Cytokine gene polymorphisms and the pathology of chronic gastritis

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ABSTRACT

Introduction: *Helicobacter pylori (H. pylori)* infection is associated with divergent clinical outcomes and these outcomes are largely influenced by the levels of cytokines in the gastric mucosa. The levels of these cytokines are dependant on cytokine gene polymorphisms. Pro-inflammatory cytokine polymorphisms are strongly associated with severe histological changes in the gastric mucosa in Caucasian populations.

Methods: In this study, we evaluated the role of cytokine gene polymorphisms in influencing the pathological severity of gastritis. 120 patients were evaluated. Cytokine gene polymorphisms of interleukin-1 (IL-1) beta, tumour necrosis factor alpha and the IL-1 receptor antagonist genes were done using polymerase chain reaction (PCR) restriction fragment length polymorphism and PCR variable number of tandem repeats markers typed on the deoxyribonucleic acid obtained from the peripheral blood. Histological analysis was done by using the revised Sydney system.

Results: There was no association between pro-inflammatory cytokine gene polymorphisms and severity of gastritis.

Conclusion: This data suggests that high cytokine levels are not seen in the gastric mucosa in Indians in spite of *H. pylori* colonisation. IL-1 beta is a potent pro-inflammatory cytokine which causes a partial clearance of the organism as well as hypochlorhydria. Corporal hypochlorhydria causes a persistent colonisation by *H. pylori* followed by the development of gastric atrophy and later carcinoma. This lack of association with a pro-inflammatory polymorphism suggests that only low levels of IL-1 beta are present in the gastric mucosa. This causes a low clearance of the organism and a high incidence of duodenal ulceration because of hyperchlorhydria. However, it is protective against the development of gastric carcinoma. This would explain the "Indian Paradox" of the apparent discrepancy of a high degree of colonisation by *H. pylori* and a low incidence of gastric carcinoma in the Indian population.

Keywords: cytokines, gastritis, gene polymorphisms, *Helicobacter pylori*

Singapore Med J 2007; 48(5):447–454

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is associated with divergent clinical outcomes that range from asymptomatic gastritis to gastric carcinoma. The severity of gastritis as evaluated by histopathology is believed to be dependant on bacterial virulence factors as well as the host genetic predisposition. In the host genetic factors, cytokine genes have been implicated in influencing the pathology of gastritis.[1-4] The secretion of cytokines is now known to depend on cytokine gene polymorphisms.[4] Gene polymorphisms are normal variants in the human genome. Deoxyribonucleic acid (DNA) sequences of the human genome reveal that many genes are polymorphic. In the coding or non-coding regions of specific genes, there may be either a single base pair substitution or a variable number of tandem repeats (VNTR) of a short repetitive DNA sequence. These variations or polymorphisms may influence the rate of gene transcription, the stability of the messenger ribonucleic acid (RNA) or the quantity and activity of the resulting protein.

Thus, the susceptibility or severity of a number of disorders will be influenced by possession of specific alleles of polymorphic genes. Cytokine gene polymorphisms have recently attracted considerable interest since it has been discovered that different alleles of cytokine genes are associated with different immunomodulatory diseases.[5,6] Genes encoding cytokines and related molecules harbour polymorphic regions, which are considered to alter gene transcription and thereby influence inflammatory processes in response to infectious disease.[7,8]

The interleukins, interleukin-1 beta (IL-1β) and its antagonist, IL-1 receptor antagonist (RA) and tumour necrosis factor alpha (TNF-α) have been studied in

gastritis.[1-4] In Caucasians, it has been seen that pro-inflammatory polymorphisms are associated with severe histological changes in gastric mucosa. It has also been seen that pro-inflammatory polymorphisms are associated with the development of chronic atrophic gastritis and gastric carcinoma.[9] No studies on the Indian population are available associating pro-inflammatory polymorphisms and severe histopathological changes.

In the Indian context, several features of *H. pylori* associated disease remain a puzzle. Firstly, although the incidence of *H. pylori* infection in Asian Indians is very high,[10] the incidence of carcinoma is low.[11] Secondly, the incidence of duodenal ulceration appears to be higher in Asian Indians,[12] as compared to the Caucasians, and the incidence of duodenal ulcer is closely related to *H. pylori*.[10] Hence, it is apparent that *H. pylori* is responsible for disease in India but it predominantly causes duodenal ulceration and not gastric cancer (the Asian Paradox). Is this difference in the pathogenesis of Caucasian populations because of a difference in the host genetic structure?

We took up this prospective study to investigate the role of host cytokine gene polymorphisms related to the severity of the pathology of gastritis. The aim of the study was to investigate if cytokine gene polymorphisms are responsible for severe histological changes in the gastric mucosa. We also aimed to explain the paradox of high *H. pylori* colonisation and low gastric carcinoma incidence in Indians based on this study.

METHODS

Between August 2004 and August 2005, 120 patients with non-ulcer dyspepsia and who underwent upper gastrointestinal endoscopy, were studied. The duration of the illness and history of tobacco and alcohol consumption were recorded. Dietary habits noted included a vegetarian or non-vegetarian diet and history of excessive consumption of spices. Vegetarians included patients who consumed only grain, vegetables and milk or milk products with the total exclusion of meat, fish or eggs in their food. A non-vegetarian diet included patients who consumed meat, fish or eggs regularly in addition to grain, vegetables and milk products. Exclusion criteria were: present or past history of gastric neoplasm or gastric surgery, long-term therapy with non-steroidal anti-inflammatory drugs, liver disease and previous treatment with antibiotics or bismuth salts. All subjects had given informed consent for the study and the local ethics committee had approved the protocol.

Endoscopy was performed after an overnight fast with standard upper gastrointestinal endoscopes (Olympus Optical, Tokyo, Japan) and biopsy specimens were obtained with standard biopsy forceps. The endoscopic evaluation was done by two experienced endoscopists (NKG and UCG) who had performed more than 15,000 endoscopies each. Three antral biopsies were taken for histological examination from the distal lesser and greater curvature, 2–3 cm from the pylorus. The biopsies were immediately fixed in formalin for histopathological examination. In addition to the biopsy samples, 4–5 ml of the blood was collected from each patient and mixed with ethylenediaminetetraacetic acid to be used for DNA isolation and cytokine gene polymorphisms analysis. The blood was stored at 4°C.

All biopsies were oriented and fixed in 10% buffered formalin. They were processed by routine techniques and stained by haematoxylin and eosin stain, modified Giemsa stain for the detection of *H. pylori* and Cookes stain for the detection of mast cells.[13] The modified Giemsa stain was used for the evaluation of *H. pylori* because it has been reported to be a reliable, cheap and reproducible method for the detection of the organism.[14] The slides were evaluated by two pathologists (NM and ANS) according to the Updated Sydney System.[15] The pathologists were unaware of the clinical, endoscopical and genetic data. A score of 0 to 3 (absent, mild, moderate, marked) was assigned to each of the morphological variables: *H. pylori* density, density of neutrophils, lymphocytes, plasma cells, eosinophils and mast cells. Glandular atrophy, glandular shortening, intestinal metaplasia and the presence or absence of fibrosis were also noted and graded into the above three categories. The presence of microulceration, activity, and foveolar hyperplasia were noted and graded as present or absent. The grading of the presence of lymphoid follicles was done as per the histological scoring index as proposed by Wotherspoon et al.[16] For each variable, the highest score was given among the antral biopsies. To minimise the interobservor variability in grading the histopathological features, we used the scoring system as proposed by Aydin et al.[17]

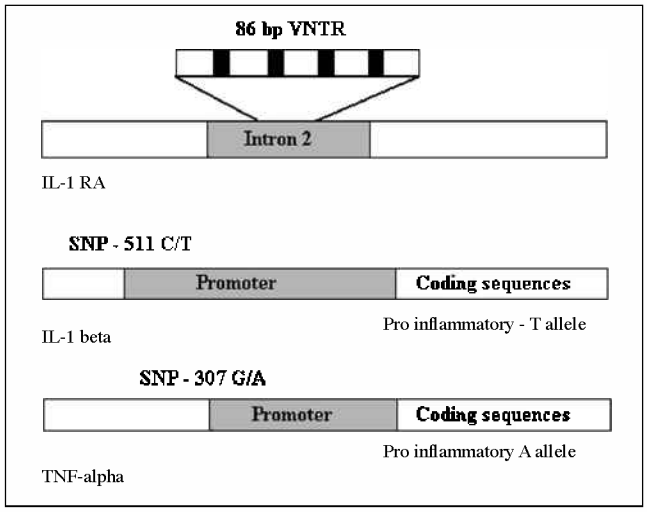

Fig 1. Diagram shows the site of polymorphism and the nucleotide substitution in the cytokine genes.

Table I. Target sequence, primer sequence and restriction enzymes of the cytokine gene polymorphisms.

Target sequence	Primer sequence	Site of polymorphism	Restriction enzyme
IL-1 RA	(F)-5' CTC AGC AAC ACT CCT AT 3'	Intron 2 (VNTR)	–
	(R)5' TCC TGG TCT GCA GGT AA 3'		
IL-1β	(F) 5' TGG CAT TGA TCT GGT TCA ATC 3'	C-511T	*Ava I*
	(R) 5' GTT TAG GAA TCT TCC CAC TT 3'		
TNF-α	(F) 5' GAG GCA ATA GGT TTT GAG GGC CAT 3'	G-308A	*Nco I*
	(R) 5' GGG ACA CAC AAG CAT CAA G 3'		

Genomic DNA was retrieved from the peripheral blood by the salting out method.[18] Cytokine gene polymorphisms were genotyped by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. Fig. 1 is a schematic illustration of polymorphisms in the genes. The primer sequences and the restriction enzymes are shown in Table I. The IL-1 RA intron 2 polymorphism was analysed by PCR using the primer sequence noted in Table I. PCR conditions were as follows: 95°C for 5 minutes, then 35 cycles of 95°C for 5 minutes, 50°C for 30 s, 72°C for 30 s and a final extension of 72°C for 5 minutes. The PCR products were analysed by electrophoresis on 2% agarose gel stained with ethidium bromide. Allele A (4 repeats) was 410 bp, allele B (2 repeats) was 240 bp, allele D (5 repeats) was 500 bp, allele E (3 repeats) was 325 bp and allele C (6 repeats) was 595 bp in length. Allele B was taken as the pro-inflammatory allele.

For RFLP analysis of the -511 IL-1β polymorphism, the region containing the polymorphic site was amplified using the primer sequences as noted in Table I. PCR conditions were as follows: 95°C for 5 minutes, then 35 cycles of 95°C for 30 s, 55°C for 30 s, 72°C for 30 s and a final extension of 72°C for 5 minutes. The products were digested with 10 U of *Ava*1 at 37°C for 3 h. Fragments were analysed by electrophoresis on 3% agarose gel and stained with ethidium bromide. This yielded products of 304 bp (TT allele), 190 bp and 104 bp (CC allele) and 304, 190 and 104 bp (CT allele) (Fig. 2). The T allele was considered the pro-inflammatory allele.

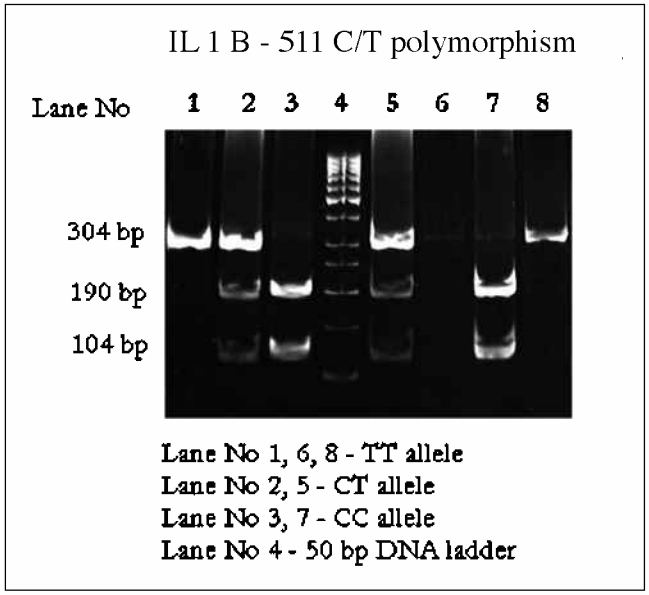

Fig 2. Gel picture of the genotyping of the IL-1 β C/T – 511 C/T polymorphism.

For RFLP analysis of the -308 TNF-α polymorphism, the region containing the polymorphic site was amplified using the primer sequence as stated in Table I. PCR conditions were as follows: 95°C for 5 minutes, then 35 cycles of 94°C for 30 s, 56°C for 30 s, 72°C for 30 s and a final extension of 72°C for 5 minutes. The products were digested with 10 U of *Nco*1 at 37°C for 3 h. Fragments were analysed by electrophoresis on 15% polyacrylamide gel and stained with ethidium bromide. This yielded products of 107 bp (AA allele), 87 bp and 20 bp (GG allele) and 107, 87 and 20 bp (AG allele). The A allele was considered pro-inflammatory. All PCR reactions were performed in a Peltier Thermal Cycler (MJ Research Inc, Waltham, MA, USA). The association between the clinical, endoscopical and histological findings was assessed by means of the χ^2 test for trend. A probability value of $p \leq 0.05$ was considered to be statistically significant.

RESULTS

69 male and 51 female patients were included in the study. The mean age of the patients was 35.9 years (range 16–70 years). The mean age of the male patients was 37.7 years (range 16–67 years). The mean age of the female patients was 34.0 years (range 16–70 years). The maximum number of patients was seen between the ages of 29 and 40 years, with a secondary peak between the ages of 49 and 54 years. 68 antral biopsies showed *H. pylori* on histopathological examination. The presence of *H. pylori* anywhere in the biopsies was taken as evidence of an *H. pylori* infection. In addition to the demonstration of *H. pylori* on the biopsy, the antibody titres against the CagA antigen and the VacA antigen were analysed by ELISA and Western Blotting, respectively. It was seen that even though *H. pylori* was absent in some of the biopsies analysed, the anti CagA titres were very high or the

Table II. Comparison between the IL-1 RA alleles and the various inflammatory parameters.

Inflammatory parameters	Grade	IL-1 RA genotypes		
		AA	AB	BB
Neutrophilic infiltrate	Nil	23	17	1
	Mild	32	17	2
	Moderate	7	11	2
	Marked	5	3	0
Lymphocytic infiltrate	Mild	18	8	1
	Moderate	20	15	0
	Marked	29	25	4
Glandular atrophy	Nil	31	23	2
	Mild	11	4	0
	Moderate	15	9	1
	Marked	10	12	2
Intestinal metaplasia	Nil	56	38	3
	Mild	11	9	2
	Moderate	0	1	0
Plasma cell infiltrate	Mild	16	10	1
	Moderate	25	14	0
	Marked	26	24	4
Mast cell infiltrate	Nil	32	16	1
	Mild	17	21	2
	Moderate	9	7	1
	Marked	9	4	1

antibody against the VacA antigen was strongly positive in those cases. This indicated that all the biopsies analysed were positive for *H. pylori* infection. Since none of the patients had taken *H. pylori* eradication therapy, it was concluded that all the patients under study had evidence of a continuing *H. pylori* infection. This combined data concluded that evidence of *H. pylori* infection was seen in 100% of the patients.

79 patients showed the presence of neutrophils on the biopsy. Of these, 51 had a mild neutrophilic infiltrate, 20 had a moderate and eight patients had a marked neutrophilic inflammatory infiltrate (64.6%, 25.3% and 10.1%, respectively). Of the 120 biopsies evaluated, surface ulceration was seen in 25 cases (21.0%) and foveolitis was seen in 50 patients (41.7%). 58 of the 120 biopsies showed a marked lymphocytic inflammatory infiltrate (49.8%), 35 patients showed a moderate infiltrate (28.3%), and 27 showed a mild chronic inflammatory infiltrate (21.6%). Of the 120 patients, 54 had a marked plasmacytic inflammatory infiltrate, 39 had a moderate infiltrate and 27 had a mild plasma cell infiltrate. (45.0%, 32.5% and 22.5%, respectively). Of the 120 biopsies evaluated, eosinophils were seen in 69 patients. 59 patients showed a mild eosinophilic inflammatory infiltrate, nine showed a moderate and only one patient showed a marked eosinophilic infiltrate. Of the 120 patients, 14 showed a marked mast cell infiltrate, 17 a moderate mast cell infiltrate and 40 a mild mast cell infiltrate. 49 patients did not show any mast cells on the biopsy. 46 of 120 patients had lymphoid follicles visualised on histopathology. Two patients had grade 4 follicles, 19 patients had grade 3 follicles, and 25 patients had grade 2 follicles. Gastric atrophy of varying degrees was seen in a total of 64 patients. Mild atrophy was seen in 15 patients, moderate atrophy in 25 patients, and marked atrophy in 24 patients. 23 cases showed the presence of intestinal metaplasia. 22 showed mild metaplasia, while one case showed moderate metaplasia. There were no cases of marked intestinal metaplasia.

When the IL-1 RA VNTR polymorphism was analysed, it was found that the A allele was the commonest allele seen in the patients (72.1%). The next commonest allele was the B allele (24.6%). These were followed by the D and E alleles, which had a frequency of 2.9% and 0.4% in the patient population, respectively. The commonest genotype was the AA genotype, which was seen in 50.8% of the patients. This was followed by the AB genotype, which was seen in 37.5% of the patients. The BB genotype was relatively rare and it was seen in 6 patients (5.0 %). In IL-1 RA, the B allele was the pro-inflammatory allele (Table II). Of the 53 patients who showed the B allele, 35 showed the concomitant

Table III. Comparison between the IL-1β alleles and the various inflammatory parameters.

Inflammatory parameters	Grade	IL-1β genotypes		
		CC	CT	TT
Neutrophilic infiltrate	Nil	7	19	15
	Mild	7	27	17
	Moderate	6	13	1
	Marked	0	5	3
Lymphocytic infiltrate	Mild	3	12	12
	Moderate	7	20	8
	Marked	10	32	16
Glandular atrophy	Nil	7	31	18
	Mild	3	8	4
	Moderate	7	11	7
	Marked	3	14	7
Intestinal metaplasia	Nil	18	52	27
	Mild	2	11	9
	Moderate	0	1	0
Plasma cell infiltrate	Mild	2	13	12
	Moderate	10	18	11
	Marked	8	33	13
Mast cell infiltrate	Nil	8	25	16
	Mild	5	25	10
	Moderate	5	6	6
	Marked	2	8	4

presence of neutrophils (66.0%). Of the 67 patients with the AA genotype, 44 showed the concomitant presence of neutrophils (64.17 %). There was no statistical difference between the groups. However 80% of the patients with the BB genotype showed the presence of neutrophils (four of five patients).

When the relationship of the chronic inflammatory infiltrate and the B allele was analysed, it was seen that of the 53 patients with the B allele, 29 (54.7%) and 28 (52.8%) had a marked lymphocytic and plasmacytic infiltrate, respectively. In the 67 patients who showed the presence of the AA genotype, 29 (43.3%) and 26 (38.8%) had a marked lymphocytic and plasmacytic infiltrate respectively. However, the BB genotype was seen in four of five patients with a marked chronic inflammatory infiltrate. When the relationship of the glandular atrophy and eosinophilic infiltrate was analysed in relation to the pro-inflammatory B allele, it was seen that glandular atrophy was seen in 28 cases (52.8%) and eosinophils in 34 cases (64.2%). Of the 67 patients showing the AA genotype, atrophy was seen in 36 patients (53.7%) and eosinophils in 35 patients (52.2%). The BB genotype showed glandular atrophy and an eosinophilic infiltrate in three and two patients, respectively.

When the relationship of the grade of intestinal metaplasia and the *H. pylori* density were analysed in relation to the pro-inflammatory B allele, it was seen that intestinal metaplasia was seen in 12 cases (22.6%) and *H. pylori* in 35 cases (66.0%). Of the 67 patients showing the AA genotype, intestinal metaplasia was seen in 11 patients (16.4%) and *H. pylori* in 33 patients (49.3%). The BB genotype showed intestinal metaplasia and *H. pylori* in two and five patients, respectively. There was no association of the pro-inflammatory or the anti-inflammatory allele of IL-1 RA with any of the inflammatory parameters, as evaluated by histopathology. However, when one considers the BB genotype, it can be seen that the neutrophilic and chronic inflammatory cell infiltrate are seen in 80% of the patients with the BB allele. However, the number of cases is too small to arrive at a statistical conclusion. When the IL-1β gene polymorphisms were analysed, it was seen that the pro-inflammatory T allele was seen in 100 patients (36 with the TT genotype and 64 with the CT genotype) (Table III).

Of the 100 patients who showed the presence of the T allele, 66 showed the concomitant presence of neutrophils (66%). Of the 20 patients with the CC genotype, 13 showed the concomitant presence of neutrophils (65%). There was no statistical difference between the groups. When the relationship of the chronic inflammatory infiltrate and the T allele was analysed, it was seen that of the 100 patients with the T allele, 48 and 46 had a marked

Table IV. Comparison between the TNF-α alleles and the various inflammatory parameters.

Inflammatory parameters	Grade	TNF-α genotypes		
		GG	AG	AA
Neutrophilic infiltrate	Nil	32	8	1
	Mild	42	7	2
	Moderate	17	2	1
	Marked	7	1	0
Lymphocytic infiltrate	Mild	23	3	1
	Moderate	27	6	2
	Marked	48	9	1
Glandular atrophy	Nil	48	7	1
	Mild	12	3	0
	Moderate	21	2	2
	Marked	17	6	1
Intestinal metaplasia	Nil	78	15	4
	Mild	19	3	0
	Moderate	1	0	0
Plasma cell infiltrate	Mild	22	4	1
	Moderate	30	7	2
	Marked	46	7	1
Mast cell infiltrate	Nil	37	11	1
	Mild	32	5	3
	Moderate	16	1	0
	Marked	13	1	0

lymphocytic and plasmacytic infiltrate, respectively (48% and 46%, respectively). In the 20 patients who showed the presence of the CC genotype, ten and eight had a marked lymphocytic and plasmacytic infiltrate, respectively (50% and 40%, respectively). There was no significant difference between the patients with the pro-inflammatory and anti-inflammatory alleles, and the grade of the marked chronic inflammation.

When the relationship of the glandular atrophy and eosinophilic infiltrate was analysed in relation to the pro-inflammatory T allele, it was seen that glandular atrophy was seen in 51 cases (51%) and eosinophils in 58 cases (58%). Of the 20 patients showing the CC genotype, atrophy was seen in 13 patients (65%) and eosinophils in 11 patients (55%). When the relationship of the grade of intestinal metaplasia and the *H. pylori* density were analysed in relation to the pro-inflammatory T allele, it was seen that intestinal metaplasia was seen in 21 cases (21%) and *H. pylori* in 58 cases (58%). Of the 20 patients showing the CC genotype, intestinal metaplasia was seen in two patients (10%) and *H. pylori* in ten patients (50%). There was no difference between the pro- and anti-inflammatory alleles with the grade of intestinal metaplasia or the *H. pylori* infiltrate. When the relationships between the pro- and anti-inflammatory polymorphisms and the various inflammatory parameters were analysed, it was seen that there was no association of the pro-inflammatory or the anti-inflammatory allele of IL-1β with any of the inflammatory parameters as evaluated by histopathology.

When the TNF-α polymorphisms were analysed, the pro-inflammatory A allele was seen in 22 patients. The AG allele was seen in 18 patients and the AA allele was seen in four patients. The anti-inflammatory GG allele was seen in 98 patients. Of the 22 patients who showed the presence of the A allele, 13 showed the concomitant presence of neutrophils (59.1%). Of the 98 patients with the GG genotype, 66 showed the concomitant presence of neutrophils (67.3%). There was no statistical difference between the groups. When the relationship of the chronic inflammatory infiltrate and the A allele was analysed, it was seen that of the 22 patients with the A allele, ten and eight had a marked lymphocytic and plasmacytic infiltrate, respectively (45.5% and 36.4%, respectively). In the 98 patients who showed the presence of the GG genotype, 48 and 46 had a marked lymphocytic and plasmacytic infiltrate, respectively (48.9% and 46.9%, respectively). There was no significant difference between the patients with the pro-inflammatory and anti-inflammatory alleles and the grade of the marked chronic inflammation.

When the relationship of the glandular atrophy and eosinophilic infiltrate was analysed in relation to the pro-inflammatory A allele, glandular atrophy was seen in 14 cases (63.63 %) and eosinophils in 13 cases (59.1%). Of the 98 patients showing the GG genotype, atrophy was seen in 50 patients (51.0%) and eosinophils in 56 patients (57.1%). When the relationship of the grade of intestinal metaplasia and the *H. pylori* density were analysed in relation to the pro-inflammatory A allele, intestinal metaplasia was seen in three cases (13.6%) and *H. pylori* in ten cases (45.5%). Of the 98 patients showing the AA genotype, intestinal metaplasia was seen in 20 patients (20.5%) and *H. pylori* in 58 patients (59.2%). There was no association between the pro- and anti-inflammatory alleles with the grade of intestinal metaplasia or the *H. pylori* infiltrate (Table IV).

When the relationships between the pro- and anti-inflammatory polymorphisms and the various inflammatory parameters were analysed, there was no association of the pro-inflammatory or the anti-inflammatory alleles of any of the cytokine gene polymorphisms with the inflammatory parameters as evaluated by histopathology. We considered the confounding role of the presence of *H. pylori* in the evaluated biopsies. In order to remove this bias, the data was re-analysed in the *H. pylori* positive biopsies only. However, there was again no relationship between the pro-inflammatory cytokine gene polymorphisms and the degree of inflammation.

DISCUSSION

It is now increasingly clear that the key pathophysiological event in *H. pylori* infection is the development of the inflammatory response. Bacteria or their products trigger this inflammatory process and the main mediators are the cytokines. An impressive cytokine cascade is the result of *H. pylori* infection with IL-1β at the centre.[19] The cytokine IL-1β induces the expression of other genes like TNF-α, IL-2, IL-6 and IL-12.[4] The amount of cytokine produced is dependant on the pro-inflammatory polymorphisms. Several studies have shown that pro-inflammatory polymorphisms are associated with increased secretions of cytokines in vitro.[3,20-22] The effect of *H. pylori* infection on cytokine secretion is as follows. Initially, IL-1β secretion is seen as being influenced by the genetic polymorphisms. This is followed by TNF-α secretion. The effect of these secretions is to contribute to the defence against *H. pylori*. However, as an added effect, the cytokines, particularly IL-1β, are powerful inhibitors of acid secretion. This causes a relative hypochlorhydria in the gastric corpus.[4] It is known that *H. pylori* infection occurs preferentially in areas of the stomach that have a higher pH.[23] The effect of the corporal hypochlorhydria is to allow the organism to colonise a wider niche, leading to a more aggressive gastritis that accelerates the development of gastric atrophy. Since atrophy is a precursor lesion of carcinoma, it is now clear why pro-inflammatory cytokine polymorphisms lead to a severe gastric pathology and gastric carcinoma in Caucasian populations.

In our study, there was no association between the pro-inflammatory polymorphisms and histopathological severity of gastritis in an Indian population. This was seen even when the confounding factor of the *H. pylori* absence/presence in the biopsy specimen was removed from the analysis. A similar finding has been reported in another Asian population[3] where there was no significant association between the different IL-1β and IL-1 RA genotypes and neutrophil infiltrate, *H. pylori* density and atrophy in the antrum. Our reasons for this apparent discordance between the Indian and Caucasian populations are purely speculative. We hypothesise that in Indians, the lack of association between pro-inflammatory polymorphisms and histopathological severity means that perhaps the levels of cytokines secreted in the mucosa are less than the Caucasian populations. This leads to a lesser degree of inflammation and hence there is no eradication of the organism. However, the relatively low cytokine secretion also has a beneficial effect. There is relatively less hypochlorhydria and hence the organisms are not able to colonise the corpus. This translates to a lesser degree of atrophy and gastric carcinoma. A damaging fallout of the high acid secretion is an increased incidence of duodenal ulceration, which is seen in Asian Indians. This would explain all the paradoxes outlined earlier: The high degree of colonisation in Indians is because of a lack of an association between the pro-inflammatory polymorphisms and severe gastritis, which translates to a relatively low cytokine secretion. This allows the organism to exist in the antrum. The low incidence of gastric cancer in spite of a high antral colonisation is again because of the low cytokine levels. There is no decrease in acid secretion because the cytokine levels are not high. The *H. pylori* thus cannot migrate to the corpus because there is still a high acid secretion there. Hence, the *H. pylori* colonisation is restricted to the antrum. Therefore, there is less severe histological change in the entire stomach, relatively less development of atrophy and consequently a lesser incidence of gastric carcinoma. However, the acid secretion is not without its attendant problems: it leads to duodenal ulceration, which would explain the higher incidence of duodenal ulcers in Asian Indians as compared to Caucasian populations.

In conclusion, our study has shown that the differences in *H. pylori* infection in Indian and Caucasian populations appear to be determined by the host genetic profile. The lack of pro-inflammatory polymorphisms in Indians would account for the high degree of colonisation

by *H. pylori* and the relatively high incidence of duodenal ulceration. However, it also has a positive effect: it would account for the relatively low incidence of gastric carcinoma in the Indian population.

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