Original Article

The correlation between helicobacter pylori and idiopathic achalasia: A case control study

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Abstract

Background: Idiopathic achalasia is a common and well-recognized primary esophageal motility disorder with unknown etiology and is characterized by the abnormality of esophageal body peristalsis associated with an impaired relaxation of the lower esophageal sphincter (LES). The aim of this study is to explore the correlation between *Helicobacter pylori* and idiopathic achalasia. **Methods:** This study was conducted on 700 patients, with dysphagia, regurgitation, and non-cardiac chest pain (NCCP), who met our inclusion criteria. The mean ± SD age was 39.8 ± 11 (13–80 years), and 60% (420) of the participants were female. Of the participants, 108 had idiopathic achalasia and 105 were normal participants who were placed in the case and control groups, respectively. They were enrolled in the study based on high-resolution manometry. *H. pylori* was confirmed by a histological study. In the biopsy, specimens were taken by esophagogastroduodenoscopy. **Results:** Our results revealed that 71.3% and 45% of the participants were *H. Pylori* positive in the case and control groups, respectively. The odds ratio (OR) was 3.3 (95% CI: 1.80–5.99, $P < 0.05$), indicating a statistically significant association between *H. Pylori* infection and the group classification. The dominant presenting symptoms in achalasia were dysphagia (97.2%) and NCCP (80.5%), but regurgitation (65.7%) was a dominant symptom in the normal participants. **Conclusions and Inferences:** Diverse autoimmune and apoptotic phenomena induced by *H. Pylori* influence the pathogenesis of idiopathic achalasia, suggesting an underlying link between *H. Pylori* infection and idiopathic achalasia. This correlation should be confirmed by other clinical and experimental studies.

Keywords: Apoptosis, autoantibody, *helicobacter pylori*, high-resolution manometry, idiopathic achalasia

Introduction

Idiopathic achalasia is a common and well-recognized primary esophageal motility disorder with unknown etiology. It is also characterized by the abnormality of esophageal body peristalsis associated with an impaired relaxation of the lower esophageal sphincter (LES), and it presents with dysphagia, regurgitation, non-cardiac chest pain (NCCP), heartburn, and weight loss.[1] The degeneration of the neural elements that innervate the muscle in the esophageal wall is the histopathological hallmark of idiopathic achalasia. It is associated with an inflammatory infiltrate (predominantly T lymphocytes [TLs]) of the myenteric plexus and provides evidence for an immune mediated destruction of the myenteric plexus. However, the potential etiologies proposed for idiopathic achalasia include viral or bacterial infection and genetic predisposition. The autoimmune mediated ganglion destruction has gained support because the serum from achalasia patients contains anti-neuronal antibodies.[2] Measles and varicella zoster virus antibodies were higher among a number of patients with idiopathy.[3] This finding suggests that idiopathic achalasia may have an autoimmune component.[4]

H. pylori is associated with an increased risk of peptic ulcer, atrophic gastritis, autoimmune gastritis, mucosa-associated lymphoid tissue (Maltoma), and adenocarcinoma.[5,6] Several

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studies indicated that active *H. pylori* infection may induce humoral and cellular immune responses through common homologous epitopes (molecular mimicry) and cross-react with components of the host's nervous tissue. As a result, it affects or exacerbates the nerve cell damage possibly through the apoptotic process, which characterizes the neurodegenerative disorders.[7] This effect may be caused by skewing the host immunologic tone away from the inflammatory Th1/Th17 response and increasing the T-regulatory cell level. Considering the immune regulation capacity of *H. pylori* and the nature of autoimmune related damage in achalasia, it is theoretically reasonable to imply that *H. pylori* is involved in the pathogenesis of idiopathic achalasia.[8-11] The aim of this study is to explore the correlation between *H. pylori* and idiopathic achalasia in an Iranian population.

Methods

This was a case-control study of patients with esophageal symptoms (persisting for >8 weeks) during 2012 to 2014. The study population consisted of 700 patients with an age range of 13–80 years. Patients with dysphagia, regurgitation, and NCCP were included. The exclusion criteria were as follows: history of malignant disease, previous foregut surgery, cardiovascular diseases, large hiatal hernia, and esophagitis of grade CorD according to the Los Angeles classification, eosinophilic esophagitis, and Barrett's esophagus on pathology. All patients provided informed consent and accepted to complete a standard questionnaire form. Esophagogastroduodenoscopy (EGD, Fujinon ED-53 DEP) was done for all the patients by expert endoscopists in the same center. The case and control groups consisted of 108 patients with achalasia and 105 normal patients, respectively, based on esophageal HRM [Figure 1]. All the selected patients were matched accurately in terms of age and gender. A trained esophageal laboratory nurse performed the procedures in collaboration with an expert gastroenterologist. Before each procedure, transducers were calibrated to 0 and 100 mmg, using externally applied pressure. The studies were conducted with the patient in the supine position after at least a 6-hour fast, and medications that could affect the esophageal motor function (e.g. metoclopramide, anticholinergics, and smooth muscle relaxants) were discontinued for 5–7 days prior to the study. The catheter used was a 23-channel silicone-customized water-perfused catheter, with an outside diameter of 3.8 mm (manufactured by Mui Scientific, Ontario, CA).The catheters had 1 distal channel for gastric recording, 5 channels 1 cm apart for the LES pressure, and 16 proximal channels each 2 cm apart. Microlumina was perfused with a pneumohydraulic perfusion system (MMS software) at a water perfusion rate of 0.15 ml/min. Pressure data were acquired and shown using a software specially designed for high-resolution manometry (MMS v 8.23), which displayed isobaric contour plots. After topical anesthetic was applied to the nostril, the high-resolution manometry assembly was passed trans-nasally, and the sensors were positioned to record from the hypopharynx to the stomach. After the LES was detected, using the stationary pull-through method, the catheter was fixed in place by taping it to the nose. Then, 10 swallows of 5 mL ambient-temperature water spaced more than 20 s apart were recorded. The definition based on the Chicago classification is presented in Table 1.[12] Four biopsy specimens were taken from the antrum and gastric body of each patient by EGD. All the specimens were stained by hematoxylin and eosin stain (H and E) or Giemsa after being fixed overnight in buffered formalin, embedded in paraffin, and cut in 5 μm thickness. A pathologist evaluated the specimens. *H. pylori* was considered positive if at least five bacilli were found in each microscopic field.

Encoding was done for each patient, and data were analyzed using SPSS software (version 18). Age was shown with age ± standard deviation. The effects of *H. pylori* positive on the risk of achalasia were expressed as odds ratios (ORs) with 95% confidence intervals (CIs), and with reference to normal manometry participants with *H. pylori* infections. Proportions were compared by Fisher's exact probability test and the Chi-squared test. A *P* value less than 0.05 was considered statistically significant.

Result

This study was conducted on 700 patients, who met our inclusion criteria. The mean ± SD age of the patients was 39.8 ± 11 (13–80 years) and 60% (420) of the patients were female [Table 2]. In the case group, (Idiopathic

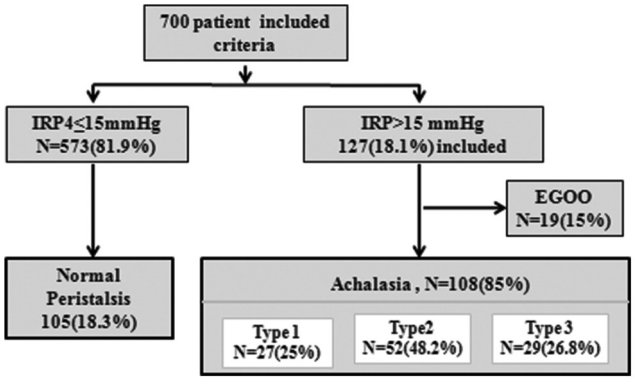

Figure 1: Algorithm of the study analysis based on the Chicago classification. IRP4, integrated relaxation pressure

Table 1: Definitions of the contractile pattern based on the Chicago classification

Contractile pattern	IRP4	Contractile pattern definition
Achalasia	>15 mmHg	Type 1 - distal pressure peristaltic esophageal contraction pressure <30 mmHg (aperistalsis) Type 2 - ≥20% of swallows with uniform pressurization of 30 mmHg IBC from the UES to the LES Type 3 - ≥20% of swallows with DL <4.5 s (premature contraction)
Normal Peristalsis	≤15 mmHg	≥60% of swallows with an intact 20 mmHg IBC (or no break >2 cm) not meeting any other code, DL >4.5 mmHg, CFV <9 mmHG

IRP4, Integrated relaxation pressure 4; IBC , Isobaric contour; DL, distal latency; CFV, contractile front velocity

achalasia) was detected in 108 participants who had high IRP4 (>15 mmHg) (85%) of whom, 66 (61%) were female. The mean age ± SD was 39.6 ± 10.5 (range 21–80 years). The control group included 105 age and sex matched participants with low IRP4 (≤15 mmHg), of whom, 67 (63.8) were female, with an average age of 40 ± 15.5 (21–80 years). The dominant presenting symptoms in achalasia were dysphagia (97.2%) and NCC P (80.5%), but regurgitation (65.7%) was a dominant symptom in the normal participants. The mean IRP4 ± SD was 29.8 ± 6.8 (range 17–42) and 5.4 ± 6 (range 1–13) in achalasia patients and normal participants, respectively [Table 2]. The rate of H.Pylori positive was significantly higher in the case group than in the control group, 71.3% vs. 42.8%. The odds ratio (OR) was 3.3 (95% CI: 1.80–5.99, $P < 0.05$), indicating a statistically significant association between *H. Pylori* infection and the group classification. These results are presented in Table 3.

Discussion

This was the first Iranian case-control study that examined the relationship between *H. pylori* in patients with or without achalasia. Our results revealed that 71.3% of the patients in the case (Idiopathic achalasia) group were infected with *H. pylori*, and this rate was higher than (45%) of the control group. Moreover, our results demonstrated a correlation between *H. pylori* and patients with idiopathic achalasia. *H. pylori* infection rate was similar in three types of idiopathic achalasia although Type 3 idiopathic achalasia was the most common (Type 2 and 3). The patients with idiopathic achalasia were often manifested by dysphagia and NCCP than regurgitation. In our unpublished study, 64.5% of the 808 patients with uninvestigated dyspepsia (ulcer and non-ulcer) were infected with *H. pylori*.

The smooth muscle of the distal esophagus is innervated by the preganglionic vagus nerve fibers with cell bodies located in the dorsal motor nucleus. The esophageal wall and LES are innervated by the excitatory (acetylcholine) and inhibitory neurons (nitric oxide [NO] and vasoactive intestinal polypeptide), resulting in esophageal and LES contractions and relaxations, respectively. It has been demonstrated that NO is a major inhibitory non-adrenergic, non-cholinergic neurotransmitter in the gastrointestinal tract. NO is released in response to nerve stimulation of the myenteric plexus, causing relaxation of the smooth muscle. NO is synthesized by neuronal NO synthase (nNOS) activation in the myenteric plexus. Therefore, impaired nNOS synthesis of the myenteric plexus is an important contributing factor to the pathogenesis of achalasia. The etiology of idiopathic achalasia may be due to the loss of the inhibitory innervation of the esophagus, the central nervous system (CNS) lesions, or the loss of the inhibitory ganglion cells in the myenteric plexus.[13]

The infectious diseases, autoimmune processes, and genetic predisposition are the three main etiologic factors in achalasia. It has been reported that esophagus dysfunction may be due to ganglion cell degeneration in the myenteric plexus, and it is predominated by TLs of the LES and body. Also, it is often associated with inflammatory infiltrates with lymphocytes based on this hypothesis that etiology is either autoimmune, viral, bacterial immune, or neurodegenerative. On the other hand, the abundant autoimmune inflammatory infiltrates, hypertrophy, and neuronal fibrosis during disease progression cause inhibitory ganglionic cell destruction.[14] Furthermore, humoral immune response occurs in some patients with achalasia as reflected by the identification of circulating antineuronal antibodies.[9] Secondly, gastric mucosal integrity is maintained by apoptosis balanced with cell proliferation. Increased apoptosis of the gastric epithelium may cause glandular atrophy. Apoptosis is implicated in various infectious autoimmune diseases. Gastric T-cell lines recognize *H. pylori* antigens and present Fas ligand and produce cytokines (TNF-α) that are synergistic with *H. pylori* in inducing apoptosis gastric epithelial and activated T-cell lines. The activated TLs and *H. pylori* virulent factors bind to

Table 2: Demographic information of the normal participants and patients with total and variant types of achalasia in our center for 2 years

Finding	Normal (%)	Achalasia (108)			
		Total (%)	Type I (%)	Type II (%)	Type III (%)
Number (%)	105 (100)	108 (100)	27 (25%)	52 (48.1%)	29 (26.9%)
Age (years)					
Mean±SD	40±15.5	39.6±10.5	38.6±7.2	40.5±12.5	39.3±13.5
Range	21–80	21–80	25–59	20–80	21–75
Sex					
Female	67 (63.8)	66 (61)	15 (55.5)	33 (63.5%)	18 (62.1%)
Male	38 (36.2)	42 (39)	12 (44.5)	19936.5)	11 (37.9)
HP-positive	45 (42.8)	77 (71.3)	19 (70.4)	38 (73.1)	20 (68.9)
HP-negative	60 (57.2)	31 (28.7)	8 (29.6)	15 (26.9)	9 (31.1)
Dysphagia	31 (29.5)	105 (97.2)	26 (96.3)	51 (98)	28 (96.5)
Regurgitation	69 (65.7)	61 (56.5)	11 (41)	28 (53.8)	22 (75.8)
NCCP	32 (30.5)	87 (80.5)	23 (85.2)	41 (78.8%)	23 (79.3%)
IRP4					
Mean±SD	5.4±6	29.8±6.8	29.5±7.9	29.6±7	30.3±5.4
Range	1–13	17–42	17–41	17–42	22–40

NCCP, noncardiac chest pain; IRP4, Integrated relaxation pressure 4

Table 3: The relation between esophageal manometry findings and *H. pylori*

	Number (%)		Odds ratio (95%CI)	*P*
	(Case) Achalasia	(Control) Normal		
Helicobacter pylori				
Positive	77 (71.3)	45 (42.8)	3.3 (1.80–5.99)	0.038
Negative	319 (28.7)	60 (57.2)		

HLA class II on gastric epithelial cells and induce their apoptosis. Kountouras *et al.* found that idiopathic achalasia is associated with HLA class II (HLA-DR-DQ) antigens in Caucasians.[4,6,9] *H. pylori* upregulates the expression of MHC class II on gastric epithelial cells of *H. -pylori*-positive patients.[5] Kountouras *et al.*[4] suggested that *H. pylori* infection increased the levels of NO by increasing the gastrin level. NO is a rapidly diffusing gas and in sufficient concentrations is a potent neurotoxin that may facilitate the apoptotic death of ganglion cells in neuropathies, possibly including achalasia. The apoptosis of the fibroblasts and smooth muscle cells in lamina propria could reduce the number of collagen fibers. It has been reported that *H. pylori* may change the expression of genes encoding growth factors and cytokine/chemokines and their receptors, apoptotic proteins, and transcriptional factors, in intra- or extra-gastrointestinal disorders. Thirdly, it was revealed that antibodies to myenteric neurons were found in 64% of the patients with idiopathic achalasia. The association between *H. pylori* autoimmunity and pathogenesis of chronic atrophic gastritis and gastric cancer is now well established. *H. pylori* lipopolysaccharide can cause human gastric epithelial cells by expressing the Lewis x and/or y blood group antigens and can induce apoptosis by anti-Lewis antibodies.[4,8] In our opinion, various apoptotic processes by several signals, or autoantibodies against the myentric plexus of esophagus by H. pylori can be the cause of the association between *H. pylori* and idiopathic achalasia.

This was the first case-control study conducted on the relationship between *H. pylori* infection and idiopathic achalasia in Iranian patients. This study had some limitations. The motility patterns may differ between liquid and solid boluses. Moreover, the technical limitations were the consequence of the patients' condition or issues related to anatomy (e.g. hernia).

Conclusion

Various autoimmune and apoptotic sequels induced by *H. pylori* influence the pathogenesis of idiopathic achalasia. However, to confirm this hypothesis, a clinical experiment should be conducted to investigate the effects of *H. pylori* in the pathogenesis of achalasia and examine whether or not the eradication of *H. pylori* infection could benefit the idiopathic achalasia patients.

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Conflicts of interest

There are no conflicts of interest.

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