Role of helicobacter pylori infection in the predisposition for chronic infective rhino-sinusitis among patients with GERD

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Background and Objectives: ***Gastro esophageal reflux disease (GERD) is believed to be important contributing factor in many disorders of upper respiratory and alimentary tracts namely rhino-sinusitis nasal polyps , adenoid enlargement , chronic tonsillitis , chronic pharyngitis , chronic esophagitis , esophageal strictures , chronic laryngitis , otitis media , and chronic chest infections . It has been reported that GERD and Helicobacter pylori (HBP) infection may be interrelated phenomenon. Although there are many theories tried to explain the pathogenesis of GERD but still Helicobacter pylori based theory is considered as strong theory via which the GERD pathophysiological mechanism factor can be presented. The successful eradication of Helicobacter pylori infection was shown to be significantly related to improvement of the symptomatology in patients with chronic upper air way and alimentary tract related disorders. Therefore this study was conducted prospectively to confirm this concept specifically in relation to the incidence as well as the management of chronic sinusitis.***

Patients and Methods: ***235 patients aged 5-85 years with already confirmed GERD at different grades according to (Savary- Millar or Savary- Monnier 1989) grading system on bases of diagnostic upper gastrointestinal tract fibrooptic endoscopic evaluating examination presented at internal medicine department and ENT department, Althwora-hospital, Elbedya- Libya with varieties of upper aero-digestive related symptoms at period from September 2005 up to March 2009 were studied as prospective study .All patients were investigated for H.pylori infection by using of ELISA as serological test to demonstrate anti-helicobacter pylori antibodies titer before the starting of the recommended medication and compared with results at the end of the course by 4-6 months. The results were correlated with the clinical presentations of the patients. Results:***

208 patients (89%) of the total number showed positive Helicobacter pylori and 203 cases (98%) were improved after medical eradicative course against Helicobacter pylori . on the other hand only 27 patients (11%) with either upper air way or alimentary tract related disorders in association with chronic infective rhino-sinusitis were found to be with a negative Helicobacter pylori results .

Conclusion: ***The Para nasal sinus disease is considered as one of ENT related common presentation in GERD. I.e. GERD can be described as one of predisposing factors of sinopathy. It is well known that, there is strong correlation between GERD pathogenesis and HBP infection. In the same time there is well –established significant relationship between GERD and Para nasal sinus disease. Therefore, as it was confirmed in this presenting study that the HBP infection may act as main predisposing factor for sinus pathology among patients with GERD.***

Keywords: GERD, HELICOBACTER PYLORI, chronic rhino-sinusitis.

INTRODUCTION

Gastro esophageal reflux disease (GERD) is believed to be important contributing factor in many disorders of upper respiratory and alimentary tracts. It is the most common esophageal disorder.[1] GERD is patho-physiologically developed due to defect in one or more than one of the normal anatomical or physiological control mechanism factors of the reflux phenomenon resulting in the exceeding of normal reflux index and thus the appearance of the clinical presentation of the disease. reflux index is considered as time factor of reflux phenomenon occurrence per 24 hours which must be normally not exceeding five minutes.[2] Therefore , if the total duration of reflux process is more than the normal upper limit this leading to the induction of reflux disease process and the appearance of GERD symptomology.[3] The defect in reflux index can be due to anatomical predisposition as lower esophageal sphincter weakness, cardio-phrenic angle anatomical disorders, increasing of the abdominal-thoracic pressure gradient, and phrenoesophageal ligament weakness, and/or physiological predisposition as increasing in gastric secretion rate , defect in gastric acid clearance which can be due to defect in esophageal mobility , defect in salivary basic secretions , and/or defect in esophageal mucosal bridges regeneration and secretions.[4] There are different theories tried to discuss the pathogenesis of the excessive promotion of gastric acid secretions . The most important theories are biliary system disorders based theory, cyclooxygenase -2 (COX-2) enzyme based theory, and helicobacter pylori infection based theory.[5]

Helicobacter pylori play an important rule in the pathogenesis of GERD.[6] It was isolated from different places of alimentary as well as respiratory tract of patients who were diagnosed as GERD.[7] Among those patients, the control of the clinical conditions was directly proportionally to the eradication of the bacteria.[8]

H. pylori is a gram negative microaerophilic, rod-shaped bacteria approximately 0.5nm in diameter and 3-5nm long. (9). H. pylori has 4-7 polar-sheathed flagella, which enable the bacterium to move freely in viscous environment such as gastric mucus. This motility is essential for the bacterial colonization of its host. The flagella sheath is a membrane containing protein and lipo -polysacharides which probably protects the flagella filaments from gastric acidity.[10] It is well recognized that stomach is the natural niche for H. pylori.

H.pylori can grow depending on the culture medium over a wide rang of pH 5.5-8.5 with good growth between pH 6.9 and 8.[11] Helicobacter pylori infection is usually acquired in childhood and persists for life unless specifically eradicated; yet, it can emerge after eradication.[12] In developing countries, the major risk factor for acquiring H. pylori infection is poor socioeconomic condition during childhood. Therefore prevalence of H. pylori infection can be greater than 80% in children less than 10 years old and up to 90% in adult.[13] In contrast children develop few infections in developed countries occurs during childhood. A gradual increase in prevalence is observed with age with infection rates of 20-30% by age of 20 and of about 50% at 50-60 years.[14] Poor socioeconomic condition during early childhood as measured by household crowding and parental income are thought to play some role in H. pylori infection.[15] There is evidence that countries with poor sanitation have greater infection rates which suggests a common water source as the reservoir rather than person to person transmission. There is a strong correlation between consumption of municipal water and H. pylori infection in some countries. Recent data suggest that a bacterium is present in river water and drinking water.[16] H.pylori was significantly higher in males than females. It was found that smoking did not cause ulcer in absence of H. pylori infection.[17] The genetic factors may influence disease prevalence, however, as evidenced by H. pylori concordance being higher in monozygotic than dizygotic twins.[18] The sources and routes of transmission have not been definitively established despite numerous studies which suggest that faecal-oral and oral-oral transmission of H. pylori is most likely.[19] In addition to gastric specimens, detection of H. pylori from different regions such as oral region suggests that bacterium may lead to a broad spectrum of clinical manifestations and may be the cause of the high incidence of H. pylori infection in the world.[20] Recent data showed that H. pylori was associated with extra gastric disorders such as coronary heart disease, rosacea,[21] glaucoma[22] chronic rhinosinusitis[23] and squamous cell carcinoma of the head and neck.[24] Compared with control subjects, a significantly higher prevalence of H. pylori in patients with these disorders were documented. Other evidence regarding the association of H. pylori with these disorders was the improvement in the conditions of some patients after eradication of H. pylori.[25] Several clinical observation suggest role for H. pylori infection in various immunological disorders. Some reports have shown healing of some autoimmune disease such as henoch-schonlein purpura Sjogren's and autoimmune thrombocytopenia after eradication of H. pylori.[26]

Furthermore, the observation of complete disappearance of some cases of extra gastric mucosa associated lymphoid tissue (MALT) lymphoma, such as those localized to the salivary gland, small intestine and rectum, following treatment for H. pylori infection is of special interest.[27]

Some studies have suggested a link between idiopathic chronic urticaria and H. pylori infection. Acne rosacea and

alopecia areata have also been associated with H. pylori infection.[28] H. pylori infection is reported to be more highly present in patients with sideropenic anaemia compared with healthy controls.[29] At least 25 epidemiological studies have been published on the association between H. pylori antibody titer and ischemic heart disease.[30] More recently, it has been suggested a pathogenic role of the H. pylori chronic infection in migraine, based on a relationship between the host immune response against the bacterium and the alterations of vascular permeability as a result of chronic release of vasoactive substances; superoxide radicals and nitric oxide during the infection.[31] It is confirmed that focal T-cell mediated immunity (delayed type of hypersensitivity reaction or a cytotoxic response) is the mechanism- ultimately responsible for tissue destruction in the recurrent aphthous ulcer.[32] It had been suggested that this mechanism is induced by H.pylori infection.[33] Recently. a high prevalence of H. pylori infection has been recognized in patients with chronic open angle glaucoma. H. pylori infection may influence the pathophysiology of glaucoma by releasing various vasoactive substances.[34] H.pylori was shown in the upper aero digestive tract in several studies; this indicates that it might be related to the pathogenesis of various ear, nose and throat diseases. H. pylori were detected in the nasal and sinus mucosa of patients with chronic sinusitis which indicates a possible role in pathogenesis of chronic sinusitis.[35,36] Furthermore, H. pylori were detected in nasal polyp tissue. The mechanism by which H. pylori reaches the nasal cavity can be explained by three possibilities. First, the nasal cavity may be a reservoir of H. pylori. Second, the oral cavity may represent the reservoir of H. pylori and the microorganisms may come to the sinonasal cavity by way of the oronasal reflux. Third, the stomach may be the primary reservoir of this infection, and transmission of H. pylori from the stomach to the nasal cavity might occur by way of Gastroesophageal reflux (GERD).[37] However reflux is believed to be an important contributing factor in many disorders of the upper respiratory tract particularly sinusitis.[38] Although the mechanism of how the GERD causes sinusitis is unclear, but there are many suggested direct- local theories which tried to explain the possibility of the pathogenesis of the sinusitis on top of GERD: 1) the change of the normal PH value of the Para nasal sinuses, which will result in the over growth of the opportunistic micro-organisms. 2) Interference with the normal muco-ciliary clearing mechanism. 3) The stimulation of the over mucosal secretions which leading to more mucosal stagnation. 4) The obliteration of the normal para nasal sinuses ostia drainage. And 5) The destruction of the normal mucosal contour.[39] On the other hand, the GERD induced sinusitis was claimed to be as a sequel of the ascending spread of the infection form already existing tonsillitis, laryngo-pharyngitis, stomatitis, and rhinitis.[40]

Chronic pharyngitis may be related to H pylori infection. The infection rate with H.pylori in the pharynx is higher in patients with stomach ailment histories than in patients without stomach ailment histories.[41] In recent years, gastroesophageal reflux has been increasingly associated with chronic middle ear problems but the underlying mechanism is unclear.[42] The demonstration of H. pylori in the middle ear indicates that gastric contents reach the middle ear due to reflux and supports that reflux and H. pylori may be involved in the pathogenesis of OME resistant to medical treatment. However, it may be postulated that H. pylori may cause secretory hyperplasia in the middle ear just as it does in the gastric mucosa.[54]

Tasker et al[43] determined higher concentration of pepsin and pepsinogen in the middle ear than serum of patients with OME indicating that gastric juice could reach as far as middle ear.[44] If gastric juice could enter the middle ear, H.pylori a common inhabitant of gastric juice and mucosa in patients with peptic ulcer and chronic gastritis, would also be expected to be found in the middle ear of patients with OME.[45] Reflux of gastric content from the nasopharynx into the middle ear is, possibly, due to the angle of the immature eustachian tube this would cause inflammation of the nasopharynx and eustachian tube,[46] thus disturbing eustachian tube clearance, therefore causing the nasopharyngeal bacteria to enter the middle ear. H. pylori may be one of such bacterium. Resolution of OME with antibiotics also supports this hypothesis and in the same time supports the concepts which were hypothesed to explain the pathogenesis of chronic rhino-sinusitis on top of GERD. In cases of sinusitis and OME resistant to medical and surgical treatment, gastroesophageal reflux and H pylori infection should be considered and evaluated.[47]

Various testes are available to diagnose H. pylori infection. These testes can be categorized into those that are based on direct assessment of biopsies specimens and indirect tests that detect an immunological response (i.e antibodies against H. pylori) or metabolic products (urease activity) of H. pylori. The gold standared for the detection of H. pylori has been defined as culture, histopathological examination of biopsies spicemence or serology, depending on the experience of investigator. In order to optimize the diagnosis of H. pylori, it usually recommended that several tests be used together.[48,49] Biopsy specimen is required for (rapid urease test, microbiological, histological and polymerase chain rection(PCR assay).[50] On the other hand the indirect non-invasive tests will include The urea breath test which is based on urease activity of the organism which liberates carbon dioxide (C02) from urea and produces ammonia to buffer its acidic environment.[51]

And several serological techniques have been used for the study H. pylori infection (e.g. complement fixation haemaglutination test, immunoblot, fluroimmunoassay) but enzyme-linked immunosorbent assay (ELISA) is currently consider the optimal serological method.[52]

Eradication of Helicobacter pylori is defined as the absence of the organisms for least a month after cessation of medication.[53] Successful eradication of Helicobacter pylori infection was shown to be significantly related to improvement of the symptomatology in the patients with chronic gastritis, duodenal and gastric ulcers and has been even associated with regression of B-cell gastric lymphoma.[54,55] .Helicobacter pylori can be eradicated from the body with proton pump inhibitors with 2 or 3 antibiotic combinations for 2 weeks. With 3 (omeprazole, clarithromycin, amoxicillin or 4 (omeprazole, clarithromycin, amoxicillin, metronidazole) drug combinations, eradication rates of 75% to 88% or 80% to 99% can be achieved, respectively.[56]

PATIENTS AND METHODS

235 patients aged 5-85 years with already confirmed GERD at different grades according to (Savary- Millar or Savary- Monnier 1989) grading system on bases of diagnostic upper gastrointestinal tract fibrooptic endoscopic evaluating examination presented at ENT department, Althwora central – teaching hospital, Albyda-Libya with varieties of upper aero-digestive related symptoms in addition to suggested sinopathic chronic headache at period from September 2005 up to March 2009 were studied as prospective study. Those patients were evaluated via the history, clinical examination including endoscopic examination as well as radiological evaluation in form of CT-scan of Para nasal sinuses with different views to confirm the chronic rhino-sinusitis. Further, the patients were diagnosed with variable chronic sinusitis related radiological finding, they were investigated for H. pylori infection by using of ELISA as serological test to demonstrate anti-helicobacter pylori antibodies titer before the starting of the recommended medication and compared with results at the end of the course by 4-6 months. The results were correlated with the degree of improvement at clinical as well as radiological presentations of the patients i.e. the patients' improvement of their sinus disease was assessed by the history, local examination, as well as CT-scan results and compared objectively with pre-medication situations. Patients who had used antacids, H2-blockers or antibiotics during the month preceding the presentation, they are excluded from the study. The patients were treated with specific recommended regimen against the H. pylori infection. The regimen was in form of oral administration of combination of (clathramycin +omeprazole+ bismuth) for 4-6 weeks, in addition to local decongestant agents as well as systemic analgesics.

An informed consent was taken from the patients or the parents of the children involved in the research prior to their participation.

Data were expressed by using descriptive analysis as means + standard error of mean (s. e. m) and percentages, test of significance was carried out, using Chi-squar test and two way analysis of variance.[3] A probability less than 0.05 was considered as significant, the degree of significance was determined by using level of standard deviation test. Student -t- test was used for dependent sample, as well as contingency coefficient was calculated as measurement of association between nominal variables.

RESULTS

As shown in (Table I) there were 96 males and 139 females. The age distribution showed that 62% of cases were > 40 years of age .On the other hand 23% of the patients were of age <15 years (Table II) ($P < 0.05$). Regarding the clinical presentation, the most frequent clinical presentation was laryngeal related disorders presentation (53%), followed by sinopathic related symptomology (49%) , then aural and upper alimentary tract related presentation (19%) as shown in (Fig. I).

As demonstrated in (Fig. II), in large number of cases (89%) the patients had a positive ELISA test for H. pylori infection with high significant rate ($P < 0.01$) as compared with 27 cases with negative ELISA test. As postulated in (Fig. III) there were different forms of radiological chronic sinus pathologies. The titer of the anti-helicobacter antibodies among the patients with positive ELISA is significantly higher (9.135+0.24) than those with negative ELISA test (0.782+0.008) ($P < 0.01$) as showed in (Table III). Table IV presented significant reduction of anti-helcobacter antibodies by 4-6 months from the end of full recommended course of treatment (1.459+0.0327) as compared with the initial titer prior to starting of treatment ($P < 0.01$). This was correlated with chronic sinusitis related clinical presentation as shown in (figure-IV) which illustrated the significant improvement in sinus related pathology by complete eradication of H. pylori ($P<0.005$).

Table I. Sex distribution. ($P < 0.05$).

Sex	Males	Females	Total
No.	96	139	235
Percent	62.5	37.5	100

Table II. Age distribution. ($P < 0.05$).

Age	<15	15-40	40-85
No.	54	35	146
Percent	23	15	62

Table III. ELISA results prior to the initiation of the treatment: (P < 0.01).

Result	Positive	Negative
No.	208	27
Anti-body titer (mean +_S.D)	9.135+_0.24	0.782+_0.008

Table IV. ELISA results after 4-6 months after the treatment: (P < 0.01).

Time of test	Prior to treatment	After treatment
ELISA results (mean +_S.D)	9.135+_0.24	1.459+_0.0327

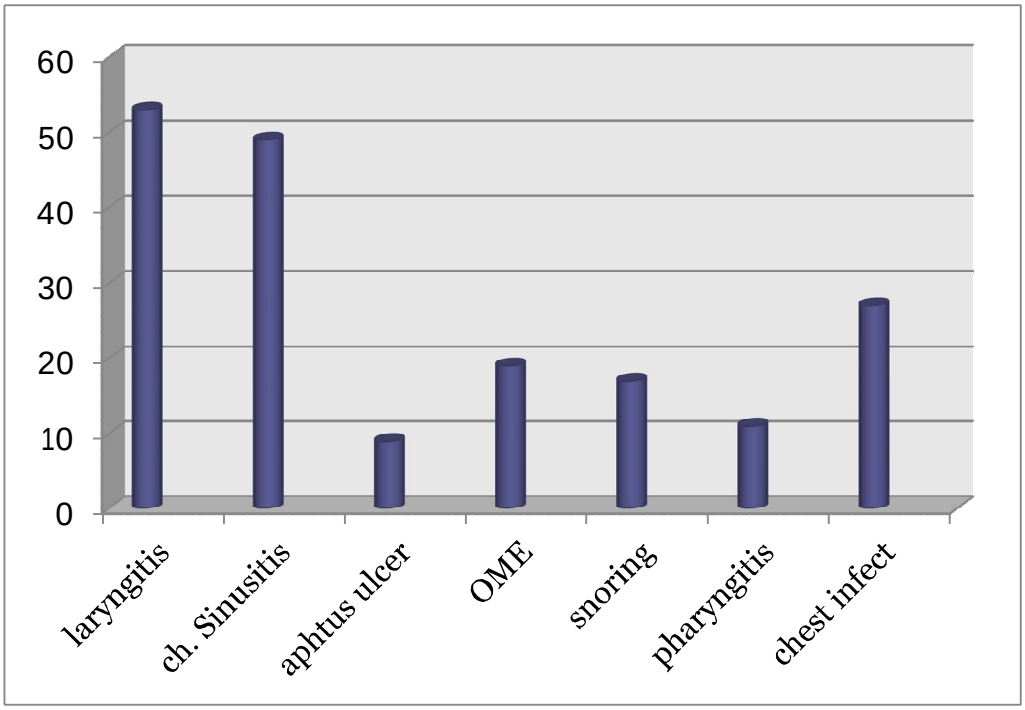

Fig 1. Relationship between GERD and sinus disease.

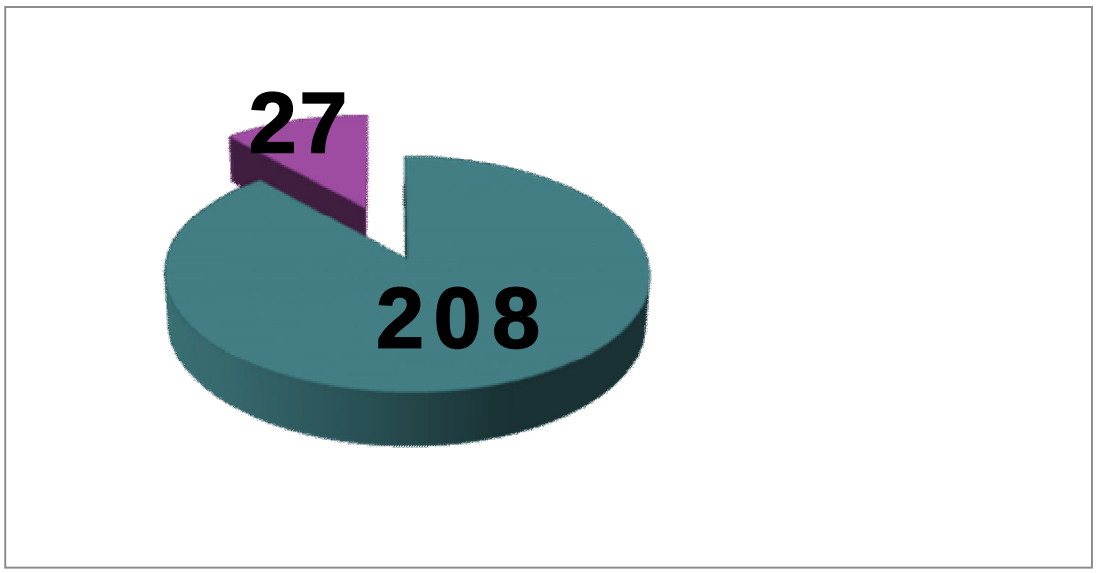

Fig 2. Relationship between GERD and helico bacter pylori infection = negative HBP, = positive HBP).

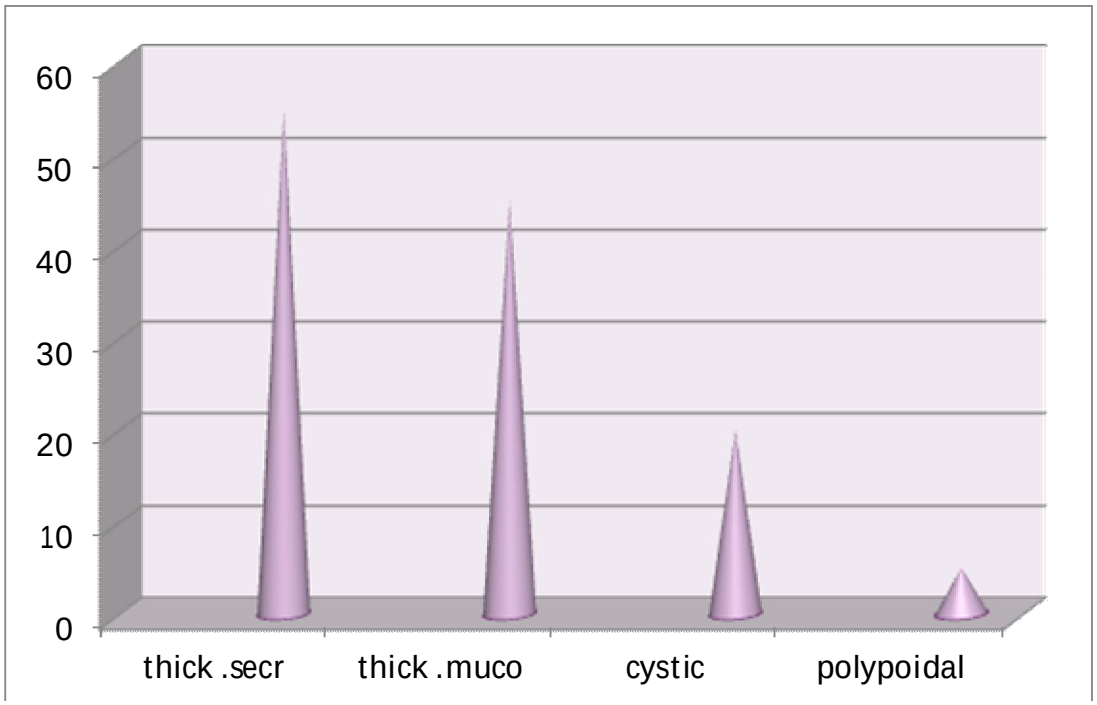

Fig 3. Different pathological varieties of sinus disease.

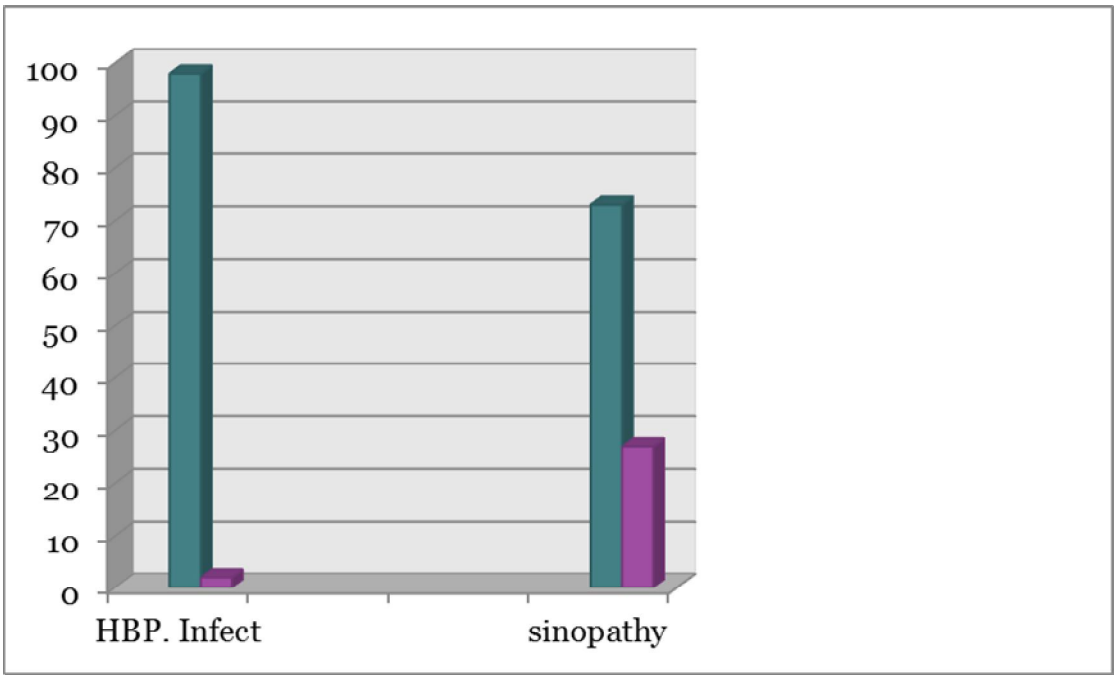

Fig 4. The degree of improvement regarding sinus pathology after complete eradication of HBP infection (= improved, = not improved).

DISCUSSION

Helicobacter pylori (H. pylori) is one of the most common bacterial infections worldwide. Estimates suggest that more than half of the world's population is infected by this gastric bacterium.[43] It is associated with chronic gastritis and peptic ulcer diseases[39,44] and constitutes a major risk factor for gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphoma.[34]

Although the stomach is the natural reservoir of H. pylori various tissues have been proposed as potential reservoirs of infection such as tonsil, gingiva, dental plate, gallbladder, para nasal sinuses, middle ear cavity, and coronary arteries.[12]

The presence of H.pylori in the upper aero-digestive tract has been investigated in more than 60 reports in the English literature; some of them examine its presence in the tonsils and/or adenoids by using various diagnostic techniques showed that there was a high rate of H pylori colonization in tonsillar and adenoid tissues however, other indicated opposite results.[44,52,54]

There are several methods (invasive and non-invasive) available for detecting H. pylori infection. Invasive methods are based on biopsy specimens as; Rapid urease test, PCR,[47] culture staining biopsy materials with H&E stain, Giemsa stain, Warthin-Stany silver stain,[56] and stains which determine the macrophage iNOS (inducible nitric oxide synthase) activity in tonsillar tissue.[29] Non-invasive methods as; urea breath test,[40,41] stool antigen test[52] and the enzyme linked immunosorbent assay (ELISA) technique to identify specific immunoglobulin G antibodies against H. pylori in serum.[53] When H. pylori was first found to colonize in the upper respiratory tract, investigators used a single diagnostic method to identify H. pylori infection.[24] In more recent investigations, multiple tests have been used comparatively in the same study.[55,56]

Smoot et al (2001) stated that the gold standard in diagnosis of H. pylori infection is the direct identification of the organism by two or more methods from Rapid urease test, culture and histopathology. Ogata et al considered a positive H. pylori infection by combining three or more positive methods (Rapid urease test, serology, histopathology, urea breath test).

The present study was carried on 235 patients .Serum samples from all patients were tested using the ELISA to identify specific immunoglobulin G antibodies against H. pylori. Serology test is used for diagnosis and follow-up of H. pylori infection and for epidemiological studies. Using ELISA, it is possible to measure anti-H. pylori antibodies of different immunoglobulin classes, and quantitative determinations are possible as well. The IgG is positive in active infection and persists for 4-6 months after eradication of infection.(30) It has been reported that serologic testing with ELISA has a sensitivity of 95% and specificity of 100 %.(41) 41% of cases were male while 59% were female. Our findings are against the findings of Blum 1996 who showed that ≥ 78% of cases were male. This can be explained by male to female ratio in the general Libyan population which is showing higher female number as compared to the males. On the other hand our study presented that the percentage of the infection among the children is lower than that in the adult. This is also not in accordance with Kuipers, et al 1993 and Imrie et al 2001. This can be explained by the presentation of the children to pediatric department rather than ENT or internal medicine department, resulting in the missing of the pediatric cases.

Finally, as recommendation at any patient with chronic sinusitis which is not associated with any local abnormalities and not responding to conservative treatment, we must exclude GERD . In addition if GERD was confirmed, we must exclude HBP infection.

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