lichen planus.

## PRURITUS AND PRURIGO NODULARIS

Pruritus, which is a common manifestation of several dermatologic diseases is defined as an unpleasant sensation that causes an intense desire to scratch. Pruritus is not only a symptom of a dermatosis, but also appears to be related with several systemic, neurologic and psychologic diseases[38]. Prurigo nodularis is a chronic dermatosis characterized by multiple lichenified papulonodular lesions located especially on extensor surfaces of the limbs. Prurigo nodularis is an intensely pruritic condition, which is almost entirely resistant to treatment. Although the etiology of prurigo nodularis has not been fully elucidated yet, a wide variety of systemic diseases have been implicated in the pathogenesis of prurigo nodularis[39,40].

*H. pylori* is one of the infections which has been reported to be associated with chronic pruritus and prurigo nodularis[19,41-44]. In 1999, Neri *et al*[42] screened 42 prurigo nodularis patients for *H. pylori* infection and found out that 40 patients were colonized with *H. pylori* and after *H. pylori* eradication treatment chronic itching was greatly reduced in 39 of these 40 patients[42]. Two Japanese studies have shown causal role for *H. pylori* in pruritic skin diseases[43,44]. Sakurane *et al*[44] examined serum levels of IgG antibody against *H. pylori* in 198 skin-diseased patients, 32 of which were diagnosed with pruritus cutaneous and 17 of which were diagnosed with prurigo chronica multiformis. One hundred and two of them were detected to be infected with *H. pylori* and after *H. pylori* eradication treatment, in 58% of patients with pruritus cutaneous and in 50% of patients with prurigo chronica multiformis intractable pruritus was subsided[44].

Likewise, Shiotani *et al*[43] investigated the prevalence of *H. pylori* infection and also the incidence of gastric cancer in patients with pruritic skin diseases. It was found out that 73.5% of patients with pruritus cutaneous and 76.2% of patients with prurigo chronica multiforme were *H. pylori* positive and early stage gastric cancer was detected in 5.6% of patients with cutaneous pruritus and 18.8% of patients with prurigo chronica multiforme. However, in the improvement of pruritus, *H. pylori* eradication treatment was effective only in one patient, who was diagnosed as prurigo chronica multiforme[43]. The association of *H. pylori* with refractory pruritus and the beneficial effect of eradication therapy in this indication have been also shown in other studies[41].

## SWEET'S SYNDROME

Sweet's syndrome, also designated as acute febrile neutrophilic dermatosis, is a neutrophilic dermatosis characterized by acute onset fever, neutrophilia, erythematous to violaceous tender plaques and nodules on face, neck, upper extremities and a typical histopathological finding of a dense upper dermal neutrophilic infiltrate[45-49]. Sweet's syndrome is classified according to etiological and pathogenetic aspects of the disorder[46,47]. Classical Sweet's syndrome, which generally occurs in women in their third to fifth decade of life is often associated with upper respiratory or gastrointestinal track infections, inflammatory bowel diseases and pregnancy. On the other hand, several other underlying diseases have been suggested as a predisposing factor for classical type of Sweet's syndrome[46,47].

In 1997, Kürkçüoğlu *et al*[50] reported a 42-year-old woman who presented with a six-month history of recurrent episodes of fever, arthralgia, colicky abdominal pain and well-defined, infiltrated, erythematous plaques measuring up to 2 cm on face, neck and extremities. Her laboratory investigations showed elevated sedimentation rate and leukocytosis with neutrophilia. Gastrointestinal endoscopy revealed gastritis and *H. pylori* was identified in the gastric mucosal biopsy. Kürkçüoğlu *et al*[50] asserted that after *H. pylori* eradication treatment, patient's skin lesions dramatically improved[50]. Although this is the only case of *H. pylori* associated-Sweet's syndrome so far, since Sweet's syndrome is considered as an abnormal immunological reaction to a variety of microbial insults[46], this case can prove the relation of *H. pylori* with Sweet's syndrome.

## ROSACEA

Rosacea is a common chronic inflammatory disorder, characterized by multiple clinical features including flushing, facial erythema, inflammatory papules, pustules and telangiectasias[51]. Several factors have been implicated in the pathogenesis of rosacea, which include genetic, enviromental, vascular, inflammatory factors and microorganisms[52]. It is known that there is an association between rosacea and some gastrointestinal disorders. In addition, since a similar seasonal variation has been observed between peptic ulcer and rosacea, also both rosacea and peptic ulcer respond well to metronidazole, it has been proposed that *H. pylori* infection might play a triggering role in the pathogenesis of rosacea[52,53].

*H. pylori* produces cytokines that contribute to inflammation in gastric mucosa and host response emerges which leads to infiltration of inflammatory cells[54]. *H. pylori* is proposed to induce rosacea by cytotoxin mediated chronic inflammation and gastrin induced flushing[55]. Increased activity of reactive oxygen species have been reported in patients infected with *H. pylori* and rosacea is associated with generation of reactive oxygen species that are released by inflammatory cells[56,57]. Since the first report of an association between rosacea and *H. pylori* by Rebora *et al*[58] in 1994, there have been numerous studies investigating the prevalence of *H. pylori* infection in

rosacea patients[58-61]. The results of those studies are conflicting, as some suggest that the prevalence of *H. pylori* infection is significantly increased in rosacea patients[59-61] and others suggest no association between *H. pylori* infection and rosacea[51,61-64]. This discrepancy might be due to different methods of evaluation of *H. pylori* infection between these studies. The effect of *H. pylori* eradication treatment in rosacea patients have been also studied. Several authors reported significant decrease in the severity of rosacea with *H. pylori* eradication therapy, especially in cases with papulo-pustular type[52,62,64,65]. But it was also suggested that the improvement of rosacea symptoms after the treatment of *H. pylori* might be due to the antioxidant effects of the drugs used rather than *H. pylori* eradication[66].

El-Khalawany *et al*[52] studied 68 patients with rosacea concomitant with dyspeptic symptoms and 54 controls only with dyspeptic symptoms to assess the role of *H. pylori* in rosacea patients who had dyspeptic symptoms. Screening for *H. pylori* was performed with *H. pylori* serum IgG and stool antigen test and gastric endoscopy was performed in *H. pylori* positive cases. *H. pylori* vacA alleles, cagA and epithelium factor antigen (iceA) genotypes were assessed by polymerase chain reaction. Significantly higher number of patients than controls were infected with *H. pylori* and 63.3% of the infected patients had papulopustular rosacea (PPR). Gastric ulceration and inflammation was also higher in PPR cases than erythematotelangiectatic (ETR) cases and controls. Analysis of *H. pylori* genotypes revealed that vacA s1m1 was more detected in PPR cases and there was a significant elevation of cagA/vacA s1m1 positivity in ETR cases. After the eradication regimen of *H. pylori*, a significant improvement was observed in PPR cases compared with ETR patients. The authors concluded that *H. pylori* had a significant etiological role in rosacea patients who had dyspeptic symptoms and the PPR type was more influenced by *H. pylori* infection. The authors suggested that the role of *H. pylori* in PPR is different from that in ETR and this is regarded to be caused by certain virulent strains that increases the inflammatory response in gastric mucosa and cutaneous lesions[52]. In addition, Boixeda de Miquel *et al*[65] observed higher improvement rates in PPR lesions compared with ETR after eradication of *H. pylori* suggesting an association between inflammatory rosacea and *H. pylori* infection[65].

Szlachcic *et al*[61] examined the prevalence of *H. pylori* by 13C-UBT, Campylobacter-like organism test (CLO-test), *H. pylori* culture and serology in rosacea patients and controls with dyspeptic symptoms. They also investigated the presence of *H. pylori* in oral cavity by CLO-test, *H. pylori* culture and saliva anti-*H. pylori* antibodies. They performed gastroduedonoscopy and fundic biopsy samples were taken for histological evaluation. *H. pylori* infection was significantly higher in the rosacea group and a noticeable number of rosacea patients showed chronic active gastritis predominantly in the anthrum and corpus while those in the control group showed mild gastritis confined to anthrum only. Among rosacea patients, 67% were CagA positive, while in the control group only 32% were CagA positive. With anti-*H. pylori* therapy the symptoms of rosacea disseapeared or decreased in most of the subjects. As the eradication rate of *H. pylori* was lower in the oral cavity than gastric mucosa the authors suggested that the lack of improvement of cutaneous symptoms in rosacea after eradication of *H. pylori* from the gastric mucosa may depend on the bacteria in the oral cavity[61]. As a conclusion, especially papulopustular rosacea can be considered as one of the extragastric symptoms of *H. pylori* infection and the eradication of *H. pylori* may lead to improvement of rosacea and associated gastrointestinal symptoms.

## BEHÇET'S DISEASE

Behçet's disease (BD) is a systemic vasculitic syndrome, characterized by recurrent aphthous stomatitis, genital ulcers, skin lesions and relapsing uveitis. Also articular, vascular, gastrointestinal, cardiopulmonary and neurological involvements may be observed in these patients[67,68]. Though the exact etiology of the disease has not been fully elucidated yet, enviromental factors including viral and bacterial agents and genetic factors are implicated in the pathogenesis of BD[67]. As *H. pylori* infection is more prevalent in areas where BD is common and both BD and *H. pylori* may cause ulcers in the gastrointestinal tract, it has been suggested that *H. pylori* may play a role in the pathogenesis BD. The possible mechanism of action of *H. pylori* and other bacterial infections in the pathogenesis of BD might be related with molecular homology of bacterial antigens and human heat shock protein, which is proposed as a possible antigen in BD[69].

Lankarani *et al*[69] investigated *H. pylori* infection in 48 patients with BD using serology and $^{13}$C-UBT. They demonstrated higher $^{13}$C-UBT positivity rates in patients with BD but the results of serology was not significantly different between two groups. They suggested that the reason for these conflicting findings may be related with the fact that serology can not differentiate between ongoing infection and previous exposure[69]. Cakmak *et al*[68] investigated 40 patients with BD with fiberoptic esophagogastroduedonoscopy and $^{13}$C-UBT and no significant difference was found in *H. pylori* positivity rates between the patient and control groups[68]. Ersoy *et al*[70] reported that there was no difference between BD patients and the control group in respect to *H. pylori* prevalence rates when biopsy specimens taken during upper gastrointestinal endoscopy were compared[70].

Apan *et al*[67] investigated *H. pylori* seropositivity and cagA status in patients with BD. While the seropositivity of *H. pylori* was not significantly different between the patient and control groups, the prevalence of cagA positivity was significantly higher in BD compared to controls and *H. pylori* eradication therapy had significantly decreased the clinical symptoms of the BD

**Table 1 Summary of some of the studies concerned with the association of *Helicobacter pylori* in the pathogenesis of inflammatory skin diseases, shown in order of publication date**

| Ref. | Study design | Result |
|---|---|---|
| Halasz[21] | Investigation of serum *H. pylori* IgG antibody titers in 33 psoriatic patients | Suggesting a potential link of *H. pylori* with psoriasis |
| Daudén *et al*[24] | Performing $^{13}$C-UBT on 84 patients with psoriasis and 61 patients with lichen planus | Suggesting no evidence of a link between *H. pylori* and psoriasis and *H. pylori* and lichen planus |
| Fabrizi *et al*[23] | Performing $^{13}$C-UBT on 20 psoriatic patients and 29 healthy controls | Suggesting no evidence of a link between *H. pylori* and psoriasis |
| Szlachcic[61] | Performing $^{13}$C-UBT, CLO-test, oral cavity CLO-test, bacterial culture and fundic biopsy, investigation of serum and saliva *H. pylori* IgG and IgA antibody titers | Suggesting a potential link of *H. pylori* with rosacea and improvement of symptoms of rosacea with *H. pylori* eradication treatment |
| Qayoom *et al*[22] | Investigation of serum *H. pylori* seropositivity in 50 psoriatic patients and healthy controls | Suggesting a potential link of *H. pylori* with psoriasis |
| Novák *et al*[73] | Investigation of serum *H. pylori* seropositivity in 11 adult HSP and 20 healthy adult patients | Suggesting a potential link of *H. pylori* with HSP |
| Shiotani *et al*[43] | Investigation of serum *H. pylori* IgG antibody titers in 134 patients with pruritic skin diseases | Suggesting a potential link of *H. pylori* with pruritic skin diseases and *H. pylori* positivity in pruritic skin diseased patients with gastric cancer |
| Moravvej *et al*[34] | Performing $^{13}$C-UBT on 80 patients with lichen planus and 80 patients with other skin diseases | Suggesting a potential link of *H. pylori* with lichen planus |
| Ersoy *et al*[70] | Performing endoscopy, histopathological examination and RUT in 45 patients with BD and 40 healthy controls | Suggesting no evidence of a link between *H. pylori* and BD |
| Cakmak *et al*[68] | Performing $^{13}$C-UBT in 40 patients with BD and 40 healthy controls | Suggesting no evidence of a link between *H. pylori* and BD |
| El-Khalawany *et al*[52] | Investigation of serum *H. pylori* IgG antibody titers and *H. pylori* stool antigen in 68 patients with rosacea and 54 healthy controls and performing *H. pylori* genotyping | Suggesting a potential link of *H. pylori* with rosacea and certain virulent strains with rosacea subtypes |
| Onsun *et al*[20] | Investigation of *H. pylori* stool antigen in 300 psoriatic patients and 150 healthy controls; investigation of *H. pylori* stool antigen in 25 patients before and after acitretin treatment | Suggesting a potential link of *H. pylori* with the etiology and the severity of psoriasis |
| Lankarani *et al*[69] | Performing $^{13}$C-UBT and investigation of *H. pylori* seropositivity in 48 patients with BD and 48 healthy controls | Suggesting a potential link of *H. pylori* with BD |

*H. pylori*: *Helicobacter pylori*; Ig: Immunoglobulin; $^{13}$C-UBT: $^{13}$C urea breath test; CLO-test: Campylobacter-like organism test; HSP: Henoch-Schonlein purpura; RUT: Rapid urease test; BD: Behçet's disease.

patients[67]. Avci *et al*[71] reported that although *H. pylori* seroprevalence between BD patients and controls did not show significant difference, in patients with BD who had *H. pylori* infection various clinical manifestations regressed after the eradication of *H. pylori*[71]. These findings suggest that although the prevalence of *H. pylori* is not increased in BD patients, eradication therapy of *H. pylori* may improve the clinical outcome of BD in *H. pylori* infected patients.

## HENOCH-SCHONLEIN PURPURA

Henoch-Schonlein purpura (HSP) is a type of leukocytoklastic vasculitis of small vessels, characterized by IgA containing deposits in the skin, joints, gastrointestinal mucosa and glomeruli[72,73]. It is commonly observed in children and characterized with palpable purpura, abdominal pain, gastrointestinal hemorrhage, arthralgia and renal involvement[72,74]. Though the pathogenesis of HSP is not clear, it is thought that an antigenic particle, which may be related with exogenous sources like bacterial and viral infections, vaccinations and drugs, elicits an antigenic stimulus, causes elevation of circulating IgA and complement activation, eventually leading to vasculitis[72,75].

Few case reports have described an association between *H. pylori* infection and HSP in children and adults[76,77]. In addition, resolution of gastrointestinal symptoms and purpuric rashes have been described in HSP patients with *H. pylori* eradication treatment[72,75,78]. These reports suggest a causative role of *H. pylori* in the pathogenesis of HSP. Xiong *et al*[79] performed a meta-analysis about the association of *H. pylori* infection with HSP development in Chinese children. They reported that 49.27% (369/749) of children with HSP had the evidence of *H. pylori* infection compared with 23.39% (131/560) of children in the control group and *H. pylori* eradication therapy was capable of reducing the recurrences of HSP. They suggested it is advisable to screen *H. pylori* infection in children with HSP, particularly in those with gastrointestinal manifestations[79].

Cai *et al*[80] investigated the effect of *H. pylori* eradication therapy on prognosis in children with HSP. 153 children with HSP were divided into three groups: group 1 included patients with *H. pylori* infection who received *H. pylori* eradication therapy in addition to conventional therapy, group 2 included control group, in which patients were *H. pylori* positive but only received conventional therapy for HSP, group 3 included *H. pylori* infection-negative group, who also received conventional therapy for HSP. The response

and recurrence rates of HSP were not significantly different between three groups but the incidence of HSP nephritis was significantly lower in the *H. pylori* infection treatment group. The authors concluded that *H. pylori* eradication therapy may be useful in reducing the incidence of HSP in children infected with *H. pylori*[80].

Novák *et al*[73] investigated *H. pylori* antibodies in 11 adult patients with HSP and the serological investigations revealed *H. pylori* infection in 10 patients. Patients in the acute phase had significantly higher levels of anti *H. pylori* IgG levels compared to patients in remission phase. In addition, anti *H. pylori* IgA levels were elevated with significant difference in patients in the remission phase[73]. We suggest that it would be useful to investigate *H. pylori* infection in patients with HSP, especially if they have gastrointestinal manifestations of HSP. Summary of some of the studies concerned with the association of *H. pylori* in the pathogenesis of inflammatory skin diseases is shown in Table 1.

## CONCLUSION

*H. pylori* is a world-wide spread bacterium, which is estimated to infect more than half of the world's population. *H. pylori* has been implicated in the pathogenesis of a number of gastrointestinal system disorders, also classified as a gastric carcinogen since it has been proven that *H. pylori*-induced chronic gastric inflammation triggers the events that can promote gastric carcinogenesis. Recent studies have suggested that *H. pylori* induces not only local inflammation, but also systemic inflammation. There is a growing body of evidence concerning the causative role of Helicobacter pylori-induced systemic inflammation in the pathogenesis of several extragastric diseases, including endocrinological, autoimmune and dermatological ones. However, conflicting results were noted among the individual studies, which evaluate the pathogenetic role of *H. pylori* in the development of these diseases. In this review, we have concentrated on the pathogenetic role of *H. pylori* in the pathogenesis of inflammatory skin diseases. On the other hand, we think that there is a need for further studies to better define the role of *H. pylori* in inflammatory skin diseases.

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MINIREVIEWS

# X linked recessive ichthyosis: Current concepts

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## Abstract

In the present review, we describe the most important aspects of the X-linked ichthyosis (XLI) and make a compilation of the some historic details of the disease. The aim of the present study is an update of the XLI. Historical, clinical, epidemiological, and molecular aspects are described through the text. Recessive XLI is a relatively common genodermatosis affecting different ethnic groups. With a high spectrum of the clinical manifestations due to environmental factors, the disease has a genetic heterogeneity that goes from a point mutation to a large deletion involving several genes to produce a contiguous gene syndrome. Most XLI patients harbor complete *STS* gene deletion and flanked sequences; seven intragenic deletions and 14 point mutations with a complete loss of the steroid sulfatase activity have been reported worldwide. In this study, we review current knowledge about the disease.

**Key words:** *STS* gene; X-linked ichthyosis; Steroid sulfatase; Gene deletion; Contiguous gene syndrome; Genodermatosis



**Core tip:** In the present study we describe the current knowledge of historical, clinical, epidemiological, physiopathological and molecular data in the X-linked ichthyosis (XLI). We consider that this review is important due to XLI is one of the most frequent genodermatosis that affects similarly to different ethnic groups worldwide.

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## HISTORY

The term ichthyosis has been used for over 2000 years

and comes from the Greek root "ichthys" meaning fish. In the nineteenth century, the Indians and Chinese referred to the disease as "a condition of snakeskin or fish scales" and at the time of the Arab physician Avicenna as "nigra albarras". The first description of ichthyosis documented in the medical literature was in the work "On cutaneous diseases" by Wilan[1] in 1908. Cockayne[2] in 1933, was the first to describe cases of ichthyosis in males and used the genetic classification. In 1965, Wells *et al*[3] could distinguish the X-linked ichthyosis (XLI) from the dominant ichthyosis vulgaris. They suggested that the onset of dominant form was present after three months with a less body affection. In 1978, Koppe *et al*[4] and Webster *et al*[5] identified the absence of the steroid sulfatase (STS) enzyme in fibroblasts of patients with XLI.

## EPIDEMIOLOGY AND ETIOLOGY

XLI (OMIM 308100) is a genodermatosis caused for STS deficiency[4,5]; it is characterized by abnormal desquamation and hiperqueratosis in the skin[6], and is due excessive amounts of cholesterol sulfate in the epidermis[7]. XLI has a frequency of one to two in 6000 men[8]. With respect to the genetics of X-linked recessive disorders, these diseases are generally restricted to males, these ones transmit the affected gene only to females (obligated carriers). Carriers of the X-linked gene defect have a risk of 50% to have affected males or carriers females.

The STS protein has 583 amino acids with a molecular weight of 62 kDa. The first 22 amino acids correspond to the leader peptide, which is cleaved post-translationally to give rise to the mature enzyme[9]. STS protein has 4 glycosylation sites[10]. The STS enzyme is attached to the rough endoplasmic reticulum and hydrolyzes the sulfate groups of the sulfated 3 β-hydroxysteroids such as dehydroepiandrosterone sulfate (DHEAS), cholesterol sulfate, pregnenolone sulfate and androstenediol 3 sulfate[11-13], metabolites that serve as precursors for estrogens, androgens, and cholesterol. STS is expressed on placenta, breast, immune system, brain, liver, reproductive tract and blood cells[10]. In placenta, STS deconjugates DHEAS, a previous step for the oestrogen synthesis during pregnancy. STS enzyme is upregulated by tumor necrosis factor α and interleukin (IL)-6, while IL-1β and interferon-γ downregulate it by inhibiting nuclear factor-kappa-B and activiting glucocorticoid receptor. Retinoids and 1,25(HO)$_2$-vitamin D3 induce its activity and expression[14,15].

The STS gene is located in the Xp22.3 region[16,17], and has 10 exons, 2 untranslated regions (at the 5' of 206 bp and at the 3' of 668 bp), and one open reading frame of 1752 bp[18-20]. The Xp22.3 region escapes to X-inactivation[16,21]. More than 90% of XLI patients present a complete *STS* gene deletion and flanked sequences, the remainders have showed 7 intragenic deletions[22-28] whereas 14 point mutations with a complete loss of the STS activity[29-38] have been reported. Contiguous gene deletions around the STS leading to a more complex phenotype associated with short stature, chondrodysplasia punctata, Kallman syndrome and ocular albinism[39].

One explanation for the deletion of the *STS* gene and flanking sequences on the short arm of the X chromosome is the presence of families of repeated sequences in low copy number (G1.3 and CRI-S232) on both sides of the *STS* gene[40-43]. In women, the presence of these sequences could produce an unequal homologous recombination; however, another proposed mechanism is a mismatch by sliding DNA chains as shown the paternal origin of the affected X chromosome[22,44-46].

## CLINICAL FEATURES

Mothers of affected fetus con XLI may present delayed or prolonged labor due the absence of STS enzyme in the placenta[47]. Onset of symptoms of the XLI is in the first months of life by the presence of polygonal, loosely adherent translucent scales with a generalized distribution[48]. The scales predominantly are in anterior abdomen, preauricular area, neck, axillae and extension zones of the limbs[3,49-52]. The scalp is affected in childhood and this affection disappears in the adulthood. Generally, scales spare palms, soles, popliteal and antecubital fossae and the mid-face[52-54]. Clinical manifestations are worse in cold/dry weather. XLI patients have low sweat production due to a decrease numbers of sweat gland[55]. Filaggrin mutations may be associated with ichthyosis vulgar, xerosis and atopic dermatitis exacerbating the XLI phenotype[56,57]. Extracutaneous manifestations, such as ocular defects, have been observed in 10%-15% of patients and up to 25% of carrier mothers[58]. Diffuse deposits in the corneal stromal and descemet membrane[59], may appear at any time of life, they predominate in the 2$^{nd}$ and 3$^{rd}$ decade without affect visual acuity[60,61]. Back embryotoxon, deuteranopia, corneal erosion[62,63] has also been observed. Cryptorchidism is observed in 20% of cases[64], with a cancer high risk of testicular germ cells[65]. Neurological alterations have been observed in patients with XLI, such as epilepsy, electroencephalogram abnormalities, mental retardation, hyposmia[66], attention deficit hiperactivity disorder, autism and speech deficit; these manifestations have been attributed to altered sterol metabolism in the central nervous system[67,68] frequently associated with contiguous gene deletion. Others anomalies less frequent are seizures, psychological disorders[69,70], pyloric hypertrophy[71,72], abdominal wall defects, leukemia, nodular heterotopia periventricular[73,74] and steroid-resistant nephrotic syndrome[75].

## PHYSIOPATHOLOGY

Cholesterol sulfotransferase (SULT2B1b) generates cholesterol sulfate (CS) in lower nucleated cell layers

(stratum basal) of the epidermis, increasing the concentration of CS from 1% to 5% on the stratum granulosum[52]. STS enzyme decreases CS to 1% in the stratum corneum (outer epidermis)[52,76,77]. The increase of CS induces the expression of the skin barrier protein filaggrin and plays a role in the differentiation of normal keratinocyte[78,79]. Rupture of CS cycle by STS defect produces an increase of CS from 1% to 10%-12% in the stratum corneum of the epidermis[7]; this results in: (1) a decrease barrier function with a failure of the normal liquid-crystalline transition phase of intercellular lipids; and (2) an abnormal corneocyte retention stimuling the hyperplasia epidermal-inflamation and a thickened stratum corneum. The increase of CS is in relation with the decrease of the activity serine protease and the increase of $Ca^{2+}$, producing corneodesmosomal retention[6,52,80]. Besides, the dark color of the scales could be explained by the presence of large amounts of melanosomes in the corneal cells[81].

## LABORATORY DIAGNOSIS

Prenatal diagnosis can be carried out through the study of triple marker in second trimester of pregnancy which detects low or absent serum levels of estriol. The suspect of a fetus with XLI is associated with a decrease level of estrogen and the presence of unhydrolyzed steroid sulfates in maternal urine[82-84]; a history of prolonged labor and delivery increases this possibility. The analysis of the *STS* gene through southern blot, *in situ* hybridization, polymerase chain reaction can be made on chorionic villi or amniotic liquid when the familial genetic defect is known[85]. Determination of steroid sulfatase activity and polymerase chain reaction, fluorescence *in situ* hibridation and DNA of the *STS* gene analyses allow to discard XLI[31,32,34,41,86]. New techniques as MLPA, DNA microarrays, total exome sequencing is helping to prove the complete deletion, partial deletions or point mutations in the *STS* gene. Histopatological study is not useful for the diagnosis of XLI, however it may be useful in the differential diagnosis of XLI with other specific histopathology entities[6].

## DIFFERENTIAL DIAGNOSIS

XLI differential diagnosis mainly is with ichthyosis vulgaris and others ichthyosis like lamellar ichthyosis[50,54,87]. Ichthyosis vulgaris (IV) is characterized by symmetric light gay scaling, generally after 3 mo of age; flexion zones are affected and inheritance pattern is dominant autosomal, nevertheless in some cases it can be acquired. Biopsy studies of skin appear similar in both cases. In sporadic cases is most difficult to stablish the correct diagnosis, because it is not present a specific inheritance pattern. In familiar cases, genealogy is an important tool to correctly identify XLI from IV. The determination of STS activity is the golden standard in the differential diagnosis of both diseases but molecular studies of *STS* or *FLG* genes are also useful to perform the correct diagnosis.

## MANAGEMENT

XLI has not definitive treatment, but fortunately, except for the aesthetic appearance, rarely affects normal life function. XLI mainly affects the skin that is exacerbated in winter, but improves in summer. Lubricants, humectants and keratolytic agents are indicated when there is excessive large scale or keratinization[88]. There are few studies on the treatment of XLI, one study used tazarotene 0.05% and glycolic acid 70% in a patient with a large deletion of the *STS* gene, with good response, but with a remission to the 8 and 2 mo, respectively[89], another study used calcipotriol in 8 cases with XLI and 11 patients with congenital ichthyosis and showed reduction of scaling and roughness[90]. On a heterogeneous study[91], liarozole *vs* oral acitretin were compared with no significant differences[92]. Generally, XLI treatment is based upon studies in other groups of congenital or heterogeneous ichthyoses[93-95]. In neonates and infants, keratolytics should be handled with caution because they are absorbed due to the immature skin barrier causing toxicity. Any treatment regimen works for everyone, and the best therapy for each patient may be the result of months or years of painstaking effort on both the physician's and the patient's behalf. It is important to keep in mind the cost of the topical treatments[88]. Multidisciplinary management with various specialists such as dermatologists, geneticists, ophthalmologists, psychologists, gynecologists should be considered.

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