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REVIEW PAPER

Cutaneous manifestation of *Helicobacter pylori* infection

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ABSTRACT

Helicobacter pylori is known as one of the most common bacteria in the world, affecting millions of people every year, with a prevalence among humans of about 50% worldwide. Moreover, *H. pylori* is well known for its gastrointestinal disorders, which nowadays are treated mostly with antibiotics, with good response. As well as these gastrointestinal diseases, *H. pylori* is also involved in the development of many other non-gastrointestinal diseases, including autoimmune and allergic diseases.

The wide spectrum activity of *H. pylori* is obtained by the phenomenon of molecular mimicry, which involves induction by the chemical structures of pathogen antibodies that react both with host antigens and pathogenic microorganism antigens.

The following review paper concentrates on several diseases induced by *H. pylori*. Chronic urticaria is characterised by recurrent itchy blisters on the skin induced by mast cells and basophilic granulocytes, which are activated by enzymes produced and released by *H. pylori*.

Helicobacter pylori infection constitutes some groups of patients with psoriasis vulgaris and vitiligo. The aetiopathogenesis of these diseases is multifactorial, but recent studies have shown the relationship between immune system triggering by *H. pylori* and the occurrence those skin diseases.

Helicobacter pylori, although discovered 30 years ago, is still the subject of many scientific investigations. Current studies are focused on the effects of *H. pylori* on organs and systems other than the gastrointestinal tract. Many pathways indicate not only negative immune reaction to *H. pylori* inflammation but also positive protective effects against certain diseases. This creates new preventive and therapeutic opportunities but also the need for further investigations.

KEY WORDS:

***Helicobacter pylori*, *Helicobacter pylori* infection, psoriasis vulgaris, chronic urticaria, cutaneous manifestation.**

INTRODUCTION

Helicobacter pylori is a widespread bacterial infection in humans. The prevalence of its infection in the population worldwide is estimated at an average of 50%. A greater prevalence of infection is revealed in developing countries (about 70%), and lower in countries with higher economic status (about 30%). Polish epidemiological data of infection prevalence in 2004 showed the infection in 84% of adults, and in 32% of the population in developmental age [1]. Results of the study conducted in 2010 by Krusiec-Świdergoł *et al.* in urban areas of Upper Silesia in

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415 children aged 7–15 years showed *H. pylori* infection only in 15.7% of the examined group [2].

Recent studies by these and other authors indicate that the actual incidence of *H. pylori* infection of Polish school-age children is probably half what it was 10 years ago. This is to a high degree affected by the social and living conditions of the population, i.e. an increase in average incomes, improvement of socio-economic conditions, increase in the care of hygiene in everyday life and in the food industry [2]. The incidence of infections is also reduced as a result of effective eradication of bacteria, especially sequential therapy and the use of probiotics during eradication therapy, as well as frequent antibiotic therapy in children due to respiratory tract infections [3].

Epidemiological and experimental studies indicate the involvement of *H. pylori* infection as a compound of many diseases, affecting non-gastrointestinal diseases, both allergic and autoimmune diseases. The phenomenon of molecular mimicry is an important risk factor in the development of autoimmune diseases, which involves the induction by the chemical structures of pathogens of antibodies that react both with host antigens and antigens of pathogenic microorganisms, i.e. cross-reacting antibodies. Such structures can be heat-shock proteins (HSP). These are, in particular, bacterial heat-shock proteins of *H. pylori* with human homolog – a 60 kDa protein (HSP 60).

Anti-HSP 60 antibodies exhibit cytotoxic effects on vascular endothelial cells. The autoimmune process can lead to, inter alia, endothelial cells damage. *H. pylori*-infected patients show high levels of anti-HSP 60 antibodies of bacterial origin. Thus, heat shock proteins play a key role in the cross-immune response with *H. pylori* antigens and the development of auto immune diseases [4].

It suggests a relationship between *H. pylori* infection and the occurrence of skin diseases such as: chronic urticaria, rosacea, nodular tingling, psoriasis, and vitiligo in adults. In children, the infection with this bacterium is probably related to atopic dermatitis, chronic urticaria, and syderopenic anaemia, idiopathic thrombocytopenic purpura, or Schönlein-Henoch purpura [5]. This is shown by the fact that in some patients *H. pylori* eradication affects the course of chronic idiopathic urticaria, alopecia areata, psoriasis, and Schönlein-Henoch purpura [6].

SURVEY METHODOLOGY

The review article was written after analysing the available articles on several databases, mostly based on PubMed in the field of experimental and clinical medicine. The search was conducted using some keywords, such as: *Helicobacter pylori* diseases, immune diseases, immune response, chronic urticaria, and *H. pylori* skin diseases. The review article is based on English-written manuscripts, published between 2000 and the present. Only full text publications were used, and all studies with only an abstract available were excluded.

HELICOBACTER PYLORI AND CHRONIC URTICARIA

Chronic urticarial is one of the most common diseases that occurs both in children and adults, induced by *H. pylori* infection. It is a skin disorder lasts more than six weeks and is characterised by recurrent, itchy blisters – urticarial –which appear every day or almost every day. The complexity of clinical symptoms of urticaria and its course are affected by numerous mast-cell mediators (histamine and other vasoactive mediators) mainly found in the skin nodules [7]. The aetiology of chronic urticaria is still unknown in more than half of cases. This significant group is defined as chronic idiopathic urticaria. The most important factors identified in the pathogenesis of chronic urticarial include primarily infections then, inter alia, medications, vasculitis, malignancy, food additives, and physical factors [8].

Infections are the most common cause of urticaria in children [9]. The pathomechanism of the disease is not fully understood. The main role is attributed to mast cells and basophilic granulocytes from which histamine is released, but also other vasoactive mediators, such as prostaglandins or leukotrienes (e.g. LTC4, LTB4, PGD2). High concentrations of interferon gamma, IL-4, IL-5, or IL-8 are found in urticaria [10].

Also, the role of immune response to infection and the production of specific IgA and IgE antibodies against antioxidant bacterial proteins is suggested in the mechanism of *H. pylori*-induced skin lesions in urticaria. *H. pylori* infection can lead to the formation of circulating immune complexes that cause urticaria [11].

Structural elements of *H. pylori* and enzymes produced and released by bacteria such as urease, phospholipase, protease, or numerous cytotoxins can also activate the complement system and induce the appearance of skin lesions characteristic for urticaria [12].

One of the suggested pathomechanisms of urticaria is increased vascular permeability during gastric and duodenal infections, which may result in an increased host exposure to food allergens. Continuous stimulation of the immune system leads, due to mediator release, to non-specific increases in the sensitivity of the skin blood vessels to external factors that increase their permeability [5].

Despite existing evidence suggesting a relationship between urticaria and *H. pylori* infection, the results of previous studies in patients suffering from urticaria with concurrent *H. pylori* infection in comparison with effective eradication of bacteria and urticaria remission are still contradictory. A meta-analysis of therapeutic trials for *H. pylori* claim that the appearance of chronic urticaria was less likely without successful antibiotic therapy than when it was effective [13, 14].

Fukuda *et al.* published the results of the study evaluating the incidence of *H. pylori* infection and the effect of eradication on dermal lesions in patients with chronic idiopathic urticaria. After *H. pylori* eradication, total or partial remission of urticaria was found in 35% and 65% of the patients, respectively. In contrast, in patients without *H. pylori* eradication, partial remission was observed in only 22% of patients, and 78% showed no improvement [15].

In the research conducted by Frediani *et al.* in a group of 100 children with chronic urticaria, the remission of urticarial bubbles was noted in 18% of children with *H. pylori* infection after eradication, and in 8% of children with *H. pylori* infection who did not receive eradication therapy. The authors did not confirm a statistically significant difference in skin lesion elimination in patients with *H. pylori* infection eradicated and untreated, as well as in children without bacterial infection (urticaria in this group disappeared spontaneously in 14% of children) [16].

Daudén *et al.* found 68% prevalence of *H. pylori* infection after the evaluation of 25 patients with chronic urticaria using ^{13}C-UBT. Therefore, only one patient after the eradication therapy showed complete disappearance of urticaria lesions, and partial improvement was observed in two other patients. Thus, the above results do not show a close relationship between *H. pylori* infection and chronic idiopathic urticaria in the examined patients [17].

There is still a need for further research to establish the relationship between urticaria and *H. pylori* infection as well as the usefulness of *H. pylori* eradication therapy in patients with chronic urticaria.

HELICOBACTER PYLORI AND PSORIASIS VULGARIS

Paediatric psoriasis is widely divided into three age groups, which include: infantile psoriasis, early onset psoriasis – a self-limited disease of infancy, and psoriasis with concurrent arthritis [18].

Almost 25% of psoriasis disease begins before adolescence ends. Different psoriasis types clinically appear in childhood mostly including plaque-type, napkin, guttate, erythrodermic, and nail-based disease. Psoriasis belongs to the auto-immunity group of diseases, so susceptibility is presumably genetic, but environmental triggers are also required to commence disease activity. The underlying pathophysiology of psoriasis involves Th1 and Th17 cells. Their interaction with human body cells engages innate immunity. The process is distinguished by exacerbation and remission periods [19].

Bacterial and fungal pathogens are suggested as the main cause of psoriasis. A number of research projects point out the possibility of a relationship between infection of gastric mucosa caused by *H. pylori* and psoriasis, and they have assumed that *H. pylori* may be one of the pathogens able to trigger psoriasis [20].

Helicobacter pylori seropositivity of psoriatic patients without any gastrointestinal complaints has been discovered to be significantly higher than in controls, and *H. pylori* is a factor in psoriasis pathogenesis [21]. One study suggests that *H. pylori* infection is an important factor for the severity of psoriasis. The eradication of such infections can significantly increase the effectiveness of psoriasis treatment [22].

On the other hand, some studies available in the literature show a lack of support for the relationship between psoriasis and *H. pylori* infection, at least in childhood [23].

HELICOBACTER PYLORI AND VITILIGO

Vitiligo is a skin disorder described as an acquired depigmenting disease. Clinically it manifests by the appearance asymptomatic, well-circumscribed, white macules with loss of functional melanocytes in the epidermis [24].

The aetiopathogenesis of vitiligo is multifactorial with a prevalence of 0.06% to 2.28% in the population. According to different pathophysiological theories, it may be associated with neurogenic dysregulation, oxidative stress, autocytotoxicity, weak melanocyte viability, and, most importantly, autoimmunity [25].

Environmental factors also seem to be significant in the pathogenesis of vitiligo, and a special role is attributed to infectious factors, particularly immunodeficiency virus, hepatitis C virus, and cytomegalovirus [26]. It was also suggested that there is a relationship between *H. pylori* infection and vitiligo, but except for increased incidence of infection with this bacteria in vitiligo, no statistically significant differences were found [27]. Rifaioğlu *et al.* demonstrated in their study that the incidence of *H. pylori* infection is significantly higher in vitiligo patients (64.7%) than in the control group (33.3%) [28]. The study did not confirm an effect of *H. pylori* infection on vitiligo disease activity score or vitiligo involvement pattern [27, 29].

HELICOBACTER PYLORI INFECTION AND ACNE VULGARIS

The aetiopathogenesis of acne is complex, the main role is played by seborrhoea, excessive follicular keratinisation, inflammatory mediators, hormonal factors, as well as the growth and invasion of *Propionibacterium acnes*. *Propionibacterium acnes* promotes the release of IL-8 and IL-12 pro-inflammatory cytokines from macrophages through toll-like receptor 2 (TLR2), causing inflammatory lesions in keratinocytes [30]. It is important that the HPA3NT3 peptide produced by *H. pylori,* exhibiting antibacterial and anti-inflammatory properties, can support the treatment of acne vulgaris [31]. This creates the opportunity for scientists to develop new medicines for acne treatment. The HPA3NT3 peptide is synthesised from HP peptide composed of 2–20 amino acids derived from the

ribosomal protein L1 of *H. pylori*. The HPA3NT3 peptide and HP peptide (2–20) have a strong bactericidal effect with poor haemolytic and cytotoxic effects [32].

Ryu *et al.* [31] highlighted the therapeutic potential of HPA3NT3 in their *in vitro* study using human keratinocyte cultures, and in a mouse study *in vivo*. After implantation in the keratinocytes of *Propionibacterium acnes* followed by administration to HPA3NT3 peptide to the cells, the authors observed under electron microscope that HPA3NT3 induces morphological disturbances and bubble formation in the walls of the bacterial cell, while in human keratinocytes it inhibits the processes stimulated by *Propionibacterium acnes*, i.e. IL-8 production, TLR2 receptor expression, and intracellular calcium mobilisation. The authors emphasise bactericidal activity with minimal cytotoxicity with respect to human keratinocytes. They also intranasally injected *Propionibacterium acnes* bacteria into the ears of mice, and after inflammation developed, they intradermally injected the HPA3NT3 peptide and observed a reduction in live bacteria numbers and reduced redness, swelling, and infiltration of inflammatory cells.

The results demonstrate that intradermal injection of HPA3NT3 has an antibacterial activity against *Propionibacterium acnes* as well as an anti-inflammatory effect. HPA3NT3 may therefore be effective in the topical treatment of acne lesions without penetration to the dermis, especially because biofilm formation by *Propionibacterium acnes* in the hair follicles limits the effectiveness of systemic treatment [31].

HELICOBACTER PYLORI AND ROSACEA

Rosacea is a widespread, chronic inflammatory dermatitis. The main role in the development of rosacea is played by disturbed innate immune response and pathologies within the vascular system of the skin. Also, the genetic background and the role of cutaneous pathogens (*Demodex foliculorum*) and others (e.g. *H. pylori*) are taken into account. The aetiology and pathophysiology of rosacea are not fully known, and its clinical course is different in different patients [33]. Genetic, hormonal, nutritional, psychogenic, atmospheric, and electromagnetic factors and local and systemic infections play a role in the disease pathomechanisms. The role of toll-like 2 receptor and antimicrobial peptides is especially emphasised [34]. There was a clear correlation between clinical course and vascular changes. Increased concentration and activity of vascular endothelial growth factor (VEGF), platelet/endothelial cell adhesion molecule 1 (PECAM1), and lymphatic endothelium cell marker (D2-40) was demonstrated.

The polymorphisms of S-glutathione transferase genes responsible for cell defence against the damage by reactive oxygen species (ROS) was also identified in genetic studies. These polymorphisms, which lead to the formation of an ROS excess caused by ultraviolet light, may be a genetic factor predisposing for rosacea development [35]. Deterioration under the influence of the sun is observed in 81–85% of patients. Dermatitis frequently coexists, mainly in women, with autoimmune disorders, including: celiac disease, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis.

Argenziano *et al.* demonstrated that the cagA gene was found in 67% of rosacea patients, and reactive antibodies against CagA cytotoxin were detected in 75% of rosacea patients [36].

It was demonstrated in the study by Gravina *et al.* that the prevalence of *H. pylori* infection was significantly higher in patients with rosacea compared with the control group. A significant improvement of skin symptoms in rosacea patients was also noticed after the eradication of *H. pylori* infection. The skin lesions of rosacea decreased visibly or even disappeared in 97.2% of patients after eradication therapy and only in 37.5% patients who did not eradicate the infection ($p < 0.0001$), within 10 weeks from the end of eradication treatment [37].

Moreover, *H. pylori* induces inflammation by stimulating the production of chemokines, and proinflammatory and proangiogenic cytokines. It is thought that the severity of rosacea-type lesions in *H. pylori* infection may be affected by decreased plasma antioxidant compounds, such as ascorbic acid, observed in patients infected with this bacteria and increased ROS activity [38]. Nitric oxide (NO), which is engaged in numerous physiological processes, especially in the skin, including vasodilatation, inflammation, and immune modulation, may be increased in serum or tissue levels by *H. pylori* infection. Thus, it has been speculated that nitric oxide produced by *H. pylori* might cause erythema and flushing related to rosacea. It may also have a pathogenic role in the inflammation apparently seen in rosacea [39].

H. pylori infection has been shown to play an initial role in rosacea, so many authors believe that before starting the treatment for acne, diagnosis should be made for the infection followed by eradication of this bacterium if necessary.

HELICOBACTER PYLORI AND IMMUNE THROMBOCYTOPAENIA

A disease with cutaneous manifestation that for about 20 years was associated with *H. pylori* infection is an idiopathic thrombocytopenic purpura (ITP), currently called immune thrombocytopaenia. It is an autoimmune disorder, distinguished by blood platelet destruction by autoantibodies. The clinical course is characterised by the occurrence of petechiosis and eruptions on the skin and mucous membranes [40].

Helicobacter pylori infection is taken into account in the pathogenesis of the disease, and other microorganisms that antigens, by molecular mimicry, stimulate the formation of autoantibodies against platelet membrane

glycoproteins and, as a result of thrombocyte coating, cause their enhanced destruction [41]. The site of antibody production in the initial phase of the disease is mainly the spleen, and after a few weeks, also the bone marrow.

There is evidence for improvement in platelet counts after eradication of *H. pylori* infection in comparison with children [42] and adult patients [43] with ITP. Abdollahi *et al.* demonstrated that *H. pylori* infection was more common among children with idiopathic thrombocytopenic purpura (90.5%) compared to the control group (28.1%).A systematic review of 25 studies revealed that platelet counts in ITP patients increased after *H. pylori* eradication [44].

According to current guidelines [45], including Polish ones [44], idiopathic thrombocytopaenic purpura is an indication for the eradication of *H. pylori* infection in adults.

HELICOBACTER PYLORI AND SCHÖNLEIN-HENOCH PURPURA

The Schönlein-Henoch purpura is an autoimmune disease, the pathogenesis of which takes into account various factors (vaccinations, viral or bacterial infections, drugs, and other environmental exposures) [46]. It is caused by IgA-deposits accumulated in vessel walls and renal mesangium. This process is described as an acute leukocytoclastic vasculitis of small vessels. *Helicobacter pylori* and local inflammation induced by this bacterium in the gastric mucosa and the immune response to infection may contribute to the development of Schönlein-Henoch purpura type lesions. The following was demonstrated in the course of purpura and *H. pylori* infection: increased serum IgA and C_3 levels, cryoglobulins, autoimmunity, proinflammatory substances, and molecular mimicry, a process known as an inducing immune complex and cross-reactive antibodies caused by *H. pylori* infection [47].

Helicobacter pylori infection was more frequent in children with Schönlein-Henoch purpura [48]. The meta-analysis of studies evaluating an effect of *H. pylori* infection eradication on Schönlein-Henoch purpura demonstrated that the eradication *H. pylori* therapy may decrease the recurrence of Schönlein-Henoch purpura and alleviate Henoch-Schönlein purpura manifestations [2, 49]. These results suggest the examination of children with Schönlein-Henoch purpura toward *H. pylori* infection, especially in the presence of gastrointestinal symptoms.

CONCLUSIONS

Helicobacter pylori bacterium, although discovered more than 30 years ago, is still the subject of many scientific investigations due to its high prevalence in the human population and the serious, still little-known health effects resulting from infection. As demonstrated in the epidemiological data, the incidence of infection decreases, making it possible, as predicted by oncologists, to reduce the incidence of gastric cancer. However, current studies are focused on *H. pylori* effects on organs and systems other than the gastrointestinal tract. The purpose of the research is also the identification of bacteria reservoirs in the human organism, except the stomach, and symptoms other than in the gastrointestinal tract, which may indicate infection.

The correlation with many skin diseases, and recently also numerous suggestions that *H. pylori* may have protective effects against certain diseases and affect various immune mechanisms of the organism, inspire further research. This creates new preventive and therapeutic opportunities for many diseases. However, there is a need for further studies concerning the relationship of *H. pylori* with many diseases, especially those other than gastrointestinal tract, the pathogenesis of which is not fully explained, and the treatment does not produce satisfactory results.

DISCLOSURE

The authors declare no conflict of interest.

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