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Inverse association between a pro-inflammatory genetic profile and *Helicobacter pylori* seropositivity among patients with chronic atrophic gastritis: Enhanced elimination of the infection during disease progression?

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ABSTRACT

Background: *Helicobacter pylori* infection is a key risk factor for chronic atrophic gastritis (CAG), an established precursor of gastric cancer. There is increasing evidence of frequent clearance of the infection during progression of CAG. We aimed to assess the association between host inflammatory polymorphisms and *H. pylori* seropositivity among CAG patients from Germany.

Methods: In the baseline examination of ESTHER, a population-based study conducted in Saarland, serum pepsinogens I and II and *H. pylori* serostatus were measured by ELISA, and selected genetic polymorphisms (*IL1A* C-889T, *IL1B* C-511T, *IL1RN* A9589T, *IL8* T-251A, *IL10* T-819C, *IL10* A-1082G, *LTA* C+80A and *TNFA* G-308A) were assessed by Pyrosequencing™ for 534 serologically defined CAG cases.

Results: *H. pylori* seropositivity strongly decreased with disease severity, which is defined by quintiles of serum pepsinogen I, from higher than 90% in the least severe cases to hardly over 50% in the most severe cases. The pro-inflammatory genotypes *IL10* -819CC and *IL1RN* 9589TT were significantly associated with decreased *H. pylori* seroprevalences with odds ratios of 0.45 (95% confidence interval (CI): 0.23–0.88) and 0.41 (95% CI: 0.18–0.92), respectively, after controlling for age, sex and disease severity. *H. pylori* seropositivity decreased with the number of pro-inflammatory genotypes ($p < 0.01$).

Conclusions: Our results disclose a clear inverse association between a pro-inflammatory genetic profile and *H. pylori* seropositivity among cases with CAG, supporting suggestions of enhanced elimination of *H. pylori* during the development of the disease.

1. Introduction

Helicobacter pylori infection, which is prevalent in about half of the world's population, is known to be a key cause to trigger chronic gastric inflammation that progresses to atrophy, metaplasia, dysplasia and gastric cancer.[1,2] Infection is mainly acquired during early childhood and chronically persistent among adults in the absence of specific treatment.[3] However, there is increasing evidence of frequent clearance of the infection during progression of chronic atrophic gastritis (CAG).[4]

Gene polymorphisms of inflammatory cytokines have been widely studied as potential predictors both for susceptibility to *H. pylori* infection and for the chronic inflammation

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leading to gastric cancer.[5] Host susceptibility to *H. pylori* infection has been associated with genotypes of interleukin-1α (IL-1α), interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α).[6,7] Pertinent cross-sectional studies conducted in the general population, where clearance of the infection is rare, mostly reflect the role of genetic polymorphisms in acquisition of chronic infection.[8] By contrast, the role of genetic polymorphisms in clearing the infection might best be studied in patients with CAG, most of whom have been infected at some time and a substantial proportion of whom are getting their infection cleared in the course of disease progression. To our knowledge, however, the role of genetic polymorphisms in this process has not been specially addressed in detail so far.

The objective of this study was to assess the association of selected inflammatory polymorphisms with *H. pylori* prevalence in CAG cases in a large population-based study among older adults from Germany.

2. Materials and methods

2.1. Study population

Our analyses are based on baseline data of the ESTHER study, a large population-based cohort study conducted among older adults in Germany to investigate new avenues of prevention and early detection of chronic diseases in the elderly. Details of the study design have been described elsewhere.[9] Briefly, 9953 participants (45% males), aged 50–74 years (mean age: 62 years) were recruited between July 2000 and December 2002 by their general practitioners during a general health check-up in Saarland, a state in the south-west of Germany. The study was approved by the ethics committees of the medical faculty of the University of Heidelberg and of the medical board of the state of Saarland. Written informed consent was obtained from each participant. Our analyses focus on all 534 cases with serologically defined CAG (see below).

2.2. Data collection

2.2.1. Questionnaires

A standardised questionnaire was completed by every participant, providing information on socio-demographic characteristics, medical history, health status, family history and lifestyle factors. Current alcohol consumption was assessed regarding the amount (consumption volumes typical for southern Germany) of average alcohol consumption within the past 12 months. Smoking status was classified into three groups (current, former and never smokers).

2.2.2. Serological examinations

Serum samples were obtained from all participants and stored at –80 °C. Serum concentrations of pepsinogens (PGs) I and II were measured by ELISA (Biohit, Helsinki, Finland) to define CAG. Applying the most commonly used serological definition, CAG was assumed to be present when PG I < 70 ng/mL and PG I/PG II < 3.[10] In addition, so-defined CAG cases were stratified according to quintiles of serum PG I in order to reflect disease severity. Status of *H. pylori* infection was assessed serologically by a commercial ELISA based on immunoglobulin G (IgG) antibodies against *H. pylori* (ravo Diagnostika, Freiburg, Germany). Classification of infection status followed the manufacturer's instructions, borderline results were treated as negative.

2.2.3. Genotyping

Eight single nucleotide polymorphisms (SNPs) in 7 cytokine genes were assessed: *IL1A* C-889T (rs1800587), *IL1B* C-511T (rs16944), *IL1RN* A9589T (rs454078), *TNFA* G-308A (rs1800629), *LTA* C+80A (rs2239704), *IL8* T-251A (rs4073), *IL10* T-819C (rs1800871) and *IL10* A-1082G (rs1800896). Genotyping of the polymorphisms was performed by Pyrosequencing™ technology (Biotage, Uppsala, Sweden).[11] Primer sequences can be obtained from the authors upon request. Repeated measurements of a random 6% subset of samples yielded >99.5% identical genotypes. Based on previous publications, *IL1A* -889TT, *IL1B* -511TT, *IL1RN* 9589TT, *IL8* -251AA, *IL10* -819CC, *IL10* -1082AA, *LTA* +80AA and *TNFA* -308AA were interpreted as pro-inflammatory genotypes.

2.3. Statistical analysis

Differences in the distribution of demographic variables and lifestyle factors between *H. pylori* seropositive and seronegative subjects were assessed by χ^2 tests. Hardy–Weinberg Equilibrium (HWE) was tested using asymptotic Pearson's χ^2 tests for each SNP. Unconditional logistic regression analysis was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CI) for *H. pylori* seropositivity according to the presence of pro-inflammatory genotypes using co-dominant, dominant and recessive models, respectively, adjusting for age, sex and severity of CAG. Latter was employed to assess the potential impact of the genetic factors on *H pylori* persistence independent of their potential relevance for disease severity. Linkage disequilibrium (LD) was assessed by Linkage Disequilibrium Analyzer software. Haplotypes were reconstructed from genotype data using Unphased software (Version 3.0.12) (http://www.stat.washington.edu/stephens/software.html). Associations between inferred haplotypes and *H. pylori* serostatus were likewise estimated by unconditional logistic regression adjusting for age, sex and disease severity. To estimate the combined impact of a pro-inflammatory profile, odds of *H. pylori* prevalence were assessed according to the number of the pro-inflammatory genotypes simultaneously carried by the same subject.

All statistical analyses were carried out using SAS statistical software, release 9.1.

3. Results

H. pylori serostatus according to the characteristics of the study population is provided in Table 1. Overall, *H. pylori* prevalence was 75.1% in 534 serologically defined CAG cases identified at baseline examination of ESTHER study. No significant association with any of the assessed factors was observed. However, as shown in Fig. 1, prevalence of *H. pylori* infection strongly varied according to disease severity defined by quintiles of serum PG I. *H. pylori* seropositivity exceeded 90% in cases with highest serum PG I levels (least severe cases) and sharply decreased to hardly over 50% in cases with lowest serum PG I levels (most severe cases).

Table 1 – *H. pylori* serostatus in the study population.

	Hp+/N[a]	(%)	p[b]
Total	401/534	75.1	
Age			
50–54 years	33/44	75.0	0.06
55–59 years	41/59	69.4	
60–64 years	106/132	80.3	
65–69 years	131/165	79.4	
70–74 years	90/134	67.2	
Sex			
Female	227/310	73.2	0.24
Male	174/224	77.7	
Education			
⩽9 years	312/408	76.5	0.10
10–11 years	41/64	64.1	
⩾12 years	34/44	77.3	
Family history of gastric cancer			
No	373/498	74.9	0.70
Yes	28/36	77.8	
Alcohol drinking			
No alcohol	144/199	72.4	0.64
<60 g/week	90/116	77.6	
60–140 g/week	78/106	73.6	
>140 g/week	48/61	78.7	
Smoking status			
Never smoker	219/292	75.0	0.31
Former smoker	115/158	72.8	
Current smoker	52/63	82.5	

Abbreviations: Hp+, *H. pylori* seropositive.
a Sum may not always add up to total because of missing values.
b χ^2 test for difference.

Genotyping data for each SNP were successfully obtained for ⩾95% of the subjects. The genotype distribution for each of the 8 assessed SNPs was in HWE in the study population (data not shown). The associations between SNPs and *H. pylori* serostatus in co-dominant, dominant and recessive models, respectively, after control for age, sex and disease severity are shown in Table 2. The pro-inflammatory genotypes *IL10* –819CC and *IL1RN* 9589TT were significantly associated with reduced *H. pylori* prevalence with adjusted ORs of 0.45 (95% CI: 0.23–0.88) and 0.41 (95% CI: 0.18–0.92), respectively. A slightly increased prevalence of *H. pylori* infection was observed for *ILB* –511TT/CT genotypes carrying cases compared with the most frequent less-inflammatory CC genotype carriers.

All the three loci in IL1 cluster genes (*IL1A* C-889T, *IL1B* C-511T and *IL1RN* A9589T) were in LD with each other in our study population. The same was true for the genotype distributions of *IL10* T-819C and A-1082G, and lymphotoxin-α gene (*LTA*) C+80A and *TNFA* G-308A, respectively. In comparison with the most common *IL1A/IL1B/IL1RN* haplotype CCA (consisting of the common allele from each polymorphic site), haplotypes containing at least one variant allele were not associated with *H. pylori* seropositivity (Table 3). The CA haplotype of *IL10* was marginally associated with decreased *H. pylori* prevalence with an adjusted OR of 0.70 (95% CI: 0.49–1.00). No difference in the distribution of *LTA/TNFA* haplotypes was observed between *H. pylori* seropositive and seronegative cases.

Compared to individuals without pro-inflammatory genotypes, an increasing number of pro-inflammatory genotypes showed a strong inverse trend with *H. pylori* seropositivity in CAG cases (p for trend <0.01) (see Table 4).

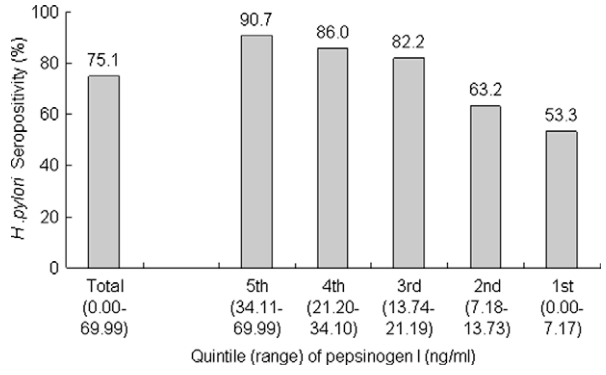

Fig. 1 – *H. pylori* prevalence among CAG cases by disease severity.

4. Discussion

To our knowledge, this is the first large-scale epidemiological study that evaluated the association of host pro-inflammatory polymorphisms with *H. pylori* seropositivity among CAG cases. Our results indicate a pro-inflammatory genetic profile to be associated with reduced prevalence of *H. pylori* infection in this group of patients, which is independent of its potential impact on the severity of disease.

In the past few years, cytokine gene polymorphisms have been linked to individual susceptibility to *H. pylori* infection and gastric carcinogenesis. However, their roles in the clearance of the bacteria during the development of the disease have received little attention. It has been suggested that the colonisation of the gastric mucosa by *H. pylori* initiates a chronic process from superficial inflammation to carcinogenesis. During the progression of CAG, clearance of the bacteria occurs due to the changed biotic microenvironment.[4,12] A humoral immune response to chronic *H. pylori* infection is elicited in nearly all *H. pylori*-infected individuals.[13] Levels of numerous cytokines are increased in the stomach, some of them, such as TNF-α, IL-1β, IL-6 and IL-8, have pro-inflammatory effects, whereas IL-10 is considered to have an important immune-suppressive effect.[14] It is therefore plausible that functional polymorphisms in genes encoding these cytokines may have an impact on *H. pylori* infection and persistence.

Our results indicate that almost all patients are infected with *H. pylori* in the early phase of CAG which is consistent with suggestions that the infection is a close to necessary condition for this disease. Our results further indicate a pro-inflammatory profile to be associated with decreased prevalence of *H. pylori* infection among CAG cases in a dose–response manner. This finding suggests a more effective clearance of *H. pylori* infection among cases carrying the pro-inflammatory profile.

Table 2 – Inflammatory genotypes and *H. pylori* serostatus.

Genotypes	*Hp*+/N[a]	(%)	OR (95% CI)[b]
IL1A C-889T (rs1800587)			
CC	206/276	74.6	Ref.
CT	162/213	76.1	1.06 (0.67–1.65)
TT	27/37	73.0	0.87 (0.37–2.01)
Dominant	TT + CT versus CC		1.02 (0.67–1.57)
Recessive	TT versus CT + CC		0.85 (0.37–1.93)
IL1B C-511T (rs16944)			
CC	187/263	71.1	Ref.
CT	167/205	81.5	**1.88 (1.17–3.02)**
TT	42/59	71.2	0.84 (0.43–1.65)
Dominant	TT + CT versus CC		**1.54 (1.00–2.36)**
Recessive	TT versus CT + CC		0.65 (0.34–1.25)
IL1RN A9589T (rs454078)			
AA	206/273	75.5	Ref.
AT	163/212	76.9	1.23 (0.78–1.94)
TT	26/39	66.7	**0.41 (0.18–0.92)**
Dominant	TT + AT versus AA		1.03 (0.67–1.58)
Recessive	TT versus AT + AA		**0.38 (0.17–0.82)**
IL8 T-251A (rs4073)			
TT	118/152	77.6	Ref.
TA	204/273	74.7	0.88 (0.53–1.47)
AA	73/100	73.0	0.73 (0.39–1.37)
Dominant	AA + TA versus TT		0.84 (0.52–1.36)
Recessive	AA versus TA + TT		0.86 (0.62–1.17)
IL10 T-819C (rs1800871)			
TT	220/283	77.7	Ref.
TC	149/200	74.5	0.89 (0.56–1.40)
CC	27/44	61.4	**0.44 (0.21–0.91)**
Dominant	CC + TC versus TT		0.77 (0.50–1.18)
Recessive	CC versus TC + TT		**0.46 (0.23–0.93)**
IL10 A-1082G (rs1800896)			
GG	92/109	84.4	Ref.
GA	180/246	73.2	0.60 (0.32–1.11)
AA	122/169	72.2	0.59 (0.31–1.13)
Dominant	AA + GA versus GG		0.59 (0.33–1.07)
Recessive	AA versus GA + GG		0.86 (0.55–1.35)
LTA C+80A (rs2239704)			
CC	122/156	78.2	Ref.
CA	189/253	74.7	0.97 (0.58–1.62)
AA	80/112	71.4	0.77 (0.42–1.42)
Dominant	AA + CA versus CC		0.90 (0.56–1.46)
Recessive	AA versus CA + CC		0.79 (0.47–1.32)
TNFA G-308A (rs1800629)			
GG	291/389	74.8	Ref.
GA	96/125	76.8	1.15 (0.69–1.91)
AA	9/13	69.2	0.53 (0.14–1.96)
Dominant	AA + GA versus GG		1.06 (0.65–1.73)
Recessive	AA versus GA + GG		0.51 (0.14–1.89)

Abbreviations: CI, confidence interval; *Hp*+, *H. pylori* seropositive and OR, odds ratio.
a Sum may not always add up to total because of missing data.
b Adjusted for age, sex and severity of CAG.

We observed a clear inverse association of the overall pro-inflammatory profile with *H. pylori* seropositivity in CAG cases, with significant associations seen for *IL10* A-1082G and *IL1RN* A9589T when individual genotypes were looked at. IL-10 is a multifunctional cytokine with great importance in balancing immune responses and a down regulatory function of pro-inflammatory cytokine (IL-1β and TNF-α) production.[15] Three polymorphisms in the 5′-flanking region of *IL10* at positions A-1082G, T-819C and A-592C were associated with high transcriptional promoter activity.[16] These polymorphisms and the respective haplotypes were suggested to be associated with host susceptibility to gastric cancer precur-

Table 3 – Frequencies of inferred haplotypes according to *H. pylori* serostatus.

IL1A C-889T	*IL1B* C-511T	*IL1RN* A9589T	*Hp*+/N	(%)	OR (95% CI)[c]
IL1A/IL1B/IL1RN haplotypes[a,b]					
C	C	A	265/357	74.2	Ref.
T	C	A	175/232	75.4	1.05 (0.70–1.58)
C	T	T	106/134	79.1	1.24 (0.74–2.08)
C	T	A	100/127	78.7	1.32 (0.76–2.30)
C	C	T	78/114	68.4	0.78 (0.46–1.33)
T-819C	A-1082G	*Hp*+/N	(%)		OR (95% CI) [c]
IL10 haplotypes[d]					
T	G	364/464	78.4		Ref.
T	A	224/300	74.7		0.89 (0.62–1.28)
C	A	200/284	70.4		0.70 (0.49–1.00)
LTA C+80A	*TNFA* G-308A	*Hp*+/N	(%)		OR (95% CI)[c]
LTA/TNFA haplotypes[e]					
C	G	363/475	76.4		Ref.
A	G	309/422	73.2		0.86 (0.61–1.20)
C	A	70/90	77.8		0.90 (0.47–1.74)
A	A	40/55	72.7		0.93 (0.44–1.94)

Abbreviations: CI, confidence interval; *Hp*+, *H. pylori* seropositive and OR, odds ratio.
a Haplotypes (TTA, TTT and TCT) with frequencies <5% are not reported.
b All the three loci were in LD with each other in the study population ($r^2 = 0.02$ and $D' = 0.35$ for IL1A C-889T/IL1B C-511T; $r^2 = 0.03$ and $D' = 0.42$ for IL1A C-889T/IL1RN A9589T; $r^2 = 0.11$ and $D' = 0.36$ for IL1B C-511T/IL1RN A9589T).
c Adjusted for age, sex and severity of CAG.
d These two loci were in LD ($r^2 = 0.30$ and $D' = 1.00$).
e These two loci were in LD ($r^2 = 0.01$ and $D' = 0.20$).

Table 4 – Combined impact of the pro-inflammatory genotypes on *H. pylori* serostatus.

No. of pro-inflammatory genotypes[a]	*Hp*+/N[b]	(%)	OR (95% CI)[c]
0	136/166	81.9	Ref.
1	145/197	73.6	**0.55 (0.33–0.93)**
2	74/105	70.5	**0.47 (0.26–0.87)**
⩾3	33/48	68.8	**0.43 (0.20–0.94)**
p for linear trend			$p < 0.01$

Abbreviations: CI, confidence interval; *Hp*+, *H. pylori* seropositive and OR, odds ratio.
a Pro-inflammatory genotypes including *IL1A* –889TT, *IL1B* –511TT, *IL1RN* 9589TT, *IL8* –251AA, *IL10* –819CC, *IL10* –1082AA, *LTA* +80AA and *TNFA* –308AA.
b Sum may not always add up to total because of missing data.
c Adjusted for age, sex and severity of CAG.

sors and carcinogenesis in different populations.[17,18] However, no significant association with host susceptibility to *H. pylori* infection was reported in several studies among children and adult populations.[19,20] In our study, *IL10* pro-inflammatory genotype –819CC was significantly associated with reduced *H. pylori* prevalence in CAG cases, pointing to a potential major role in elimination of the infection. Animal models in which the colonisation of the gastric mucosa by *H. pylori* was successfully and rapidly eliminated in mice that are deficient in IL-10 also suggested an important role of IL-10 in regulating immune response to *H. pylori* infection.[21]

IL1 gene cluster (*IL1A*, *IL1B* and *IL1RN*) polymorphisms have been widely studied as predictors for host susceptibility to *H. pylori* infection and the development of clinical outcomes. IL-1RN (interleukin 1 receptor antagonist) inhibits the activities of IL-1α and IL-1β, and modulates a variety of IL-1-related immune and inflammatory responses. The IL-1RN gene has a penta-allelic variable number tandem repeat polymorphism which has been associated with GC risk[22] but not *H. pylori* infection.[6,23] To our knowledge, this is the first study that provided evidence for an association of the IL-1RN genetic polymorphism (A9589T) with *H. pylori* serostatus. *IL1A* –889T allele, expressing a higher level of IL-1α,[24] was found to be associated with a lower risk of *H. pylori* infection among Jamaican children.[20] In our study, no association was seen between this allele and *H. pylori* serostatus in CAG cases. IL-1β plays a role both as a pro-inflammatory cytokine and as an inhibitor of gastric acid secretion.[25] Whether the stronger inflammatory response induced by its genetic variants will result in the elimination of *H. pylori* or whether the higher

intragastric pH will render people more susceptible to *H. pylori* infection remains unclear. *IL1B* –511T allele and –31T allele have been reported to exhibit higher expression levels of IL-1β[26] and were associated with increased host susceptibility to *H. pylori* infection among Asians.[6,27] However, some other studies failed to confirm such associations.[28,29] In our study, we found an increased prevalence of *H. pylori* in CAG cases carrying the pro-inflammatory allele. A possible explanation might be that increased gastric juice pH induced by higher level of IL-1β may support the persistence of the bacteria.[26]

In addition, we repeated the analyses among 534 non-CAG controls (frequency matched to CAG cases on sex and 5-year age group). Among the 8 assessed genotypes, significant association with *H. pylori* seropositivity was observed only for *IL1A* –889TT, which may be partly explained by IL-1α-induced inhibition of gastric acid secretion.[30] Furthermore, the inverse relationship between an increasing number of pro-inflammatory genotypes and *H. pylori* seropositivity observed among CAG cases was not found among non-CAG controls. These patterns suggest that the pro-inflammatory genetic profile may play a more important role in clearing the *H. pylori* infection during the development of *H. pylori*-related diseases than in modulating host susceptibility to *H. pylori* infection.

In the interpretation of our data, some limitations have to be considered. First, due to the cross-sectional study design, disease associated loss of *H. pylori* colonisation could not be observed directly, even though it is strongly suggested by the observed pattern of decreasing *H. pylori* seropositivity with increasing severity of CAG. Second, even though disease severity (defined by quintiles of serum PG I level) was controlled for in the analyses, we cannot determine with certainty from these cross-sectional data to what extent the relationship between pro-inflammatory profile and *H. pylori* seropositivity observed among CAG cases may still be mediated by disease-related changes of stomach environment. Longitudinal analyses are required to further elucidate the mechanism underlying the observed association. Third, the definition of CAG based on serum pepsinogen concentrations cannot be claimed to be perfect. However, high levels of agreement with classification by histological examination of biopsies have been observed,[31,32] even though the latter has been shown to bear considerable observer variation[33] and to suffer from sampling error.[34] In addition, an advantage of pepsinogen-based definition of CAG is that serological measurements are highly standardised and suitable for application in large-scale population-based studies. Fourth, we examined only 8 SNPs in 7 genes, the small number of selected SNPs may not reflect the whole picture of pro-inflammatory polymorphisms. However, we selected variants with strong indication of their functional relevance in relation to pro-inflammation phenotypes. Furthermore, no adjustment for multiple comparisons was made, and the possibility that the significant associations were due to chance has to be kept in mind. Further and larger studies are needed to investigate a broader range of polymorphisms in inflammatory genes.

In conclusion, our study supports the suggestion that a pro-inflammatory genetic profile may favour the elimination of *H. pylori* infection during the development of CAG. These results do not imply a protective effect of the pro-inflammatory profile with respect to gastric carcinogenesis. On the contrary, an increased risk of gastric cancer associated with a pro-inflammatory profile has been reported in multiple studies from different parts of the world.[35–37] Rather, a pro-inflammatory profile appears to be associated with more rapid progression of carcinogenesis accompanied by more frequent loss of *H. pylori* infection. Therefore, further functional studies and larger population-based prospective cohort studies are warranted to clarify the role of host inflammatory polymorphisms in *H. pylori* infection and *H. pylori*-related diseases.

Conflict of interest statement

None declared.

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