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Helicobacter pylori infection in patients with selective immunoglobulin a deficiency

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Summary

Selective immunoglobulin A (IgA) deficiency (IgAD) is the most common primary immunodeficiency in the western world. The aim of the study was to investigate the prevalence and clinical characteristics of *Helicobacter pylori*-infected dyspeptic patients with IgAD. Case samples were drawn from all subjects ≥ 12 years of age (n = 104729) who had undergone serum total IgA measurements during 2004–14 for any reason at Leumit Healthcare Services (Israel) and had serum total IgA < 0·07 g/l. The control group was comprised of a random sample of remaining patients with a case–control ratio of 10 controls for each case. The dyspeptic diseases were identified and retrieved from Leumit Health Care Services electronic database using specific ICD-9-CM diagnostic codes. The case group included 347 subjects and the control group 3470 subjects. There were no significant differences in the prevalence of patients with dyspepsia [84 (24·2%) *versus* 821 (23·6%) for cases and controls, respectively]. Additionally, there was no difference in a proportion of dyspeptic *H. pylori*-positive subjects [59 (17·1%) *versus* 524 (15·1%)] between the case and control groups. Only 59 (17%) among the 347 IgAD patients underwent gastroscopy. A significantly larger proportion of case subjects experienced several forms of gastritis [13 (61·9%) *versus* 38 (21·6%), $P < 0·001$), duodenal ulcers [seven (33·3%) *versus* 19 (10·8%); P = 0·01] and nodular lymphoid hyperplasia (NLH) [two (9·5%) *versus* none; P = 0·011]. IgAD is not associated with increased prevalence of *H. pylori*-associated dyspepsia; nevertheless, *H. pylori*-infected dyspeptic IgAD subjects experience more EGD-proved gastritis, duodenal ulcers and NLH.

Keywords: deficiency, IgA, immunoglobulin, *Helicobacter pylori*, selective

Introduction

IgA deficiency (IgAD) is the most common primary immunodeficiency in the western world [1], with prevalence rates ranging from 1 : 155 in Spain [2] to 1 : 18 550 in Japan [3]. In Israel IgAD prevalence is approximately 1 : 500–600 in the general population [1]. The current definition, established by the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies, defines the disorder as serum IgA levels < 0·07 g/l with normal IgM and IgG levels in individuals ≥ 4 years of age [4]. It appears to be a polygenic disorder and several of the genes involved have recently been identified [5].

Helicobacter pylori is a Gram-negative spiral bacterium that colonizes the gastrointestinal mucosa of its host and, despite a strong persistent humoral and cellular immune response to *H. pylori* at the local and systemic level, the organism persists for the lifetime of its host. Virtually all people carrying *H. pylori* have co-existing gastric inflammation; however, only a small percentage of colonized individuals develop clinically apparent disease [6]. Mucosal IgA and IgG are involved in the immune defence against *H. pylori* in infected patients. In contrast to IgG, IgA is transported into the gastric lumen and is responsible for first-line defence [7]. Mucosal IgA was not represented by serum IgA and IgG, and the *H. pylori*-specific mucosal IgA and IgG immune responses differ in antigen-recognition pattern [6,7]. Mucosal IgA specific for urease was found in patients with *H. pylori* gastritis [7]. Moreover, sampling of

gastric secretions from H. *pylori*-infected individuals revealed an active mucosal antibody response, primarily of the IgA isotype. This response was consistent with the predominance of secretory IgA (sIgA) in gastric secretions; however, sIgA anti-*H. pylori* antibodies were also found in saliva and breast milk [8]. Theoretically, sIgA anti-*H. pylori* antibodies can play some protective role against *H. pylori* infection. For example, children breastfed by mothers having high titres of specific anti-*H. pylori* sIgA in their milk were protected from infection for a longer period than children whose mothers had lower anti-*H. pylori* antibody titres [9].

sIgA can interfere with the ability of some enteric pathogens to establish infection [10] by inhibition of bacterial adherence [11]. However, the systemic antibody response and the sIgA response against *H. pylori* do not inhibit the organism from adhering to gastric cells *in vitro* [12].

Recently, we found that selective deficiency of another mucosal immunoglobulin E (IgE) in humans is associated with higher rates of *H. pylori*-associated gastritis and peptic duodenal ulcers [13].

The aim of the present study is to investigate the prevalence and clinical characteristics of *H. pylori*-infected patients with IgAD who presented with dyspeptic symptoms at the primary-care setting.

Materials and methods

Data source

This retrospective matched case–control study was based on data from Leumit Healthcare Services (Israel) Database. The health-care organization covers approximately 740 000 residents of Israel, and its electronic database includes comprehensive information on the insured population, such as demographic data and records of clinical visits; laboratory tests performed at a single centralized laboratory and diagnostic codes using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). This database was used to obtain information on diagnoses and laboratory results by means of cross-linkage using a unique patient identifier.

This study was approved by the Barzilai Medical Center and Leumit Healthcare Services Institutional Review Committee.

Subjects

The database was searched for all subjects aged $\geq$ 12 years who had undergone serum total IgA measurements during 2004–14 for any reason.

All patients identified with serum total IgA of $<$ 0·07 g/l were included in the case group. The control group was comprised of a random sample of remaining patients (serum total IgA $\geq$ 0·07 g/l), with a case–control ratio of 1 : 10. The randomization was performed using the Epi Info version 6 software (Atlanta, GA, USA) using simple random sampling. The dyspeptic diseases, diagnosed by the board-certificated family physicians and/or gastroenterologists during $\leq$ 5 years before serum total IgA testing, were identified and retrieved from the Leumit Healthcare Services' electronic database using specific ICD-9-CM diagnostic codes. Dyspepsia was diagnosed as a syndrome consisting of pain or discomfort centred in the upper abdomen (epigastric pain), burning, fullness, discomfort, nausea, vomiting and belching.

Patients were excluded from the study if one or more of the following criteria were documented in their electronic health record: common variable immunodeficiency (CVID), human immunodeficiency virus/acquired immunodeficiency syndrome, chronic systemic corticosteroid therapy, or on any other form of immunosuppressive therapy during the 4 weeks before serum total IgA measurement. Patients with alarm symptoms (weight loss, anaemia, haematemesis, melaena, abdominal tumour, use of non-steroidal anti-inflammatory drugs) were not included into the study.

IgM, IgA and IgG immunoglobulin measurements

Serum immunoglobulins (IgM, IgA, IgG, IgG1, IgG2, IgG3, IgG4) were measured by nephelometry (BN II System; Dade Behring, Deerfield, IL, USA).

Assessment of *H. pylori* infection

C^{13}-urea breath test (C^{13}-UBT) for *H. pylori* was performed in the central laboratory of Leumit Healthcare Services, Israel. Proton pump inhibitors, H2 antagonists and antibiotics were not permitted for 15 days before having the C^{13}-UBT performed. Trained nurses in regional laboratories performed the C^{13}-UBT, and the samples were analysed by a mass spectrometer (Analytical Precision 2003, Edinburgh, UK). The patients were given 75 mg urea labelled with C^{13} in 200 ml orange juice, and breath samples were collected at time 0 (before C^{13} intake) and 30 min later. The cut-off C^{12}/C^{13} at T30 min/T0 min was 3·5, according to referral laboratories and the manufacturer's instructions [14].

Oesophago-gastro-duodenoscopy (EGD)

EGD was performed by experienced board-certified gastroenterologists with video-oesophago-gastro-duodenoscope (Olympus Evis Smartage Gastro GIF V70 Serial; Olympus, Tokyo, Japan). Procedures were video-recorded and representative findings documented on high-resolution images using a software program.

H. pylori infection was evaluated by rapid urease test (RUT) and at histology. One biopsy from each patient was used for RUT immediately after removal, using the *H. pylori* ONE kit (GI Supply, Camp Hill, PA, USA). Multiple gastric biopsies (two from the antrum, two from body

Table 1. Clinical and laboratory characteristics of the subjects.

	Subjects with IgAD $n = 347$	Control $n = 3470$	P	Multiple logistic regression model OR (95% CI)
Sex; female, *n* (%)	159 (45·9%)	1594 (45·9%)	1	
Age (years ± s.d.)	34·1 ± 15·7	35·3 ± 16·1	0·71	
Serum IgA (mg/dl ± s.d.)	0·4 ± 0·2	114·1 ± 73·2	<0·001	
Serum total IgG (mg/dl ± s.d.)	1598 ± 359	1631 ± 483	0·215	
Serum IgG_1 (mg/dl ± s.d.)	1095 ± 537	1124 ± 671	0·435	
Serum IgG_2 (mg/dl ± s.d.)	591 ± 403	613 ± 458	0·388	
Serum IgG_3 (mg/dl ± s.d.)	121 ± 55	117 ± 61	0·240	
Serum IgG_4 (mg/dl ± s.d.)	95 ± 42	92 ± 47	0·252	
Serum IgM (mg/dl)	121 ± 75	118 ± 51	0·320	
C^{13}-urea breath test performed *n* (%)	106 (30·5%)	929 (26·8%)	0·145	
C^{13}-urea breath test positive *n* (%)	68 (19·6%)	534 (15·3%)	0·043	1·21 (0·91–1·59) $P = 0·19$
Dyspepsia	84 (24·2%)	821 (23·6%)	0·352	1·03 (0·79–1·34) $P = 0·82$
Dyspepsia + positive C^{13}-urea breath test *n* (%)	59 (17·1%)	524 (15·1%)	0·437	1·13 (0·84–1·51) $P = 0·43$
Coeliac disease *n* (%)	24 (6·9%)	119 (0·34%)	< 0·001	2·09 (1·32–3·29) $P < 0·01$
Food allergy *n* (%)	19 (5·4%)	31 (0·9%)	< 0·001	6·24 (3·59–11·5) $P < 0·001$
Ulcerative colitis *n* (%)	7 (2%)	18 (0·5%)	0·006	3·95 (1·64–9·52) $P < 0·01$
Crohn's disease *n* (%)	5 (1·4%)	21 (0·6%)	0·081	2·40 (0·89–6·41) $P = 0·08$

Ig = immunoglobulin; IgAD = Ig deficiency; OR = odds ratio; CI = confidence interval.

and additional specimens from any visible endoscopic visible lesions, if needed) were taken and stained with haematoxylin and eosin [9].

Only 59 (17%) of the 347 IgAD patients underwent gastroscopy (those with positive *H. pylori* RUT), not all the 347 patients with IgAD.

Statistical analysis

Comparisons of the categorical variables were analysed using Fisher's exact test. Comparisons of the continuous variables were analysed using the χ^2 test. All values are expressed as mean ± standard deviation (s.d.). Statistical analyses were performed using software Statistica version 6 (StatSoft Inc., Chicago, IL, USA). Two-tailed *P*-values less than 0·05 were considered significant.

Results

Demographic and laboratory characteristics of cases and controls

A total of 104 729 subjects, aged 12–76 years, were identified as having received a serum total IgA test between 1 January 2004 and 31 December 2014. Among these, 347 subjects aged 2–74 years were identified as having serum total IgA of < 0·07 g/l. The corresponding control group therefore consisted of 3470 subjects; there were no differences between the cases and controls with regard to demographic characteristics and other immunoglobulin levels (Table 1).

There were no significant differences in the prevalence of patients with dyspepsia [84 (24·2%) *versus* 821 (23·6%) for cases and controls, respectively). Additionally, there was no difference in a proportion of dyspeptic *H. pylori*-positive subjects [59 (17·1%) *versus* 524 (15·1%)] between the case and control groups.

The case group was characterized by the higher rates of coeliac disease [24 (6·9%) *versus* 119 (0.34%), $P < 0·001$], food allergy [19 (5·4%) *versus* 31 (0·9%), $P < 0·001$] and ulcerative colitis [seven (2%) *versus* 18 (0·5%), $P = 0·006$] (Table 1).

EGD results

EGD was performed on 42·8% (21 of 59) and 32·9% (176 of 524) of the *H. pylori*-positive dyspeptic cases and control subjects, respectively (Table 2). A significantly larger proportion of case subjects experienced several forms of gastritis [13 (61·9%) *versus* 38 (21·6%), $P < 0·001$]. The difference was evident, particularly for multi-focal atrophic gastritis [13 (61·9%) *versus* 38 (21·6%), $P < 0·001$]. In addition, a larger proportion of case subjects presented with duodenal ulcers [seven (33·3%) *versus* 19 (10·8%), $P = 0·01$] and with nodular lymphoid hyperplasia [two (9·5%) *versus* none, $P = 0·011$].

Endoscopic features of nodular lymphoid hyperplasia included nodules ranging in size ≈ 5 mm in diameter, presenting in the stomach and the duodenal bulb. Histologically, the hyperplasic lymphoid follicles were characterized by mitotically active germinal centres with well-defined lymphocyte mantles, localized in the mucosa and

Table 2. Upper GE endoscopy findings in the subjects with dyspepsia + positive C^{13}-urea breath test.

	Subjectswith IgAD	Control	*P*	Multiple logistic regression model OR (95% CI)
Upper GE endoscopy performed	21 (42·8%)	176 (32·9%)	0·206	
Sex; female, *n* (%)	8 (38·1%)	94 (53·4%)	0·248	
Age (years)	42·7 ± 5·9	45·1 ± 8·7	0·220	
Antral-predominant gastritis *n* (%)	5 (23·8%)	27 (15·3%)	0·347	1·72 (0·58–5·11) $P = 0·32$
Body-predominant gastritis *n* (%)	2 (9·5%)	9 (5·1%)	0·331	1·95 (0·39–9·71) $P = 0·41$
Multi-focal atrophic gastritis *n* (%)	6 (28·6%)	2 (1·1%)	<0·001	34·8 (6·45–187·65) $P < 0·001$
All cases of gastritis *n* (%)	13 (61·9%)	38 (21·6%)	<0·001	5·90 (2·28–15·27) $P < 0·001$
Gastric ulcer *n* (%)	0	3 (1·7%)	1	2·72 (0·11–68·91) $P = 0·54$
Duodenal ulcer *n* (%)	7 (33·3%)	19 (10·8%)	0·010	4·11 (1·47–11·43) $P < 0·01$
Nodular lymphoid hyperplasia	2 (9·5%)	0	0·011	45·26 (2·09–977·09) $P < 0·001$

IgAD = immunoglobulin Ig deficiency; OR = odds ratio; CI = confidence interval.

submucosa. The pathological findings from biopsied gastric tissues were comparable in case and control subjects. Histopathological analyses showed marked chronic inflammation, lymphoid follicle formation and prominent germinal centres, with polymorphonuclear cell infiltration of gastric glands.

Discussion

The results of this study show a similar prevalence of *H. pylori* infection in dyspeptic patients with IgAD and in the subjects with normal total serum IgA levels. Nevertheless, *H. pylori* infection in dyspeptic patients with IgAD was associated with a higher prevalence of gastritis, peptic ulcer disease (PUD) and nodular lymphoid hyperplasia (NLH).

Our patients with IgAD were characterized by a higher prevalence of coeliac disease (CD), food allergy and ulcerative colitis. IgAD was shown previously to be associated with CD, with a reported overall prevalence of ≈ 1 : 40, indicating a five- to 15-fold increase in the prevalence of IgAD among subjects with CD [15,16]. Previously, IgAD deficiency was found to increase a risk of milk protein intolerance and food hypersensitivity [17–19]. In Individuals with IgAD a higher prevalence of inflammatory bowel diseases, specifically ulcerative colitis, was also noted in previous studies [20,21].

In the earlier study, the seropositivity and titre against *H. pylori* in IgAD patients and age-related normal blood donors was compared [22]. It appeared that lack of secretory IgA does not seem to have any major influence on the prevalence of the infection, nor was it reflected in titres of specific IgG antibodies; therefore, the authors argued against a pivotal role for IgA in the defence against *H. pylori* [22].

The main finding of this study is that *H. pylori*-infected dyspeptic IgAD patients had a higher prevalence of gastritis, PUD and NLH. A recent paper from Spain described 12 IgAD patients (adults and children) in which chronic gastritis predominated [23]. Matsukura *et al.* previously examined tissue *H. pylori* IgA antibody in biopsy specimens obtained at endoscopy and showed that indexes of tissue IgA antibody against *H. pylori* were correlated with the severity of chronic gastritis and metaplastic mucosa [24].

Production of anti-*H. pylori* IgA antibodies has also been associated with a CagA-positive *H. pylori* infection [25] which, in turn, is associated with an increased risk of PUD [26], atrophic gastritis and intestinal metaplasia [27]. The findings of the present study imply that these complications of *H. pylori* still occur in the absence of IgA production, as is seen in patients with IgAD. At this stage we have no explanation why *H. pylori* infection in IgAD subjects is associated with prominent T helper type 1 (Th1)-related immunopathology. Several studies indicate that Th1 polarization of the *H. pylori*-specific T cell response is associated with more severe disease [28]. Perhaps the high rates of gastritis and PUD in the patients with IgAD and *H. pylori* infection demonstrate an underlying inappropriate 'tolerance' to the infection.

NLH of gastrointestinal tract is a rare disorder, often associated with common variable immunodeficiency and X-linked agammaglobulinaemia [29]. Nevertheless, in the prospective study of 40 patients with NLH, presented with intractable dyspepsia, none of the patients had immunoglobulin deficiency, but all of them were infected with *H. pylori* infection [30]. Recently, Basylgit *et al.* described NLH in an IgAD patient with *H. pylori* infection [31]. Our study also suggests that a small number of dyspeptic *H. pylori*-infected IgAD subjects could suffer from NLH.

Surprisingly, despite this critical role of sIgA in mucosal immunity, most IgA-deficient individuals are usually asymptomatic and are thus rarely diagnosed. Moreover, it is possible that the individuals diagnosed with IgAD may still have some IgA in the mucosal systems enough to provide some protective functions; additionally, using a compensatory mechanism in IgAD production of secretory IgM is increased [32]. Furthermore, assessment of the true

contribution of IgA to *H. pylori* infection is complicated by the fact that associated mutations in transmembrane activator and calcium-modulating cyclophilin ligand interactor may contribute further to the pathogenesis of gastrointestinal diseases in patients with IgAD [5]. Importantly, it has to be mentioned that IgA production is regulated by regulatory T cells (T_{reg}) in an antigen-specific manner [33]. Thus, disturbances in the T_{reg}–IgA axis might play an important role in the pathophysiology of *H. pylori* infection in IgAD patients.

Some limitations of the study should be acknowledged. First, this was a retrospective study, which is vulnerable to information bias from inaccurate clinical records and missing data. Secondly, we did not investigate immunological mechanisms of *H. pylori* infection in IgAD. Further experimental studies are needed to assess the role of IgA in the pathogenesis of *H. pylori* infection.

Disclosure

All authors declare that they have no competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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