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Full Length Research Paper

Clinicoepidemiological study in Sudanese patients: Prevalence and effect of eradicative triple therapy on extra digestive *Helicobacter pylori* skin manifestations, EdHpSm

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Helicobacter pylori **are gram-negative; microaerophilic spiral rod-shaped bacteria and they lead to gastritis, duodenal or gastric ulcer and even in rare cases to gastric carcinoma or Mucosa Associated Lymphoid Tissue (MALT) lymphoma. Based on a number of reports, a possible relationship of *H. pylori* infection to a variety of different dermatosis has been suggested, including urticaria, rosacea, acne-rosacea, atopic dermatitis, alopecia areata, Sjögren's syndrome, Schönlein-Henoch purpura, and Sweet's syndrome. This study is intended to identify the prevalence of extra digestive (extra gastric) *H. pylori* skin manifestations, and to observe the influence of *H. pylori* eradication through triple therapy on the clinical evolution of patients' skin conditions. A clinical descriptive study of 149 patients with skin manifestations and immunologically detected *H. pylori* by rapid test, in association with gastric, chest, joints and nasal symptoms were considered as study population. *H. pylori* (Hp) triple therapy have been given to all positive cases as first, second and relapse modality in 12 weeks duration treatment, 4 weeks interval each with no any added other type of treatment allowed. The study revealed that: 20.5% of the skin cases examined (3723) were considered extradigestive *H. pylori* skin manifestation (746). Most of the skin manifestations cases were females (67.1%), and approximately 60.4% of EdHpSm were at the age group 14 to 45 yr- old. Most of the patients with EdHpSm are of Northern Sudanese origin (87.2%), the Southerners, the Easterners and the Westerners showed lower percentages, that is, 1.3, 3.4 and 8.1%, respectively. EdHpSm is common among professional. Hay fever and gingival disease were among the most commonly associated diseases where they represented ca. 27.7 and 12.2%, respectively. Chronic Idiopathic Urticaria, CIU represent a higher prevalence (20.6%), where: Polymorphous Light Eruption (PLE) alone represented 12.7%, and Polycystic Ovary Syndrome, PCO was 11.6%. Vitiligo 2.6% among the least presented cases. Consequently, it was concluded that: all cases of EdHpSm responded to triple therapy; 60.0% are of good response and 37.0% are dramatically responded to triple therapy, while 2.0% poorly responded to therapy. *H. pylori* infection found to have an important role in the etiology of chronic idiopathic urticaria, Urticarial vasculitis, and Atopic dermatitis and other skin diseases. Patients received antimicrobial triple therapy, found to respond dramatically in (37%).**

Key words: Immunologically, lymphoma, lymphoid, *Helicobacter pylori.*

INTRODUCTION

Helicobacter pylori are gram-negative, microaerophilic spiral rod-shaped bacteria that live just beneath the antral gastric mucous layer, on the surface of epithelial cells. Stomach infection with this organism causes inflammation of the gastric mucosa, which can lead to gastritis, duodenal or gastric ulcer and even in rare cases to

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gastric carcinoma or Mucosa Associated Lymphoid Tissue (MALT) lymphoma (Covacci et al., 1999).

Approximately 50% of the world's population is believed to be infected with *H. pylori*. Most infections are probably acquired in childhood (Czesnikiewicz-Guzik et al., 2004), but geographic locale, age, race, socioeconomic status, and hygiene seem to play roles in the prevalence of *H. pylori*. Most of the informations about H. pylori infection rates come from seroprevalence studies. Higher rates of infection tend to occur at a younger age in developing countries compared to developed countries and in regions characterized by lower socioeconomic status and higher density living.[1] Looking at racial differences in the US, it is found that whites of non-Hispanic origin have lower prevalence of infection compared to African-Americans or Hispanics (Brown, 2000). It has been speclated that dental plaque might harbor *H. pylori* and, therefore, might be a source of gastric infection (Czesnikiewicz-Guzik et al., 2004). Aside from iatrogenic transmission of *H. pylori* via endoscopy, no definite modes of transmission for *H. pylori* have been identified. However, association studies suggest that there are three other potential routes for the transmission of *H. pylori*: person-to-person transmission (example, oral-oral or fecal-oral), waterborne transmission (example, contaminated water), zoonotic (example, cats and other pets and animals) or vector borne transmission (example, flies). Person-to-person transmission is considered to be the most likely route of transmission considering that isolation of *H. pylori* from non-human reservoirs has been inconsistent (Brown, 2000). Chronic urticaria (CU) and concurrent angioedema are frustrating problems for both physicians and patients (Wedi et al., 1998). Based on a number of reports, a possible relationship of *H. pylori* infection to a variety of different dermatosis has been suggested, including urticaria, rosacea, acne-rosacea, atopic dermatitis, alopecia areata, Sjögren's syndrome, Schönlein-Henoch purpura, and Sweet's syndrome. Larger case-control studies, however, do not confirm this relationship. Therefore, *H. pylori* eradication therapy cannot be generally recommended in this dermatosis (Boni et al., 2000).

Pathogenic strains of *H. pylori* have been shown to activate the epidermal growth factor receptor (EGFR), a membrane protein with a tyrosine kinase domain. Activation of the EGFR by *H. pylori* is associated with altered signal transduction and gene expression in host epithelial cells that may contribute to pathogenesis (Tomb et al., 1997).

There are several types of immunological tests available for the diagnosis and management of *H. pylori* infection:

(a) Stomach biopsy tests (susceptibility or sensitivity testing) can be done to determine which antibiotic should not be used to treat the infection. A stomach biopsy is the most difficult and expensive method to test for *H. Pylori* infection.

(b) Urea breathe test is accurate and safe.

(c) Blood antibody test: Most commercially available serological kits use the enzyme linked immunosorbent assay (ELISA) test format. Originally the kits used crude antigen preparations although many of the newer kits use a more purified antigen preparation, with often increased specificity but lower sensitivity. Near patient test kits are based either on latex agglutination or immunochromatography Technique ICT. Generally they have low sensitivities compared with laboratory tests. Western blotting, ELISA, and recombinant immunoblot assays (RIBA) have also been developed into commercially available kits and can be used to indicate the presence of specific virulence markers.

(d) Stool antigen test: An antigen detection kit has been developed for the detection of *H. pylori* in faeces. Immunological reagents have also been combined with other diagnostic modalities to develop immunohistochemical stains and DNA immunoassays.

Serology is an important method of determining colonization status and can be used for diagnosis, as a screening procedure, or to follow the efficacy of eradication regimens. Most assays detect IgG in serum although some detect serum IgA. More recently developed assays detect IgA in saliva and the production of affinity purified antibodies has led to the development of an antigen detection assay for faecal specimens. Serological reagents have also been used in immunocytochemistry and to speed up the detection of amplified products of the Polymerase Chain Reaction (PCR)-DNA immunoassays (Vaira et al., 1999).

The triple therapy with omeprazole, amoxicillin and metronidazole failed to eradicate *H. pylori* in the majority of patients, which is an essential argument to withdraw this regimen out of the national recommendations. Macrolide with amoxicillin are preferable to achieve higher eradication rates. Azithromycin (1 g od for the first 3 days) can be considered as a successful component of the triple PPI-based regimen (Ivashkin et al., 2002).

The retreatment with tetracycline combination regimen cured 77.7% of patients: that seems to be a promising option, in clinical practice, after an eradication failure (Auriemma and Signorelli, 2001).

In case of treatment of chronic urticaria in children, always keeping in mind those medications may need to be adjusted to meet pediatric requirements (Wieczorek et al., 2004).

PURPOSE OF STUDY

This study intended to detect prevalence of extra digestive (extra gastric) *H. pylori* skin manifestations, and to determine the influence of *H. pylori* eradication through triple therapy on the clinical prognosis of patients with

Table 1. Prevalence of EdHpSm cases out of total skin diseases.

	No. 1	No. 2	%No. 2	No. 3	%No. 3
Cases	**3723**	**746**	**20.5**	149.0	19.9

No1= Number of all skin disease cases. No. 2= Number of Extra digestive skin manifestations EdHpSm study population. % No. 2= Percentage of EdHpSm out of the total. No. 3= Number of study sample cases with EdHpSm out of the total (746). % No. 3= Percentage of study sample out of study population (746).

Table 2. Prevalence of study sample EdHpSm cases out of the total skin diseases.

Total attendance	EdHpSm ICT positive patients	Percentage
3723	149	4.0

Table 3. Prevalence of EdHpSm, according to sex.

Sex	Frequency	Percentage
Male	49	32.9
Females	100	**67.1**
Total	149	100

chronic idiopathic urticaria (CIU), Urticarial vasculitis, Atopic dermatitis and some other skin conditions.

PATIENTS AND METHODS

This study was compiled in Al Jawda Medical Centre JMC, Khartoum, Sudan. Everyday cases were chosen for data collection, the data collection period extended from January 2005 to December, 2008. 3723 patients with skin manifestations have been seen during the period of study June 2008 to December 2008, 746 cases associated related diseases, and immunologically detected *H. pylori* by rapid test Immuno Chromatographic Technique (ICT), of chronic idiopathic urticaria, Urticaria Vasculitis, Atopic dermatitis, any other skin conditions were considered as study population (old + new), in association with gastric, chest, joints and nasal symptoms. 149 cases are taken as study samples as randomized every 5th. *H. pylori* (*Hp*) immunoglobulin G and A (IgG and A) antibody rapid test has been done to all cases as a diagnostic tool before and 2 months has been taken for after treatment confirmative test. 12 weeks triple therapy alone; Clarithromycin 1g bd for 10 days + Amoxicillin and Clavulinic acid 2 g bd for 10 days+ Esomeprazole 40 mg daily dose for 28 days given to all positive cases as first modality treatment, Azithromycin 1 g od on empty stomach daily for 3 days + Tinidazole 2 g daily single dose for 5 days+ Pantoprazole 40 mg for 28 days as second modality treatment, and Doxycyclin 100 mg od for 10 days + Tinidazole 2 g daily single dose for 3 days + Rabeprazol 20 mg for 28 days as a relapse therapy. 4 weeks interval has been taken as a period between each treatment modalities. For all cases, any other topical or systemic treatment for the case is condemned during case treatment. Questionnaires were filled out, and patients were cross-examined by the researcher personally. The questionnaire main points were: The patients serial number, name, sex, age, which is categorized as 0 to 2, 3 to 13,14 to 45 and >46; tribe, associated diseases (Hay fever, Bronchial asthma, food sensitivity, Peptic ulcer, oesphagitis, hypertension, arrhythmia, DM, arthritis and other diseases), clinically confirmed skin diseases (Atopic dermatitis, urticaria, rosacea, lichen planus, psoriasis, alopecia areata, vitiligo,..), treatment modalities, response after eradication, have been defined as Dramatic, good, poor and no response, measured clinically based on Skin Area Severity Index (SASI) as mild less than 10 lesions, Moderate 10 to 20 and severe more than 20, as response of 75% or more of clinical signs compared to baseline was considered as main response for dramatic , 50 to 75% as good response, 25 to 50% as poor response and less than 25% for no response, confirmatory investigations as *H. Pylori* (ICT) rapid test, final diagnosis and comments. Lesions diagnostic criteria have been followed in this study to define specific disease cutaneous manifestations.

RESULTS AND DISCUSSION

Table 1 shows the prevalence of EdHpSm out of total skin diseases and Table 2 shows the Prevalence of study sample EdHpSm cases out of the total skin diseases. Table 3, 4, 5, 6, 7 shows prevalence of EdHpSm according to sex, age tribe, occupation and family history respectively. Table 8 shows the incidence of EdHpsm from consanguinity at various degrees. Table 9 shows prevalence of EdHpSm Associated disease. Table 10 shows response after eradication therapy. Table 11 shows response of EdHpSm after Hp eradicative therapy. This study revealed that 20.6% of the skin cases examined have extradigestive *H. pylori* skin manifestation which considered as a high prevalence as compared with literature. The results showed that most of the skin manifestations cases were females (67.1%), that's could be explained with less immunity as compared with males, and 60.4% of EdHpSm are at the age group 14 to 45 yr-old. Most of the patients with EdHpSm are of Northern Sudanese origin (87.2%), the Southerners, the

Table 4. Prevalence of EdHpSm patients in the different age categories.

Age group (years)	Frequency	Percentage
3-13	15	10.1
14-45	90	**60.4**
>46	44	29.5
Total	149	100

Table 5. Prevalence of EdHpSm patients according to their tribes.

Tribes	Frequency	Percentage
Northern	130	**87.2**
Western	12	8.1
Southern	2	1.3
Eastern total	5	3.4
Total	149	100.0

Table 6. Prevalence of EdHpSm patients according to their occupations.

Occupation	Frequency	Percentage
Farmer	2	1.3
Laborers	1	0.7
Skilled	2	1.3
Student	33	22.1
Professional	73	**49.0**
Others	38	25.5
Total	149	100.0

Others: 33 patients, house wife, 4 patients, business man, I patient, child.

Table 7. Prevalence of EdHpSm patients according to the presence of family history of similar conditions.

Family history of similar conditions	Frequency	Percentage
Father	7	4.2
Mother	16	9.5
Brothers	12	8.1
Sisters	14	8.3
Others	8	4.8
none	111	**66**
Total	168	100

Others, Cousins: 5 patients. Aunt: 1 patient. Grandfather: 2 patients.

Table 8. possible effect of consanguinity of EdHpSm.

Consanguinity	Frequency	Percentage
First degree	59	39.6
Second degree	66	**44.3**
None	24	16.1
Total	149	100

Table 9. Prevalence of EdHpSm Associated disease in patients with Ed H p S m.

Associated diseases	Frequency	Percentage
Hay fever	41	**29.3**
Bronchial Asthma	17	12.1
Food sensitivity	5	3.6
Chronic Dyspepsia	12	8.6
Duodenal ulcer	4	2.8
Gastric ulcer	5	3.6
Oesphagitis	17	12.1
Joints deformity	5	3.6
Diabetes mellitus	6	4.3
Hypertension	2	1.4
Thyroid disorders	3	2.1
Gingival disease	18	12.9
Others	5	3.6
Total	140	100

All patients included in the study, received the three modalities of Hp eradication therapy, which include, first modality, second modality and relapse therapy.

Table 10. Response after eradication therapy.

EdHpSm	Dramatic response	Good response	Poor response	No. response	Frequency	(%)
CIU	29	10	0	0	**39**	**20.6**
PCO	2	20	0	0	22	11.6
PLE	11	13	0	0	24	12.7
Gravitational eczema	0	11	0	0	11	5.8
Atopic eczema	4	9	0	0	13	6.9
Chronic superficial Scaly dermatitis	1	7	1	0	9	4.8
Eczema xerosis	2	4	0	0	6	3.2
Contact dermatitis	4	2	0	0	6	3.2
Follicular eczema	1	3	1	0	5	2.6
Pomphylix	1	2	0	0	3	1.6
Seborrheic Dermatitis	2	7	0	0	9	4.8
Discoid eczema	2	3	0	0	5	2.6
Erythrodermic eczema	1	1	0	0	2	1.1
Intertriginous eczema	0	4	0	0	4	2.1
Nail eczema	0	2	0	0	2	1.1
Chielitis	1	4	0	0	5	2.6
Perianal eczema	2	0	0	0	2	1.1
Sebopsoriasis	0	1	0	0	1	0.5
Alopecia areata	2	3	0	0	5	2.6
Lichen planus	1	2	0	0	3	1.6
Vitiligo	1	2	**2**	0	5	2.6
Behçet's syndrome	0	1	0	0	1	0.5
Dermatitis herpetiformis	1	0	0	0	1	0.5
Levido reticularis	0	1	0	0	1	0.5
Rosacea	2	1	0	0	3	1.6
Sézary syndrome	0	1	0	0	1	0.5
Subcorneal pustular dermatosis	0	1	0	0	1	0.5
Total	70(37%)	115(60%)	4(2%)	0	189	100

Table 11. Response of EdHpSm after Hp eradicative therapy.

Response	Frequency	Percentage
Dramatic	70	37.0
Good	115	60.0
Poor	4	2.0
No response	0	0.0
Total	189	100.0

Easterners and the 0Westerners showed lower percentages, that is, 1.3, 3.4 and 8.1%, respectively.

EdHpSm is common among professional. Hay fever and gingival disease were among the most commonly associated diseases where they represented ca. 27, 7 and 12.2 %, respectively. Chronic Idiopathic Urticaria, CIU represent a higher prevalence (29%), where Polymorphous Light Eruption, PLE alone represents 24%, and Polycystic Ovary Syndrome, PCO was 22%. Vitiligo 5% among the least presented cases.

Consequently, it was concluded that: all cases of EdHpSm responded to triple therapy; 60.8% are of good response and 37% are dramatically responded to triple therapy while 2.1% are poorly responded to therapy.

CONCLUSION AND RECOMMENDATIONS

Therefore, prevalence of *H. pylori* infection is signify-cantly high in chronic urticaria patients (20.6 %), atopic dermatitis and other skin conditions. Eradication of the bacterium has a dramatic influence (37.0%) and good response in (60.8%) that is, most of the skin disorders associated. Therefore, prevalence of *H. pylori* infection is significantly high in chronic urticaria patients (20.6%), atopic dermatitis and other skin conditions. So,

(1). It is highly recommended to perform *H. pylori* test in a suspected skin cases; skin disease associated with gastric manifestations, respiratory, joints, diabetes mellitus and vascular manifestations.

(2). 12 weeks eradication triple therapy, 4 weeks interval in between, three modalities are recommended for *H. Pylori* positive cases as (37.0%) dramatically responded and (60.8%) show a good responseas well as the tolerance was excellent and the side effects were those usually found with other antibiotics and Proton Pump Inhibitor (PPI).

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