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Long-Term Outcome Of Patients With Functional Dyspepsia Infected With A Cag-Positive Helicobacter Pylori Strain. A Descriptive Study.

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Abstract

Introduction: An important virulence factor of *H.pylori* is the Cag-pathogenicity island. The clinical sequel in patients with functional dyspepsia treated for *H.pylori* on the long-term is not known.

Aim: Establish long-term outcome and relate this to the initial *H.pylori* status (CagA- positive or negative).

Patients and Methods: In 1994/1995 a study on presence of *H.pylori* was done. IgG antibodies against cagA were determined. Three groups of patients were made: group 1: *H.pylori* + and CagA+; group 2: *H.pylori* + and CagA-; and group 3: *H.pylori* -patients. An extensive chart review and several questionnaires were used (a general questionnaire, the GerdQ, theSAI, and, the GSRS). Use of acid suppressive drugs was assessed.

Results: 411 patients were included. New upper GI-endoscopies were significantly more often done in patients of group 1 ($p<0.001$). Reflux disease was significantly more often diagnosed in group 1 patients ($p=0.02$). After exclusions 239 patients (58.2%) received the questionnaires, 101 respondents were evaluable. Patients in group 1 reported significantly more often complaints. There was no significant difference in the overall presentation when patients of group 1 were compared with patients of group 2. However, there was a significant difference between the scores in *H.pylori*+ patients when compared with patients of group 3. Patients of group 1 significantly used more often acid suppressive therapy.

Conclusion: functional dyspeptics with *H.pylori* CagA+strain, may develop more often complaints in the future necessitating a new endoscopic investigations. Signs of reflux disease are more often present.

Key-words: Dyspepsia; H.pylori; Cag-A; Follow-up; Upper Gastrointestinal Endoscopy

Introduction

The description of *Helicobacter pylori* was a major breakthrough in Gastroenterology in the past decennia. The bacterium causes ulcer disease and distal gastric cancer. Since the establishment of the anti-Helicobacter treatment prevalence of peptic ulcer disease, once a chronic problem, dramatically decreased. Despite many studies, there still is discussion on the necessity of eradicating the microorganism in patients with functional dyspepsia.Zhao et al did a meta-analysis on the long-term effects of therapy in patients with functional dyspepsia and concluded that this therapy is associated with consistent improvement of dyspeptic symptoms [1]. The number needed to treat to cure one case of dyspepsia is fourteen according to a large meta-analysis of the Cochrane institute [2].

An important virulence factor of *H.pylori* is the so-called Cag-pathogenicity island, containing the cytotoxin associated gene (cagA). The product of this gene is the immunodominant antigen CagA [3,4]. Patients with *H.pylori* positive ulcer disease are almost invariably cagA-positive [5,6]. Patients with CagA positivity also have an increased risk of gastric cancer [7].

Obviously, nowadays, all patients diagnosed with *H.pylori* infection are treated with anti-Helicobacter therapy. It is not known what the clinical sequelis in functional dyspeptics treated for *H.pylori* positive gastritis on the long-term. Most studies have a follow-up of six months till one year [1]. Another important point is the hypothesis that *H.pylori* might be protective against the development of gastroesophageal reflux disease [8].

A study was done in order to establish long-term out come in the sense of upper abdominal complaints, reflux complaints, and consultations for upper gastrointestinal complaints and relate this to the initial *H.pylori* status (CagA-positive or negative).

Patients and Methods

In 1994/1995 a study on presence of *H.pylori* in all consecutive patients sent to the Endoscopy Department of the Zaans Medisch Centrum, the community Hospital of the Zaanstreek region in the Netherlands, was performed [9]. Endoscopy was done with EVIS-100 Video endoscopes from Olympus (Olympus Nederland BV Zoeterwoude).

In the present study only patients in whom no macroscopic abnormalities were seen during the endoscopy were included. These patients were diagnosed with functional dyspepsia (non-ulcer dyspepsia). During the procedure biopsy

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specimens were taken from the gastric antrum for haematoxilin/eosin and immunoperoxidase stain (n=2), rapid urease test (n=1), and Gram stain with culture (n=1) according to previously described methods [10]. A patient was considered *H.pylori*-positive if one or more of the detection methods was positive. A patient was *H.pylori*-negative if all methods were negative. A serum sample was taken and frozen at minus 70 degrees Celsius. Specific IgG antibodies against the *H.pylori* cagA were determined as described earlier [9,11].

For the present follow-up study, the dyspeptic patients were grouped in three groups. Group 1:*H.pylori* positive and CagA positive; Group 2: *H.pylori* positive and CagA negative; and finally Group 3: patients negative for *H.pylori*.

Part of the patients diagnosed with functional dyspepsia participated in a trial with so-called reversed randomisation [12]. These patients were treated with the combination of omeprazole and amoxicillin. The trial did not include standard biopsies after completion of the study. Non-participants in this study were treated with the classic triple therapy or the classic quadruple therapy with bismuth, amoxicilline, metronidazole and protonpump inhibition. The majority of patients did not undergo follow-up endoscopy after treatment. The present study consists of two parts: first a chart review of all patients, and, second, the application of a number of questionnaires sent to all patients still alive at the date of evaluation.

Chart review

An extensive chart review was done of all hospital records and endoscopy reports from all patients in order to obtain data on consultations, new endoscopies, and abnormalities related to oesophagus, stomach or duodenum. In other words a period of more than 20 years was covered. If patients still visited their community hospital, it was assumed that they also would have been sent for new upper gastrointestinal endoscopy to the open-access department or to the out-patient clinics for consultation in case of upper abdominal complaints. In addition, the national registry of pathology was searched for presence of histological examinations in oesophagus or stomach from the patients done in other hospitals.

Questionnaires

In December 2015, all patients still alive received an extensive questionnaire by mail. Patients not capable of reading the Dutch language were excluded. The questionnaire was already used and validated in previous studies [13,14]. The questionnaire was composed of four different lists of questions pertaining to upper abdominal complaints.

A general questionnaire consisted of 20 questions [13,14]. The first question in the general questionnaire was: "Do you experience any upper abdominal complaint?" Severity and frequency of complaints were scored on a five and six point Likert scale respectively. Severity was scored as: 0 none; 1 light; 2: moderate; 3: serious; 4: serious complaint interfering with daily life. The minimum overall mean score for severity was 1, the maximum score 40. Severity score was calculated per patient. The overall mean frequency was scored as: 6: several times a day; 5: once daily; 4: several times a week; 3: once a week; 2: several times a month; 1: once a month. The minimum score on frequency was 1, the maximum score 60.

The GerdQ is a validated questionnaire that reveals a scoring on reflux symptomatology on the 7 days prior to receiving the list [15]. It calculates the probability that a patient has gastrointestinal reflux disease using six questions.

The SAI (symptom activity scale), which is a modified functional bowel disorder severity index, takes into account a subjective evaluation of the patients complaints, whether or not they have been present for over 6 months (chronic complaints) and how many times a patient consulted a general practitioner because of these complaints. A score of 36 or lower indicates mild complaints, a score between 37 and 110 is consistent with average complaints and a score of 111 or higher indicates severe complaints [16,17]. The gastrointestinal symptom rating scale (GSRS) ranges from 0 points when a patient has no complaints up to 18 points when a patient has all of six specified symptoms on a regular basis [18]. Use of acid suppressive drugs was assessed with the questions whether or not a patient used acid suppressive therapy. Statistical analysis was done with chi-square test for contingency tables and t-test. A value below 0.05 was considered statistical significant.

Results

Chart review

In total 411 patients were included. Table 1 shows the characteristics in the three groups. There was no difference in men or women. Mean age was 49 years (standard deviation 16, range 15-86) in group 1; 53 years (SD 18,range 23-83) in group 2; and 45 (SD 17.5, range 12-67) in group 3. Patients in group 2 were significantly older ($p<0.001$), although significant overlap is present. Hence, as to be expected, more patients in group 2 had died by the time of the evaluation. New upper GI-endoscopies were significantly more often done in patients of group 1 ($p<0.001$). But if new endoscopies were done, there was no difference in the number of new endoscopies in the individual patients in the three groups in the entire follow-up period (Table 1).

Only a minority of the patients in group1were not in the hospital system anymore, implying that they either moved out of the region or never went for any consultation again. This number was significantly higher in groups 2 and 3 ($p=0.03$). Table 2 shows the yield of the new endoscopies in the three groups of patients. In follow-up, reflux disease was significantly more often diagnosed in patients of group 1 ($p=0.02$). If biopsies were obtained during the endoscopy, these mostly were negative for *H.pylori*, indicating successful prior treatment. In all groups ulcers were detected.

The main reason was use of NSAID's. Stomach cancer was detected in one patient of group 1, 14 years after the initial

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Table 1: The characteristics of the three groups of patients (The number between brackets is the percentage). Group 1: H.pylori positive and CagA positive; Group 2: H.pylori positive and CagA negative; and Group 3: patients negative for H.pylori.

	Group 1	Group 2	Group 3	
Number	130	91	190	
Men	51(60.7)	42(46.2)	78(40)	
Women	79(53.8)	49(53.8)	112(58.9)	P = ns
Not in the hospital system				
Anymore	12(9.3)	20(21.9)	31(16.3)	
Deceased	29(22.3)	34(38)	36(19)	
No consultations in 2015	89(68.4)	37(40.1)	123(64.7)	
No pre-mortal consultations	12	12	14	
New endoscopy	72(55)	37(41)	57(30)	P < 0.001
Number of new endoscopies				
1	33(45.8)	20(54)	35(61.4)	
2	17(23.6)	8(21.6)	10(17.5)	
3	12(16.6)	4(10.8)	7(12.3)	
>3	10(14)	5(13.6)	2(8.8)	

Table 2: Yield of the new endoscopy (The number between brackets is the percentage). Group 1: *H.pylori* positive and CagA positive; Group 2: *H.pylori* positive and CagA negative; and Group 3: patients negative for *H.pylori*. Signs of reflux disease = presence of typical reflux complaints with or without oesophagitis or hiatal hernia.

	Group 1	Group 2	Group 3
No abnormalities	59(82)	24(65)	38(67)
Signs of reflux disease	11(15)	6(16)	14(25)
Ulcer	1(15)	6(16)	4(7)
Unknown	-	-	1(1)
H.pylori positive	1	2	–
H.pylori negative	25	3	14

diagnosis of functional dyspepsia. Oesophageal cancer was seen in one patient of group 2 already one year after the initial study.

Questionnaires

Of the 411 patients, 172 were excluded because they had either died or were not able to read or understand the Dutch language. Two hundred and thirty nine patients of the initial group (58.2%) received the questionnaires. Of these 131 (54.8%) responded. Of these 5 additional patients had died, 13 returned the questionnaires without answering to the questions, and 12 moved to another address. Finally 101 respondents were evaluable.

Patients in group 1reported significantly more often complaints compared with those in groups 2 and 3 (Table3).

Table 3: Overall presence or absence of upper abdominal complaints scored by the questionnaire, the Gerd-Q, the SAI or the GSRS in the three groups of patients (the number between brackets is the percentage). Group 1 = Hp+Cag+, Group 2 = Hp+Cag-, Group 3 = Hp-.

	Hp+ Cag+	Hp+ Cag-	Hp-
Complaints	19(67.8)	7(36.8)	18(33.3)
No complaints	9(32.2)	12(63.2)	36(66.7)
Hp+ Cag+	versus	Hp+Cag-	p<0.001
Hp+ Cag+	versus	Hp-	p<0.001
Hp+ Cag-	versus	Hp-	p = ns

There was no significant difference in the scores of the general questionnaire, the GerdQ, the SAI, and the GSRS when patients of group1were compared with patients of group 2. However, there was a significant difference between the scores in H.pylori-positive patients when compared with patients of group 3. Table 4 shows the results of the general questionnaire, the frequency score of complaints, the GerdQ, SAI, and GSRS in the three groups of patients.

Table 5 shows the use of acid suppressive therapy in the three groups of patients. As can be seen the patients who were H.pylori+ and CagA+ used significantly more often acid suppression when compared with the other two groups.

Discussion

Ever since H.pylori was described and its role in ulcer disease and gastritis was established, a link between H.pylori colonisation and dyspepsia has been sought [19-21]. There is definitely a link between the clinical presentation and the virulence status of H.pylori [9].

The present study shows follow-up of more than 20 years in patients with functional dyspepsia especially related to H.pylori status. The majority of patients still visited their community hospital for all kinds of reasons. Some are treated in the out patients clinics of Internal Medicine or Gastroenterology, many visit other departments. Patients show great loyalty towards their community hospital.Hence, it can be assumed that if a patient had upper abdominal complaints, he/she again will visit his/her hospital and will undergo endoscopy if the general practitioner or the medical specialist feels the procedure is

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indicated.

Table 4: Results of the general questionnaire, the frequency score of complaints, the GerdQ, SAI, and GSRS in the three groups of patients. Group 1 = Hp+Cag+, Group 2 = Hp+Cag-, Group 3 = Hp.

	General questionnaire	Frequency	GerdQ	SAI	GSRS
Hp+ Cag+					
Mean	10.37	20.68	6.05	36.53	6.58
SD	6.21	13.23	4.39	32.25	2.78
Median	9	17	5	42	7
Range	26-Mar	Mar-53	0-14	0-101	10-Jan
Hp+ Cag-					
Mean	13.67	27.67	7.17	45.17	7.33
SD	7.79	14.38	3.76	29.4	3.72
Median	10	23.5	7	53.5	7.5
Range	24-Jun	Oct-50	13-Feb	May-72	11-Mar
Hp-					
Mean	6.72	12.06	2.67	18	4.33
SD	4.79	9.4	2.25	19.67	2.85
Median	7	13	0.53	21.9	0.67
Range	0-19	0-39	0-7	0-54	0-12

General questionnaire	
Hp+ Cag+ versus Hp+ Cag-	
Hp+ Cag+ versus Hp-	p = 0.05
Hp+ Cag- versus Hp-	p = 0.01
Frequency	
Hp+ Cag+ versus Hp+ Cag-	p = ns
Hp+ Cag+ versus Hp-	p = 0.02
Hp+ Cag- versus Hp-	p = .005
GerdQ	
Hp+ Cag+ versus Hp+ Cag-	p = ns
Hp+ Cag+ versus Hp-	p = 0.07
Hp+ Cag- versus Hp-	p = 0.03
SAI	
Hp+ Cag+ versus Hp+ Cag-	p = ns
Hp+ Cag+ versus Hp-	p = 0.04
Hp+ Cag- versus Hp-	p = 0.03
GSRS	
Hp+ Cag+ versus Hp+ Cag-	p = ns
Hp+ Cag+ versus Hp-	p = 0.02
Hp+ Cag- versus Hp-	p = 0.05

Table 5: Use of medication (acid suppressive therapy) in the three groups of patients at time of the evaluation. + = positive for medication use or complaints, - = negative. The number between brackets is the percentage.Group 1 = Hp+Cag+, group2 = Hp+Cag-, group 3 = Hp-.

	Hp+ Cag+	Hp+ Cag-	Hp-
Medication+/ complaints+	16	5	13
Medication+/ complaints-	4	2	5
Medication -/ complaints +	3	2	5
Medication -/ complaints -	5	10	31
Total			
Medication +	20(71.4)	7(36.8)	18(33.3)
Medication -	8(28.6)	12(63.2)	36(66.7)

Hp+ Cag+ versus Hp+ Cag-	p = 0.04
Hp+ Cag+ versus Hp-	p =0.001
Hp+ Cag- versus Hp-	p = ns

Data are missing in this study. Patients, who were dead at time of the evaluation, obviously cannot respond to the questionnaires anymore. It is also normal that a number of patients are non-responders. On the other hand, given the long follow-up, the number of actually responding patients could be called rather high. Despite these missing data, in our opinion, conclusions can be drawn.

An important finding in the present study is the fact that patients initially diagnosed with an *H.pylori* Cag-positive strain reported significantly more often that they still experienced upper abdominal complaints when compared with the Cag-negative strains or the *H.pylori*-negative patients. However, on the long-term patients who was *H.pylori* negative experienced significantly less often complaints or had a lower score in the different questionnaires. Harvey et al. studied the long-term effect of Helicobacter eradication. After 2 years, a 35% reduction in consultations for dyspepsia occurred. An extension of this study showed an ongoing trent in reduction of consultations in the next 2 and 7 years [22]. In another study it was shown that only 36% of functional dyspeptics were without any complaint seven years after treatment with anti-Helicobacter treatment [23]. Hansen et al. studied a very large population of individuals screened for presence of *H.pylori* after five years of follow-up. The response rate in Hansen's study was very high, 94%.A modest effect on dyspepsia, and a modest, but significant effect on the consultation rate and sick leave days for dyspepsia were noted [24].

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Another finding in the present study, although largely as indirect evidence, is the fact that patients who initially were infected with CagA-positive bacteria had the highest number of new endoscopies in the years to follow. Implicating more consultations because of complaints. Also these patients had a higher prevalence of reflux disease.

Also the fact that higher number patients in groups 2 and 3 were not in active the hospital system anymore is indirect evidence that they did rather well after being treated for their dyspepsia. Of course, it is always possible that they were referred to another hospital. But on the other hand why would a larger percentage of patients from group 1 still visit their hospital?

Patients received different anti-Helicobacter treatments. Triple therapy or even quadruple therapy is the most effective. However, anti-Helicobacter dual therapy with high dose proton pump inhibition can be as effective [25]. In the initial study biopsy specimens after therapy were not done routinely. But, if a patient underwent a new endoscopic investigation, biopsy specimens were often taken and proved to be H.pylori- negative in many cases implying successful prior anti-Helicobacter therapy (Table 2).

On the long-term the prognosis of functional dyspepsia is rather fair. The scores in the general questionnaire are lower than reported in a previous study in patients with active disease [22]. It can be concluded that patients with functional dyspepsia and *H.pylori* gastritise infected with a more virulent*H.pylori* strain (this is CagA-positive), may develop more often complaints in the future necessitating a new endoscopic investigations and treatment. Signs of reflux disease are more often present. *H.pylori* possibly seems to be protective against development of reflux disease [8].

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