Helicobacter pylori Infection In HIV-Positive Versus HIV-Negative Patients

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Introduction: Responsible for one the most frequent infections worldwide, Helicobacter pylori is involved in the pathogenesis of acute/chronic gastritis, peptic ulcer and gastric cancer. It has been suggested that patients infected with human immunodeficiency virus (HIV) register a lower frequency of Helicobacter pylori infection, due to extensive use of antibiotics for opportunistic infections.
Purpose: a comparison between the frequency of Helicobacter pylori infection in HIV-positive and HIV-negative patients, noting the differences between diagnostic methods.
Material and method: We performed a retrospective, analytical, case-control study, over a period of 40 months, by analyzing 1165 Helicobacter pylori tests (serology or stool antigen) performed in the Laboratory of Infectious Diseases from Clinical District Hospital Mures. Group A included 94 HIV-infected patients, while group B – 1071 non-HIV infected patients. Statistical analysis was performed (Chi2 test, Odds Ratio (OR) calculation) with the help of GraphPad programme.
Results: 45.74% HIV-infected patients and 62.5% HIV-negative subjects had positive Helicobacter pylori tests (either serology or stool antigen), which resulted in a statistically significant negative association between HIV and Helicobacter pylori infection, with $p=0.0013 < \alpha=0.05$ and OR=0.5046. However, only 8.33% stool antigen tests in HIV-positive and 6.78% in HIV-negative patients were positive for Helicobacter pylori, while 51.21% serological tests were positive in HIV-infected subjects and 69.46% in HIV-negative patients.
Conclusions: Although HIV infection seems to be associated with less Helicobacter pylori positive tests, the clinician needs to consider the existing differences between diagnostic methods.

Keywords: Helicobacter pylori, human immunodeficiency virus, frequency of infection, diagnostic methods

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Introduction

Helicobacter pylori (Hp) is a gram-negative curved rod infecting more than half of the world's population [1,2]. It has been associated to peptic ulcer, either duodenal or gastric [3], gastric adenocarcinoma [3] and mucosa-associated lymphoid tissue (MALT) lymphoma [4]. As both patients with peptic ulcer [3] and MALT lymphoma [4] seem to benefit from infection eradication, a number of diagnostic methods and therapy regimens were developed. While invasive methods, implying upper endoscopy, may bring more clinical information, their discomfort sometimes makes the patients opt for a non-invasive method: serology testing, stool antigen detection, urea breath test.

Helicobacter pylori stool antigen detection by immunochromatographic or immunoenzymatic methods registers a sensitivity of 91–98% and a specificity of 94–99% [3], but its accuracy may be decreased by gastrointestinal bleeding or treatment with proton pump inhibitors [5]. Immunoenzymatic serological tests (Enzyme-Linked Immunosorbent Assay – ELISA), detecting anti-Helicobacter pylori IgG antibodies have a sensitivity of 85% and a specificity of 79% [3], as serum antibodies may persist for 1 year or more after eradication [4].

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Several studies suggested that Helicobacter pylori infection registers lower prevalence in patients infected with human immunodeficiency virus (HIV) [6,7], probably due to extensive use of antibiotics for extradigestive indications, colonization by other microorganisms secondary to hypochlorhydria or reduction of gastric mucosa damage secondary to the decrease in CD4 T-cells level [6]. Other research indicates that its frequency in HIV-positive subjects is similar to that encountered in general population [8,10]. Lower prevalence of Helicobacter infection was registered in patients with Acquired Immunodeficiency Syndrome (AIDS) [9], or at CD4 T-cells count below 200/µl [6,10]. Gastrointestinal disorders in HIV-infected patients may have other causes, such as medication side effects [11], cytomegalovirus [6,7] or fungal infections [6].

Material and method

We performed a retrospective, analytical, case-control study over a period of 40 months (January 2009 – April 2012), with the purpose of comparing the frequency of Helicobacter pylori infection in HIV-positive versus HIV-negative patients, noting the differences between diagnostic methods: stool antigen detection and serological tests. We analyzed 1165 Helicobacter pylori tests (serology or stool antigen) performed in the Laboratory of Infectious Diseases on patients from various departments of the Clinical District Hospital Mureș, most of them (71.79%) ad-

mitted to Infectious Diseases Clinics I and II. One-thousand thirty-five serological tests and 130 antigen stool tests were performed. We divided the patients into two groups. Group A included 94 HIV-infected patients and group B included 1071 non-HIV infected patients, both presenting for dyspeptic symptoms. The two groups had comparable gender and environment distribution, but different age characteristics. The average age in the HIV-infected group was 21 years, median and mode: 20 years, extremes: 15–45 years, while the HIV-negative group had an average age of 43 years, median: 45 years, mode: 52 years, extremes: 1–82 years, differences explained by the particularities of HIV epidemics in our country.

Apart from the result of Helicobacter pylori testing and the type of used method, other data were collected from group A: the clinical-immunological stage, CD4 T-lymphocyte level and plasma RNA (ribonucleic acid)-HIV viral load.

We compared data regarding the frequency of Helicobacter pylori infection in the two groups and the methods used for diagnosis. Data were interpreted with the help of a statistical programme (GraphPad): analysis of contingency tables, by using Chi^2 test (or Fisher exact test for data regarding stool antigen probes) and calculating Odds Ratio (OR).

Results

The distribution of HIV-infected patients according to the clinical and immunological classification of the United States Centers for Disease Control and Prevention was in favour of advanced stages: 2 subjects (2.12%) were in each of the A2, B2 and C1 stages, 4 (4.25%) B1, 6 (6.38%) B3, 15 (15.96%) C2 and 63 (67.02%) in C3 stage, 82 subjects (87.23%) with AIDS. The average CD4 T-lymphocyte level was 362/μl, its median 304/μl and extremes 3–1414/μl. Thirty (31.91%) patients had CD4 T-cells count < 200/μl. Plasma RNA-HIV viral load ranged from undetectability (12 patients – 12.76%) under antiretroviral therapy to an extreme of 1,548,816 c/ml, with an average of 73,995 c/ml and median of 6018 c/ml.

Forty-three (45.74%) HIV-infected patients and 670 (62.5%) non-HIV infected subjects tested positive for Helicobacter pylori infection, either by serology or stool antigen detection. By comparing the results obtained in the two groups and applying Chi^2 test, we obtained a statistically significant negative association between HIV and Helicobacter pylori infections, with $p = 0.0013 < \alpha = 0.05$ and OR = 0.5046, for 95% confidence interval (CI) = 0.3301–0.7714. When considering only serological tests, the frequency of Helicobacter pylori infection was 51.21% among the HIV-positive patients and 69.46% in general population, which resulted in a similar statistically significant negative association between HIV infection and the presence of Helicobacter pylori: $p = 0.0007 < \alpha = 0.05$ and OR = 0.4616, for 95% CI 0.2930–0.7272. However, upon repeating the calculations with results of stool antigen tests, we found a rate of Helicobacter pylori infection of only 8.33% in the HIV-infected group and 6.78% in the HIV-negative one, without statistically significant association between HIV and Helicobacter pylori infections: $p = 0.5939 > \alpha = 0.05$, OR = 1.250, for 95% CI 0.1427–10.9460.

We performed the same statistical tests upon the 82 AIDS patients, with an overall Helicobacter pylori infection rate in this category of 47.56% (39 subjects). The frequency was 54.28% when considering only serological tests, but it decreased to 8.33% upon analyzing stool antigen tests alone. Out of the 12 HIV-infected patients in non-AIDS stages of infection, the rate of Helicobacter pylori infection was of 33.33%, all tested only for anti-Helicobacter IgG antibodies. Upon comparing the frequency of Helicobacter pylori infection in AIDS and non-AIDS patients, we did not obtain any statistically significant difference p = 0.5367. By comparing the rates of Helicobacter pylori infection in AIDS-stage patients versus HIV-negative population, we obtained a statistically significant association between AIDS-stage disease and Helicobacter pylori infection, with p = 0.0072, OR 0.5428, 95% CI 0.3458–0.8520, a result that was checked by repeating the comparison in case of serological tests (p = 0.0084), but

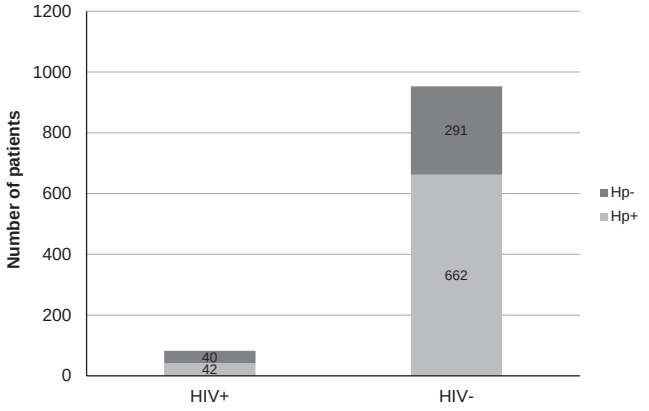

Fig. 1. The frequency of Helicobacter pylori (Hp) infection in HIV-positive versus HIV-negative patients (by serological tests)

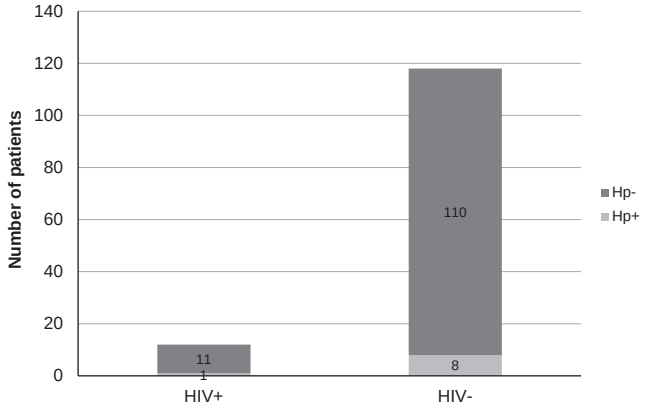

Fig. 2. The frequency of Helicobacter pylori (Hp) infection in HIV-positive versus HIV-negative patients (by antigen stool tests)

was not confirmed by the results of stool antigen testing (p = 0.5939).

We did not find any statistically significant association between CD4 T-cells level < 200/μl and Helicobacter pylori infection p = 0.9863, OR 1.008, 95% CI 0.4056–2.505. Low plasma RNA-HIV viral load was positively, but not statistically significant associated with Helicobacter pylori infection p = 0.3433, OR 1.930, 95% CI 0.6659–5.594.

Discussions

Our study appeared to have two discordant results. Although the overall rates of Helicobacter pylori infection were significantly lower (p = 0.0013) in HIV-infected patients (45.74%) compared to general population (62.5%), this result seems to have reflected the conclusions of the more numerous serological tests, but did not concur to the results of stool antigen detection. Unfortunately, technical conditions did not allow us to detect both serum antibodies and stool antigen simultaneously. Impaired immune response in HIV-positive patients may also play a role in the difference between serology results in the two groups.

Stool antigen testing has registered very low rates of positivity (8.33% in HIV-positive and 6.78% in HIV-negative subjects) compared to the results of serology (51.21% in the HIV-positive, 69.46% in the HIV-negative group), but also to the percentage suggested by literature, as Romania is a developing country and such settings are reported to experience rates of Helicobacter infection as high as over 80% [5].

These differences may be explained by the inconveniences of both methods. Helicobacter stool antigen detection may be negatively influenced by recent proton pump inhibitor treatment [5], which was given to almost all HIV-infected patients admitted to our clinic for abdominal pain and dyspepsia. On the other hand, a positive serological result indicates recent Helicobacter pylori infection rather than the presence of the microorganism at the time of the determination, as serum antibody levels may persist for over one year after eradication [4]. Helicobacter infection eradication under antibiotics therapy prescribed for another infection in a patient with impaired immunity may not soon reflect in serology.

We explain the low rate of positivity in Helicobacter pylori stool antigen testing by the possibility of infection eradication under antibiotic therapy prescribed for other infectious conditions. Most patients included in our study (71.79%) were admitted to the Infectious Diseases Clinics I and II for various infectious conditions, ranging from pneumonia to sepsis and were therefore undergoing antibiotic treatment at the time of or before the moment of stool antigen testing. Some of the most frequently used antibiotics in our clinic include beta-lactamines and macrolides, which could eradicate Helicobacter infection as well, so that the stool antigen testing came out negative. Recent infection eradication would not reflect in the result of serological tests, as anti-Helicobacter pylori antibodies may persist for as long as one year after eradication [4].

Several studies concluding that the prevalence of Helicobacter pylori infection is lower in HIV-infected patients than in general population [6,7] used invasive methods of diagnosis, which we could not perform due to HIV-infected patients' difficulties in accepting upper endoscopy. A study performed in a developing country [8] registered similar rates of infection among HIV-positive/negative subjects by detecting Helicobacter ureB and hpaA genes in the stool of HIV-infected patients, a result concordant to our study.

Age differences between the two groups may also lead to bias, as literature data indicate that the prevalence of Helicobacter infection varies with age [4]. Due to the peculiar features of HIV epidemics in our country, most HIV-infected patients in group A were young adults (average age: 21 years, compared to the average of 43 years in group B).

Although our study did not reveal any statistically significant impact of CD4 T-cells level and plasma RNA-HIV viral load upon the frequency of Helicobacter infection, further research is required, on a larger HIV-positive group, in order to draw a firm conclusion upon this issue.

Conclusions

Although the overall rate of Helicobacter pylori positive testing was significantly lower in HIV-infected patients compared to HIV-negative subjects, the differences between the two used methods impose thorough clinical judgement upon deciding a patient's Helicobacter pylori infected or non-infected status. Each of the two methods has its own indications and practical applications, as well as inconveniences. Confirmation of the diagnosis by invasive methods would be welcome, if the patient agrees to undergo upper endoscopy. Our study did not emphasize a statistically significant direct impact of immunologic and virologic status upon the presence of Helicobacter pylori infection, but further research is needed in this direction.

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Abbreviations

HIV – human immunodeficiency virus
OR – odds ratio
Hp – Helicobacter pylori
MALT – mucosa-associated lymphoid tissue
ELISA – Enzyme-Linked Immunosorbent Assay
AIDS – Acquired Immunodeficiency Syndrome
RNA – ribonucleic acid
CI – confidence interval

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