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Anti-*Helicobacter Pylori*, Anti-Thyroid Peroxidase, Anti-Thyroglobulin and Anti-Gastric Parietal Cells Antibodies in Czech Population

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Summary

Autoimmune thyropathies are frequently linked to many infections, such as *Helicobacter pylori,* which are also supposed to play a role in their pathogenesis. The aim of this study was to evaluate the relationships between thyroid and gastric autoimmunity and *H. pylori* infection on a large sample of Czech population (n=1621) by monitoring the autoantibodies against thyroglobulin (anti-Tg) and thyroid peroxidase (anti-TPO) and gastric parietal cell (anti-GPC, representing thyrogastric syndrome) in correlation with antibodies against *Helicobacter pylori* (anti-*H. pylori*) of classes IgG and IgA. The interrelation between autoantibodies and *H. pylori* antibodies was assessed by *H. pylori* seropositivity. In *H. pylori* seropositive persons as compared to seronegative irrespective of age and sex, a higher occurrence of anti-TPO (10.4 % vs. 5.8 %, p=0.001) and anti-GPC (6.1 % vs. 1.7 %, p<0.001) was found. Differences in anti-TPO occurrence were significant in both men (7.0 % vs. 3.3 %, p=0.03) and women (12.7 % vs. 8.0 %, p=0.02), differences in anti-GPC occurrence were significant only in women (7.2 % vs. 1.7 %, p<0.001). Results of this study support the idea of a connection between infection of *H. pylori* and the occurrence of anti-TPO autoantibodies representing thyroid autoimmunity and gastric parietal cells autoantibodies representing the thyrogastric syndrome.

Key words

Helicobacter pylori • Thyroid peroxidase • Thyroglobulin • Gastric parietal cells • Antibodies

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Introduction

Autoimmune thyroiditis (AT) is one of the most frequently encountered endocrinopathies belonging to organ-specific autoimmune diseases. AT can also occur as a part of autoimmune polyglandular syndrome (APS) or of polyglandular autoimmunity activation (PAA). (Muir *et al.* 1995, Laureti *et al.* 1998). As serological markers of AT serve autoantibodies against thyroid peroxidase (anti-TPO) and against thyroglobulin (anti-Tg). Their occurrence has been reported in healthy women in the range from 9 % to 26 % and in healthy men in the range from 3 % to 12 % (Prentice *et al.* 1990, Vanderpump *et al.* 1995, Hawkins *et al.* 1980).

The etiological causes for autoimmune thyroiditis development are multifactorial, involving genetic predisposition (Hrdá *et al.* 2004, Todd *et al.* 1988) and external factors, most common being infections, such as *Yersinia enterocolitica* (Bech *et al.* 1977, Bech *et al.* 1974) and *Helicobacter pylori* (de Luis *et al.* 1998, Figura *et al.* 1999). *H. pylori* causes chronic, usually lifetime infection and is associated with a wide spectrum of other clinical diseases, ranging from peptic ulcer disease to gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma (Suerbaum and Michetti 2002) and also with many extragastroduodenal diseases: cardiovascular diseases, respiratory tract diseases, growth retardation, cerebrovascular diseases, headache and migraine, Raynaud's syndrome and with organ specific autoimmune diseases (autoimmune thyropathies, diabetes mellitus), systemic autoimmune diseases (Tsang and Lam 1999, Figura *et al.* 1999). In patients with autoimmune

thyropathies an increased prevalence of *H. pylori* has been found (de Luis *et al.* 1998, Figura *et al.* 1999). Bertalot *et al.* (2004) reported a decrease in anti-thyroid autoantibodies after eradication of *H. pylori* infection.

Reports about *H. pylori* infection indicate higher infection rates (about 90 % during adulthood) in developing countries (Bardhan 1997), while infection rates in developed countries were about 60 % in higher age groups (Frenck and Clemens 2003). The World Health Organization estimates show that approximately 50 % of the world's populations are infected with *H. pylori*, however, the majority of infected subjects develop no clinical symptoms (Rothenbacher and Brenner 2003). The occurrence of antibodies against gastroparietal cells of the stomach has been reported as high as 12 % (Šterzl *et al.* 1996).

Autoimmune gastritis and its sequel gastric atrophy predispose the subject to, albeit weakly, development of adenocarcinoma in the stomach, however, a strong association with infectious gastritis was recognized well before the identification of *H. pylori* as the cause of gastritis in this context.

As the most readily demonstrable serologic marker of autoimmune gastritis serve the gastric parietal cell autoantibodies, which, in diagnostic laboratories, are usually detected by immunofluorescence on a frozen section of murine stomach. They are highly associated with histologic evidence of gastritis and particularly with fundal gastritis (Whittingham and Mackay 2002).

The aim of this study was to evaluate the relationships between thyroid and gastric autoimmunity and *H. pylori* infection on a large sample of Czech population by monitoring the autoantibodies against thyroglobulin (anti-Tg) and thyroid peroxidase (anti-TPO) and gastric parietal cell (anti-GPC, representing thyrogastric syndrome) in correlation with antibodies against *Helicobacter pylori* (anti-*H. pylori*) of classes IgG and IgA.

Methods

Subjects were selected from the population of the regions of Jablonec nad Nisou (Zamrazil *et al.* 2004), Příbram and Ždár nad Sázavou in the years 2004-2006. (n=1621, mean age ± SD: 27.7±18.7; men: n=700, 25.2±18.8 years, women: n=921, 29.5±18.4 years). The ethical prerequisite of informed consent of the people involved was met.

Antibodies against *H. pylori* IgG and *H. pylori* IgA were determined using ELISA kits Pyloriset EIA-G III Pyloriset EIA-A III from Orion Diagnostica. Results were considered positive when higher than 20 U/ml. Anti-Tg and anti-TPO autoantibodies were determined using ELISA kits AESKULISA a-Tg (results were considered borderline when higher than 125 IU/ml and positive when higher than 150 IU/ml) and AESKULISA a-TPO (results were considered borderline when higher than 25 IU/ml and positive when higher than 50 IU/ml) (AESKU.DIAGNOSTICS, Wendelsheim, Germany). Autoantibodies against gastric parietal cells were determined using the indirect fluorescence kit Rat Kidney, Stomach IFA Kit from The Binding Site Limited (Birmingham, UK).

People were considered positive to *Helicobacter pylori* when having positive at least one antibody. People were considered as showing signs of thyroid autoimmunity, when positive at least to one of the anti-Tg and anti-TPO autoantibodies.

Differences in the prevalences were evaluated using two-sided Fisher's exact test using R statistical package (R Development Core Team 2007).

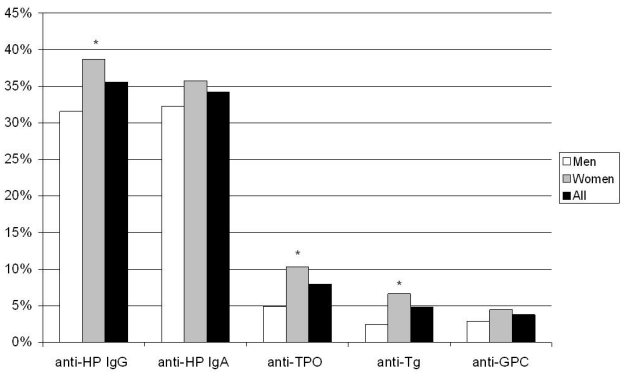

Fig. 1. The occurrence of anti-*H. pylori*, anti-TPO, anti-Tg and anti-GPC in the selected population. anti-HP IgG – anti *H. pylori* IgG; anti-HP IgA – anti-*H. pylori* IgA;, * significant difference ($p<0.05$).

Results

Occurrence of antibodies and autoantibodies

The occurrence of anti-*H. pylori* IgG was 35.6 %, anti-*H. pylori* IgA 34.2 %, anti-TPO 8.0 %, anti-Tg 4.8 % and anti-GPC 3.8 % (Fig. 1). Women showed higher occurrence of anti-*H. pylori* IgG, anti-Tg and anti-TPO and lower occurrence of anti-GPC than men (Fig. 1). Persons older than 18 years showed higher occurrence of anti-*H. pylori* and of all monitored

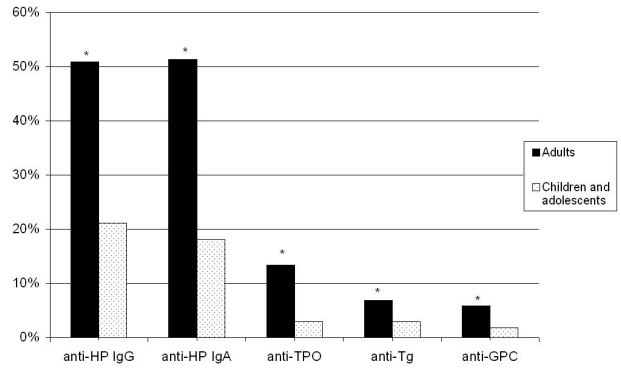

Fig. 2. Differences in the occurrence of anti-*H. pylori*, anti-TPO, anti-Tg and anti-GPC in the selected population. anti-HP IgG – anti *H. pylori* IgG; anti-HP IgA – anti-*H. pylori* IgA; adults – persons of age 18 years and older, children and adolescents – persons under 18 years of age; * significant difference ($p<0.05$).

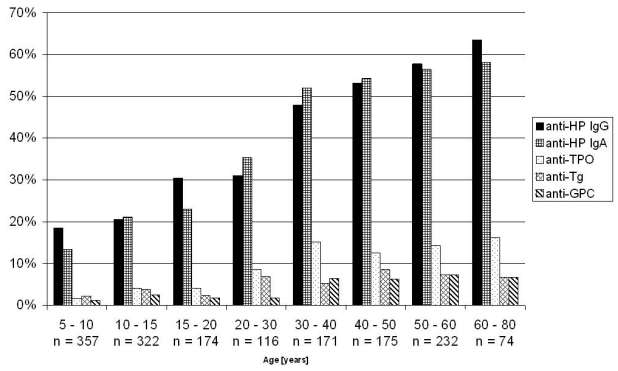

Fig. 3. Age dependence of the occurrence of anti-*H. pylori*, anti-TPO, anti-Tg and anti-GPC in the selected population. anti-HP IgG = anti *H. pylori* IgG; anti-HP IgA = anti-*H. pylori* IgA.

autoantibodies (Fig. 2, $p<0.001$). The age dependence of anti-*H. pylori* and of all monitored autoantibodies is shown in Figure 3.

Relationship of the occurrence of autoantibodies on H. pylori seropositivity

In *H. pylori* seropositive persons as compared to seronegative irrespective of age and sex higher occurrence of anti-TPO (10.4 % vs. 5.8 %, $p=0.001$) and anti-GPC (6.1 % vs. 1.7 %, $p<0.001$) was found. Differences in anti-TPO occurrence were significant in men (7.0 % vs. 3.3 %, $p=0.03$) and also in women (12.7 % vs. 8.0 %, $p=0.02$), anti-GPC occurrence only in women (7.2 % vs. 1.7 %, $p<0.001$). In persons up to 18 years of age, irrespective of sex, a difference showed up in anti-TPO (4.7 % vs. 2.1 %, $p<0.05$) and anti-GPC occurrence (3.9 % vs. 0.9 %, $p=0.004$), with respect to sex only in young females a difference in the anti-GPC occurrence (4.6 % vs. 0.7 %, $p<0.02$) appeared. In persons older than 18 years, irrespective of sex, a difference in anti-GPC occurrence (7.2 % vs. 3.5 %, $p=0.04$) appeared, with respect to sex however, only in women (8.3 % vs. 3.2 %, $p=0.02$) (Table 1).

Relationship of anti-GPC and anti-H. pylori occurrence on the positivity of anti-thyroid autoantibodies

In persons with positive autoantibodies against any of the thyroid antigens higher anti-*H. pylori* IgG (44.4 % vs. 34.5 %, $p=0.01$) and IgA (43.9 % vs. 33.0 %, $p=0.005$) and anti-GPC (7.2 % vs. 3.3 %, $p=0.02$) were found as compared to autoantibody negative persons irrespective of age and sex. With respect to sex differences were found for anti-*H. pylori* IgA in women (44.4 % vs. 34.3 %, $p=0.03$) and for anti-GPC in men (8.5 % vs. 2.5 %, $p=0.04$). These differences were not confirmed in the age group under 18 years, in the group older than 18 years only the difference for anti-GPC in men was confirmed (Table 2).

Relationship of anti-GPC and anti-H. pylori occurrence on the positivity of anti-thyroid autoantibodies

In persons with positive autoantibodies against any of the thyroid antigens higher anti-*H. pylori* IgG (44.4 % vs. 34.5 %, $p=0.01$) and IgA (43.9 % vs. 33.0 %, $p=0.005$) and anti-GPC (7.2 % vs. 3.3 %, $p=0.02$) were found as compared to autoantibody negative persons irrespective of age and sex. With respect to sex differences were found for anti-*H. pylori* IgA in women (44.4 % vs. 34.3 %, $p=0.03$) and for anti-GPC in men (8.5 % vs. 2.5 %, $p=0.04$). These differences were not confirmed in the age group under 18 years, in the group older than 18 years only the difference for anti-GPC in men was confirmed (Table 2).

Discussion

Infection with *H. pylori* in connection to autoimmune thyroiditis has been studied by many researchers (Bertalot *et al.* 2004, de Luis *et al.* 1998, Figura *et al.* 1999, Raymond *et al.* 2000). The putative mechanism to explain how *H. pylori* infection in the stomach can pathogenically influence remote organs is the induction of an autoimmune reaction by molecular mimicry (Moran *et al.* 1996, Negrini *et al.* 1996). Antigens involved in this cross-reaction were partially identified as Lewis antigens of blood groups (Appelmelk *et al.* 1996, Moran 1996). In addition, eradication of

Table 1. Significant differences between *H. pylori* negative and *H. pylori* positive persons.

Age group	Gender	Antibody	*H. pylori* positive	*H. pylori* negative	p-value
All	All	anti-TPO	10.4 %	5.8 %	0.001
All	All	anti-GPC	6.1 %	1.7 %	<0.001
All	M	anti-TPO	7.0 %	3.3 %	0.032
All	F	anti-TPO	12.7 %	8.0 %	0.022
All	F	anti-GPC	7.2 %	1.7 %	<0.001
Children and adolescents	All	anti-TPO	4.7 %	2.1 %	0.046
Children and adolescents	All	anti-GPC	3.9 %	0.9 %	0.004
Children and adolescents	F	anti-GPC	4.6 %	0.7 %	0.015
Adults	All	anti-GPC	7.2 %	3.5 %	0.039
Adults	F	anti-GPC	8.3 %	3.2 %	0.024

Children and adolescents - persons under 18 years of age. Adults – persons older than 18 years.

Table 2. Significant differences between anti-thyroid autoantibody negative and anti-thyroid autoantibody positive persons.

Age group	Gender	Antibody	Thyroid ab* positive	Thyroid ab* negative	p-value
All	All	anti-*H. pylori* IgG	44.4 %	34.5 %	0.010
All	All	anti-*H. pylori* IgA	43.9 %	33.0 %	0.005
All	All	anti-GPC	7.2 %	3.3 %	0.019
All	F	anti-*H. pylori* IgA	44.4 %	34.3 %	0.031
All	M	anti-GPC	8.5 %	2.5 %	0.039
Adults	M	anti-GPC	12.9 %	3.7 %	0.046

Children and adolescents - persons under 18 years of age. Adults – persons older than 18 years. *autoantibody.

H. pylori infection reduced the symptoms of autoimmune process, i.e., caused a decrease in the levels of anti-thyroid autoantibodies (Bertalot *et al.* 2004). Several authors described a relationship between *H. pylori* infection and gastric autoimunity (D'Elios *et al.* 2004, Presotto *et al.* 2003).

Detection of antibodies against CagA antigen of *H. pylori* has not been subject of this study, however, in a previous study (Šterzl *et al.* 2006), we could not show a significantly higher prevalence of antibodies to CagA in patients with AT as compared with controls, in contrast to another study (Figura *et al.* 1999).

Our study of 1621 people is, up to now, the largest study of *H. pylori* seropositivity reported in the Czech Republic. The population sample was selected from different regions of the Czech Republic during 2004-2006. In our study, the prevalence is somewhat higher than in other developed countries (anti-*H. pylori* IgG 35.6 %, IgA 34.2 %.) (Goodman and Correa 1995, Pounder and Ng 1995). Bureš *et al.* (2006) showed similar results in the Czech Republic in spite of using a different method, namely the urease breath test. Roberts *et al.* (2000) showed that the sensitivity and specifity of serological tests is generally lower than those of breath tests. In accordance with other authors (Sorberg *et al.* 2003, Robertson *et al.* 2003) we found an age dependence of the occurrence of *H. pylori* seropositivity increasing with age. The observed occurrence of anti-TPO (8.0 %) and anti-Tg (4.8 %) in the population under study, without regard to age or gender was slightly lower, as compared with other authors (Tajtaková *et al.* 2000, Prummel and Wiersinga 2005, Vanderpump *et al.* 1995).

In accordance with other authors (Vanderpump *et al.* 1995, Hawkins *et al.* 1980, Prentice *et al.* 1990) the occurrence of anti-Tg and anti-TPO autoantibodies increased with age – anti-Tg (6.8 % in older vs. 2.9 % in younger, $p<0.001$), anti-TPO (13.3 % vs. 2.9 %, $p<0.001$) and certain results were more frequent in women,

specifically anti-Tg (6.6 % vs. 2.4 %, p<0.001), and anti-TPO (10.3 % vs. 4.9 %, p<0.001).

Several authors point to the relationship of autoimmune thyroiditis and *Helicobacter pylori* infection (de Luis *et al.* 1998, Figura *et al.* 1999). Helicobacter pylori might be the possible etiological factor for autoimmune thyroiditis development. A significant interaction between HLA-DRB1*0301 and *H. pylori* infection was present in AT patients and not controls (Larizza *et al.* 2006).

In the group of the *H. pylori* seropositive subjects, higher occurrence of anti-TPO and anti-GPC was found. On the other hand, in people with laboratory signs of thyroid autoimmunity, a higher occurrence of anti-*H. pylori* antibodies, and also a higher occurrence of anti-GPC autoantibodies was observed. When taking into account gender and age, only differences in anti-GPC in men, especially of higher age, persisted.

The occurrence of anti-GPC autoantibodies in the selected population was 3.8 %. No previous studies were found regarding the anti-GPC prevalence in the general, randomly selected population. All studies describe the occurrence of anti-GPC in various pathological states (Carmel 1992, Annibale *et al.* 2005, De Block *et al.* 2003). The occurrence of anti-GPC was not age or gender dependent. Results of this study suggest a possible relationship between anti GPC and the time course of *Helicobacter pylori* infection – the occurrence of anti-GPC was higher in *H. pylori* positive people (6.1 % vs. 1.7 %, p<0.001) and also in people with laboratory signs of autoimmune thyroiditis (7.2 % vs. 3.3 %, p=0.02). *H. pylori* infection can induce gastric autoimmunity, since of the bacteria leads to the production of antibodies cross-reacting with human gastric mucosa (Appelmelk *et al.* 1998, Negrini *et al.* 1991). The gastric mucosal pathogen *Helicobacter pylori* induces autoantibodies against the gastric proton pump H^+,K^+-ATPase in 20-30 % of infected patients. The presence of these autoantibodies is associated with severity of gastritis (D'Elios *et al.* 2004). Our results suggest that gastric autoimmunity caused by *H. pylori* could also induce thyroid autoimmunity.

To conclude, we would like to point out that this study of a sample of the Czech population showed the occurrence of *H. pylori* in the same rates as in other developed countries. A slightly lower occurrence of seropositive anti-TPO and anti-Tg autoantibodies was found. Further, the supposed links were confirmed between anti-TPO autoantibodies and anti-GPC autoantibodies, which suggests the involvement of thyrogastric syndrome, i.e. autoimmune polyglandular syndrome type III on one hand and *H. pylori* seropositivity on the other, as a link between gastric and thyroid autoimmunity.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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