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Association of *Helicobacter pylori* Infection with Seasonal Behavior of Duodenal Ulcer

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In the present study we investigated the existence of duodenal ulcer activity monthly changes and clarify the roles played by gender, age and *Helicobacter pylori* We performed a hospital based cross sectional study of 939 patients with an incident duodenal ulcer out of 4339 dyspeptic patients from April 2004 to March 2006 in Baqihyatollah University of Medical Sciences, Tehran, Iran. On endoscopy two biopsy specimens were taken from antral gastric greater curvature within approximately 3 cm from the pylorus for rapid urease test. The number of duodenal ulcers and percentage of HP infection with regard to the time of evaluation were analyzed. There was a significance increase in the occurrence of duodenal ulcer in cold period of the year (autumn and winter), ($p<0.0005$, $\chi^2 = 18.1$), After applying adjustment for age, gender and the year of evaluation, there was Also an increment in the percentage of HP infection in cold period of year in comparison to hot one (spring and summer), ($p = 0.009$, Odds ratio = 1.6, 95%CI 1.1-2.3). The present findings indicate that the observed duodenal ulcer occurrence increment in some cold months of the year was a manifestation of the cold month's increments in percentage of HP infection diagnosis in dyspeptic patients who come to our center. For clarification of the biological basis of this phenomenon, further studies, including the interactions of climate, HP and neuroendocrine transmitters and usage of a reliable diagnostic method capable of distinguishing recent from old HP infection may be required.

Key words: *Helicobacter pylori*, seasonal variation, duodenal ulcer, Iran

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INTRODUCTION

There have been numerous studies on seasonal, diurnal, geographical and cultural behavior of duodenal ulcer (Tsai and Lin, 1998). Taking into account the dominant environmental conditions of the location of any given investigation, these studies have shown an increment in the incidence of duodenal ulcer and its complications (including bleeding and perforation) in winter and autumn (Nomura *et al*., 2001), i.e., cold seasons (Shih *et al*., 1993; Laine and Peterson, 1994) and highlands (Gupta and Pal, 1998). Some of these studies, having dealt with the environmental effects more precisely, indicate a relationship between the incidence of duodenal complications and such factors as atmospheric pressure, temperature and vapor pressure in cold seasons (Nomura *et al*., 2001; Liu *et al*., 2003; Budzynski *et al*., 2000). Studies on HP infection, Nonsteroidal anti-inflammatory drugs consumption and gastric acid, which play an important role in the pathogenesis of duodenal ulcer, have been conducted so as to clarify the reason for seasonal changes (Nomura *et al*., 2001; Dominguez-Bello *et al*., 2002; Silverstein *et al*., 1995; Ciociola *et al*., 1999). The results indicate that these seasonal changes are independent of gastric acid or Nonsteroidal anti-inflammatory drugs consumption (Thomopoulos *et al*., 1997; Shvarts *et al*., 1989; Raschka *et al*., 1999; Savarino *et al*., 1996). There is, nonetheless, controversy over the possible role of HP in these seasonal fluctuations (Dominguez-Bello *et al*., 2002; Raschka *et al*., 1999; Savarino *et al*., 1996; Moshkowitz *et al*., 1994). This study sought to investigate the possible role of HP infection in the temporal incidence of duodenal ulcer.

MATERIALS AND METHODS

Study design: This retrospective study was conducted at the endoscopy unit of Bagqiyatollah Hospital in Tehran, one of the major referral centers in Iran. Inpatients and outpatients are currently referred to this unit for endoscopy with an outpatient prevalence of approximately 70%. Eighty percent of our endoscopies were elective; the remainder was urgent (performed within 24 h after admission). All the consecutive endoscopic examination reports of the upper gastrointestinal tract performed between 1st April 2004 and 31st March 2006 were reviewed to identify patients with duodenal ulcer.

Endoscopy: The indications for endoscopy were clinical suspicion of, or evaluation or treatment of the upper gastrointestinal tract lesions (Tsai and Lin, 1998). Patients with active ulcers, considered as any three-dimensional ulcer crater diagnosed in an upper gastrointestinal endoscopy by a gastroenterologist, were included (Tsai and Lin, 1998; Nomura *et al*., 2001; Laine and Peterson, 1998). Such factors as double diagnosis of gastric and duodenal ulceration, recent gastrointestinal bleeding, esophageal varices and any cancer, which could influence the temporal occurrence of peptic ulcer or detection of HP infection, were excluded (Tsai and Lin, 1998; Nomura *et al*., 2001; Savarino *et al*., 1996), furthermore all patients receive no HP eradication therapy in the past. Control diagnosis for the study was acute cholangitis, which was treated during the same study period (Bulajic *et al*., 2002).

Statistical analysis: We used SPSS for Windows 13 (SPSS, Inc., Chicago, Illinois) for the analysis of our data employing Chi-square test, independent-samples t-test and binary logistic regression test. We calculated odds ratios and their corresponding 95% confidence intervals, if appropriate. A p-value of <0.05 was considered statistically significant and all p-values were calculated two-sided.

The number of peptic ulcers and percentile frequency of HP infection in the peptic ulcer patients was recorded each month so that the temporal intervals for the evaluation of diurnal fluctuation of these two parameters could be defined. Temporal intervals were defined with regard to the total number of endoscopies performed in each interval; there were no significant differences between the intervals (Tsai and Lin, 1998; Nomura *et al*., 2001; Shvarts *et al*., 1989; Savarino *et al*., 1996). Between 2004 and 2006, 4339 upper gastrointestinal endoscopies were performed in the gastroenterology unit of this Hospital with the number of the procedures performed each month being recorded. In light of significant differences in the number of total endoscopies performed in different months and seasons (respectively shown in chi-square test by $p<0.001$, $\chi^2 = 215.7$, df = 11, $p<0.001$, $\chi^2 = 58.6$, df = 3) we tried to divide the whole year into periods that had equal number of endoscopies. By taking into account the division of a year in many parts of Iran into cold period and hot period and the possible role of hot and cold seasons in the incidence of duodenal ulcer (Nomura *et al*., 2001; Shih *et al*., 1993; Laine and Peterson, 1994; Liu *et al*., 2003), we compared the cold period (autumn to winter) versus the hot period of the year (spring to summer) and discovered that there were no significant differences between the number of endoscopies performed in these two periods ($p = 0.09$, $\chi^2 = 2.84$, df = 1). Furthermore, there was a significant difference between the years 2004 and 2005-2006 (with

regard to Iran's working system, 1st April, 2005 to 31st March, 2006, considered as one annual working period) in terms of the number of endoscopies performed during hot and cold periods of each year ($p<0.001$); this discrepancy was dealt with in the final step of our analysis. During each endoscopy, two biopsy specimens were obtained from the antral mucosa of the gastric greater curvature within approximately three centimeters from the pylorus for rapid urease test (Pyloritek Test Kit, Shim Anzim CO., Iran) and all positive results were confirmed by histopathological evaluation, in which the specimens were fixed in formalin and stained with Warthin-Stary and modified Gimsa method in order to detect HP infection (Dominguez-Bello *et al*., 2002; Savarino *et al*., 1996).

Present analysis was performed in three stages to investigate the existence of possible temporal fluctuation in the incidence of peptic ulcer; the correlation of this possible fluctuation with HP infection and background factors such as age, sex and year of admission, separately and the simultaneous effects of the above-mentioned variables by multivariate logistic regression analysis when p-value was less than 0.25. If a continuous variable could enter the final step of the analysis, it was divided into four groups by quartiles and used for further analyses. An Institutional Review Board approved this study.

RESULTS

In our center, duodenal ulcer was diagnosed in 979 out of 4339 subjects. After the application of our exclusion criteria (Table 1), the study population comprised 729 patients [67.1% male and 32.9% female, mean age (SD): 42.6 (17.9) years]. 88.1% of these 979 patients were infected by HP.

Table 1: Percentage distributions of exclusion criteria in duodenal ulcer patients in a hospital-based cross-sectional study of duodenal ulcer, Iran, April 20004 to March 2006

Exclusion criterion	Number (%)
Gastrointestinal malignancies	26(2.7)
Varices	24(2.5)
Gastric ulcers	126(12.9)
Bleeding due to duodenal ulcers	74(5)
Total	250(25.5)

Using Chi-square test to see the existence of seasonal differences in the incidence of duodenal ulcer, the first stage of our analysis showed that there was a significant increase ($p<0.001$, $\chi^2 = 21.4$, df = 1) in the occurrence of duodenal ulcer in the cold period of the year (autumn to winter) compared with the hot one (spring to summer): 427 (58.6%) cases in the cold period of the year versus 302 (41.4%) cases in the hot one. The second step of our analysis was the evaluation of the relationship between this seasonal difference and HP infection. For the evaluation of possible background factors, the relationship between these seasonal differences and age, gender and the year of evaluation was also investigated (Table 2).

The percentage of HP infection had a significant association with the cold period of the year in comparison with the hot one, but there was no significant association between cold/hot periods of the year and age, gender and the year of evaluation.

The third step was the analysis of variables in duodenal ulcer, shown by univariate test to have a $p<0.25$, i.e., HP infection, age, by a multivariate conditional model for evaluation of possible simultaneous effect of age and HP on this periodic behavior, we divide the age to four groups with regard to quartiles: 31, 40, 53 years. We used backward conditional elimination; the remaining factor was still HP infection. Table 1 and 2 demonstrate that in addition to the increase in the incidence of duodenal ulcer during the cold period of the year, there is an increase in the percentage of HP infection. Step-wise division of the year into wider intervals can progressively flatten the base of our diagram, formed by non- infected individuals, to illustrate this seasonal phenomenon in relation to HP infection.

In the control diagnosis of 198 patients with acute cholangitis for this study [57.6% male and

Table 2: HP infection and potential background variables in a hospital-based cross- sectional study of duodenal ulcer, Iran, April 2004 to March 2006

	Mean (SD)				
Variable	Cold period	Hot period			p-value*
Age (year)	40.9(16)	42.9(17)			0.164(NS†)
	Yes (%)				
	Cold period	Hot period	Crude odds ratio*	95% CI†	p-value*
Gender (Male)	66.3	68.2	1.1	0.8,1.5	0.58 (NS)
Year of evaluation (2004)	39.1	35.4	0.9	0.6,1.2	0.31(NS)
HP‡ positive patients	90.6	80.1	2.3	1.6,3.7	<0.001

*: p-values and odds ratios were calculated by unadjusted analysis; †: NS: Not Significant; CI = Confidence interval; ‡: HP

42.4% female, mean age (SD): 47.8 (18.5) years], we could find no significant periodic fluctuation ($p = 0.26$, $\chi^2 = 1.29$, $df = 1$) in the cold period of the year (autumn to winter) compared with the hot one (spring to summer): 98 (49.5%) cases in the cold period of the year versus 100 (50.5%) cases in the hot one. In this group, the cold period of the year compared with the hot one with regard to the percentage of HP infection, showed no significant difference ($p = 0.34$, Odds Ratio = 0.7, 95% CI 0.4-1.4).

DISCUSSION

Present study demonstrated that there was an increment in the incidence of duodenal ulcer during the cold period of the year and this difference was independent of possible background variables (i.e., age, gender and year of evaluation).

Moreover, we showed that the difference in frequencies of duodenal ulcer was not related to the number of endoscopies performed in each defined period. We also discovered the association between these temporal fluctuations and HP infection. In other words, we observed that the increment in the incidence of duodenal ulcer in the cold period of the year paralleled the increment in the percentage of HP infection.

These results are similar to those reported by Moshkowitz *et al.* (1994) who presented the existence of a parallel increment in the incidence of dyspepsia and HP infection in winter (Moshkowitz *et al.*, 1994). A study in the tropical country of Venezuela, in which there are two periods of dry and rainy seasons and the temperature changes around 25°C during the whole year, pointed out a simultaneous increment in the incidence of dyspepsia in the rainy season with the HP infection rate (Dominguez-Bello *et al.*, 2002). Another recent research in Japan showed that there was an association between the changes in meteorological factors (such as atmospheric vapor pressure, pressure and temperature) and the increase in the complications of duodenal ulcers during the cold periods of the year (Nomura *et al.*, 2001). Before coming to any conclusion, however, we should consider the following facts: (1) The person-to-person mode of transmission of HP by the fecal-oral route plays a very important role (Konno *et al.*, 2005; Dore *et al.*, 1996) (2) There is the important role of the water-borne mode of transmission in addition to the person-to-person mode of transmission in developing countries (such as Iran), with lower socio-economic and health status (Kato and Sherman, 2005; Karita *et al.*, 2003; Hulten *et al.*, 1996) (3) There are several strains of HP with different pathogenicity (Spechler *et al.*, 2000; Akopyans *et al.*, 1998) and (4). In contrast to near to zero probability of adulthood HP acquirement in developed countries, there is a significant rate of transmission during adulthood, which reaches almost 20% in each year for every individual in developing countries (such as Iran).

Everyone is susceptible to infection by multiple strains of HP; a considerable number of these infections may be transitional and can be eradicated spontaneously (Konno *et al.*, 2005; De Schryver *et al.*, 2004; Leal-Herrera *et al.*, 2003; Malekzadeh *et al.*, 2004; zendehdel *et al.*, 2005). Consequently, in developing countries, in addition to the existence of a high transmission rate in early childhood, acquisition likelihood of new strains of HP in adulthood remains considerably noticeable and water-borne transmission along with person-to-person transmission has a significant role. It can be posited that Iran possesses such suitable environmental factors for the transmission of HP infection as low socio-economic status, poor public and personal health care and overcrowding in confined spaces.

Furthermore, changes in environmental factors such as temperature, vapor pressure and daytime in cold periods of the year may lead to intrinsic change in duodenal ulcer patients (Shvarts *et al.*, 1989; Komarov *et al.*, 2003) or possibly lead to a rise in the survival rate of the coccoid form of bacteria in environmental media, like water and higher transmission rates of HP (Wang and Wang, 2004). We could depict these parallel fluctuations of HP acquisition and duodenal ulcer incidence and postulate that perhaps the cause of these periodic fluctuations in the incidence of duodenal ulcer is periodic fluctuations in the transmission rate of HP or with regard to our control group, this behavior was more likely due to a periodic increment in the duodenal ulcer susceptibility to HP Periodic HP transmission rates may lead to an increased probability of contact with more virulent HP strains or ingestion of higher loads of bacteria which, in turn, may lead to an increased incidence of duodenal ulcer.

On the other hand, seasonal intrinsic changes in duodenal ulcer patients may lead to an increment in HP infection susceptibility in cold period of the year, which beside existence of significant rate of HP transmission throughout the year, may lead to an increased incidence of duodenal ulcer. The question remains as to why other studies have not noted any periodic difference in duodenal ulcer or HP infection incidence or why no correlation between these two variables has been reported. Maybe difficulties in differentiating new infections from old ones and detecting different strains in countries where the transmission rate of HP infection,

especially in adulthood, is lower than that in Iran has led to researchers' only being able to show a fluctuation in the incidence of duodenal ulcer and its complications and not in HP acquisition.

In countries where the transmission rate of HP infection is much lower, researchers can show no fluctuation in the incidence of duodenal ulcer and HP acquisition (Budzynski *et al*., 2000; Savarino *et al*., 1996; Soszka and Kusz-Rynkun, 1998; Braverman *et al*., 1992; Graham *et al*., 2003).

In conclusion, the present study recommend that the probability of the existence of HP infection be considered when a patient with a confirmed duodenal ulcer or even dyspepsia presents a history of increment in dyspeptic symptoms during the cold period of the year.

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