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Effect of *H. pylori* presence on the severity of Crimean Congo hemorrhagic fever

Kırım Kongo kanamalı ateşine *H. pylori* varlığının etkisi

İlyas DÖKMETAŞ[1], Özlem YÖNEM[2], Sebila DÖKMETAŞ[3], Levent ÖZDEMİR[4], Fatih KILIÇLI[5], Aynur ENGİN[1], İbrahim BÜYÜKHAN[1]

Departments of [1]Infectious Diseases, [2]Gastroenterology, [4]Public Health, and [5]Endocrinology Cumhuriyet University School of Medicine, Sivas

[3]Department of Endocrinology, Medipol University, İstanbul

Background and Aims: *Crimean Congo hemorrhagic fever can cause a fatal hemorrhagic syndrome. We aimed to investigate whether the presence of Helicobacter pylori increases the bleeding or severity of Crimean Congo hemorrhagic fever.* ***Materials and Methods:*** *Forty-two patients with Crimean Congo hemorrhagic fever who had dyspepsia and were hospitalized between April 2009 and July 2009 were included in the study. The patients were divided into two groups according to their fecal Helicobacter pylori antigen positivity. Clinical and laboratory severity criteria for Crimean Congo hemorrhagic fever were investigated in both groups.* ***Results:*** *We could not find any difference between the two groups with regard to severity as defined by clinical and laboratory criteria.* ***Conclusion:*** *This is the first study in the literature investigating the role of Helicobacter pylori in the severity of Crimean Congo hemorrhagic fever from a country in which both Crimean Congo hemorrhagic fever and Helicobacter pylori are endemic. Further studies including a larger number of Crimean Congo hemorrhagic fever patients are necessary to recommend Helicobacter pylori screening and eradication in Crimean Congo hemorrhagic fever.*

Key words: *Crimean Congo hemorrhagic fever, Helicobacter pylori, severity*

Giriş ve Amaç: *Kırım Kongo kanamalı ateşi ölümcül hemorajik bir sendroma neden olabilir. Bu çalışmada Helicobacter pylori varlığının Kırım Kongo kanamalı ateşi hastalığının şiddeti ya da kanama üzerine etkisinin olup olmadığını araştırdık.* ***Gereç ve Yöntem:*** *Kırım Kongo kanamalı ateşi nedeniyle Nisan 2009-Temmuz 2009 arası hospitalize edilen kırk iki dispeptik hasta çalışmaya dahil edildi. Hastalar fekal Helicobacter pylori antijeni pozitifliği durumuna göre iki gruba ayrıldı. Her iki grupta Kırım Kongo kanamalı ateşi'nin klinik ve labaratuvar olarak şiddet kriterleri değerlendirildi.* ***Bulgular:*** *Klinik ve laboratuvar kriterleri açısından iki grup arasında Kırım Kongo kanamalı ateşi hastalık şiddeti açısından farklılık saptanmadı.* ***Sonuç:*** *Bu çalışma Helicobacter pylori'nin Kırım Kongo kanamalı ateşi'nin şiddeti üzerine etkisini araştıran ilk çalışma olması ve hem Helicobacter pylori hem de Kırım Kongo kanamalı ateşi'nin endemik olduğu bir bölgeden yapılması nedeniyle önemlidir. Ancak Kırım Kongo kanamalı ateşi hastalarında rutin Helicobacter pylori taranması ve eradikasyonunun önerilebilmesi için daha geniş vaka sayılı çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler: *Kırım Kongo kanamalı ateşi, Helicobacter pylori, şiddet*

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is an acute and generally self-limiting disease caused by a tick-borne virus belonging to the Bunyaviridae family. It can also exhibit a severe hemorrhagic profile, with a reported mortality rate of 15–30% (1). Gastrointestinal hemorrhages can be life-threatening in CCHF, and control of the factors contributing to upper gastrointestinal bleeding is important.

Helicobacter pylori is a Gram-negative bacterium that is the main cause of gastritis and peptic ulcer disease (2). In certain hemorrhagic diseases such as hemophilia, detection and eradication of *H. pylori* are important in preventing fatal gastroduodenal bleeding (3). Furthermore, *H. pylori* is associated with idiopathic thrombocytopenia purpura (ITP), which can have an additive thrombocytopenic effect on CCHF. We thus investigated whether or not *H. pylori* presence has an impact on the course of CCHF.

MATERIALS and METHODS

Study design

Forty-two patients with CCHF who had dyspepsia (defined as pain and/or discomfort of the upper abdomen) and were hospitalized in the Infectious Diseases Clinic of Cumhuriyet University Hospital between May 2009 and July 2009 were consecutively included in the study. We performed *H. pylori* antigen rapid test (feces) in all patients, and they were divided into two groups according to their fecal *H. pylori* antigen positivity. The study was approved by the local ethical committee.

Criteria for a case definition of probable CCHF were as follows: 1. Epidemiological risk factors: history of tick bite or tick contact, work in animal husbandry or on a farm, contact with the body fluid of a CCHF patient, or close contact with a CCHF case. 2. Clinical symptoms: fever, hemorrhage, headache, myalgia/arthralgia, lethargy, nausea/vomiting, and abdominal pain/diarrhea. 3. Laboratory findings: thrombocytopenia (platelets 150,000/mm^3) and/or leukopenia (white blood cells [WBC] <4000/mm^3), elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK). Among the probable cases, those with positive immunoglobulin (Ig)M antibodies and/or polymerase chain reaction (PCR) for CCHF virus in the blood or body fluids were considered as confirmed CCHF cases. Acute and convalescent phase serum samples were analyzed with immunological (specific enzyme-linked immunosorbent assay (ELISA) IgM)

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Corresponding Author: Özlem YÖNEM
Department of Gastroenterology, Cumhuriyet University, 58140, Sivas, Türkiye
E-mail: ozlemyonem@gmail.com
Phone: +90 346 258 09 99 • Fax: +90 346 258 13 05
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and molecular (reverse transcription (RT)-PCR, direct sequence analyses) assays for the confirmation of the disease by the virology laboratory of Refik Saydam National Hygiene Center.

For severity criteria, the cut-off values of hemoglobin (Hb), international normalized ratio (INR), AST, and platelet count, which were determined by Yılmaz et al. (4) to be independent variables, were used. The highest values for ALT, AST, LDH, CPK, C-reactive protein (CRP), and fibrin degradation products, the lowest values for platelet counts, and the longest values for prothrombin time (PT) and partial thromboplastin time (PTT) determined during the hospitalization stay were included in the statistical evaluation.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 14 package software. Mann-Whitney U, Fisher's exact test, and chi-square test were used for statistical analysis. A value of $p<0,05$ was considered significant.

RESULTS

Forty-two patients with CCHF were included in the study. Of these, 22 were male (52,4%) and 20 were female (47,6%). The mean age of the patients was 50,1±18,3 years. Seventeen of the patients were *H. pylori*-negative and 25 were *H. pylori*-positive. None of the patients died, and all of them were discharged from the hospital without any sequelae. Mean hospitalization stays for *H. pylori*-negative and *H. pylori*-positive groups were 5,29±0,82 and 5,52±0,50 days, respectively ($p>0,05$).

There was also no statistical difference between the two groups with respect to CCHF-related clinical symptoms and findings such as headache, hematemesis, epistaxis, hemoptysis, maculopapular rash, somnolence, diarrhea, hepatomegaly, and splenomegaly (Table 1).

There were no significant differences between the two groups with respect to age, time interval between tick bite and application to the hospital, longest PT and PTT, lowest platelet value, highest AST, ALT, LDH, bilirubin, CPK, and CRP values, lowest fibrinogen, or highest fibrin degradation products values (Table 2).

None of the patients in either group had been diagnosed previously as either gastritis or peptic ulcer, and none of them had undergone upper gastrointestinal endoscopy. None of the patients in either group had been using proton pump inhibitors for their dyspeptic complaints. Only one patient in the *H. pylori*- positive group had been using antacids for the dyspeptic complaints.

We investigated the risk factors for upper gastrointestinal bleeding such as chronic non-steroidal anti-inflammatory drug, aspirin and warfarin use before hospitalization. None of the patients in either group had been using warfarin, and there was no statistical difference between the two groups with respect to chronic non-steroidal anti-inflammatory drug or aspirin use.

Tablo 1. Comparison of symptoms in *H. pylori* negative and *H. pylori* positive CCHF patients.

Symptom/Finding	*H. pylori* (-)	*H. pylori* (+)	p
Headache	94,1%	100%	0,38
Hematemesis	-	4%	1
Melena	-	4%	1
Epistaxis	11,8%	-	0,16
Hemoptysis	-	4%	1
Maculopapular rash	52,9%	40%	0,68
Conjunctivitis	94,1%	80%	0,37
Somnolence	-	8%	0,51
Diarrhea	35,3%	44%	0,57
Hepatomegaly	5,9%	4%	1
Splenomegaly	5,9%	-	0,41

Tablo 2. Comparison of the labaratory parameters of CCHF patients in the *H. pylori*-negative and *H. pylori*-positive group during the hospitalization period.

Fecal *H. pylori* Antigen	Negative X±SEM	Positive X±SEM	P
Longest PT	13,1±0,3	13,5±0,3	0,323
Longest PTT	38,9±2,3	42,9±2,9	0,450
Lowest platelet count	88294,1±33800,8	131500±39888,0	0,382
Highest ALT	102,9±22,7	239,1±126,9	0,377
Highest AST	154,8±39,0	300,1±95,1	0,199
Highest LDH	531,5±99,0	603,9±104,7	0,711
Highest total Bilirubin	0,8±0,1	0,9±0,1	0,838
Highest direct Bilirubin	0,23±0,03	0,24±0,03	0,939
Highest CPK	451,9±139,3	600,6±104,7	0,404
Lowest fibrinogen	309,0±28,4	301,6±7,3	0,615
Highest fibrin degradation products	1786,9±600,7	2104,5±464,4	0,328
Highest CRP	24,02±9,37	17,06±2,13	0,260

There was no difference between the two groups with respect to independent variables such as Hb, INR, platelet count, and AST that predicted the severity of CCHF (Table 3).

DISCUSSION

Crimean Congo hemorrhagic fever virus (CCHFV) infection has become an important public health problem in our country. The first case was reported in 2002. There were 1820 confirmed cases by the end of 2007 and 92 deaths, with a case-fatality rate of 5% (5). It is common in the central, northern and eastern regions of Turkey, including our city, Sivas, which is located in central Anatolia (6). In the Tokat and Sivas provinces of Turkey, the overall CCHFV seroprevalence was 12,8% among 782 members of a high-risk population (7). The most important factor that makes CCHF a se-

Tablo 3. Comparison of the *H. pylori* negative and *H. pylori,* positive groups with respect to severity criteria

	Fecal Helicobacter antigen (-)		Fecal Helicobacter antigen (+)		
	n	%	n	%	Total
PT (X2=0,075, p=0,784)					
≤14	13	76,5	20	80,0	33
14≥	4	23,5	5	20,0	9
PTT (X2=0,632, p=0,426)					
<34	6	35,3	6	24,0	12
>34	11	64,7	19	76,0	30
Platelet count (X2=0,0, p=0,986)					
<90.000	12	70,6	17	70,8	29
>90.000	5	29,4	7	29,2	12
Hb (X2=2,888, p=0,089)					
<13,5	12	70,6	11	44,0	23
>13,5	5	29,4	14	56,0	19
INR (X2=1,140, p=0,286)					
<1,1	11	64,7	12	48,0	23
>1,1	6	35,3	13	52,0	19

rious disease is its capability of causing a fatal hemorrhagic syndrome. Bleeding predicts the mortality of the disease and may present as petechiae, ecchymosis, hemoptysis, epistaxis, hematuria, hematemesis, melena, and vaginal and gingival bleeding. Pulmonary and gastrointestinal hemorrhages can be life-threatening and carry a very high risk for mortality. Thus, disclosure of the risk factors contributing to the bleeding in these two organs is important in CCHF (3).

The pathogenetic mechanism underlying bleeding complications in CCHF has not yet been elucidated, but disseminated intravascular coagulation (DIC) is noted in patients with fatal CCHF [3]. Thrombocytopenia appears to be a consistent feature of CCHF infection, and platelet counts can often be extremely low in fatal cases (8). *H. pylori* is a Gram-negative bacterium that is the main cause of gastritis and peptic ulcer disease (2). Screening and treatment of *H. pylori* in endemic areas are recommended in some hemorrhagic diseases such as in hemophilia in order to prevent possible upper gastrointestinal bleeding. Turkey is endemic for *H. pylori*. Abasiyanik et al. (9,10) found an overall 70% infection rate of *H. pylori* in asymptomatic Turkish subjects. We thus investigated whether the presence of *H. pylori* increases gastrointestinal bleeding in dyspeptic CCHF patients. However, we had only one patient with upper gastrointestinal bleeding, and he was in the *H. pylori*-positive group. Hence, statistical evaluation was not possible, as one case is insufficient for drawing a conclusive statement.

Pooled data from 13 cohort studies indicate a 52% platelet response rate after *H. pylori* eradication in ITP. However, although this clinical observation suggests the involvement of *H. pylori*, little is known about the pathogenesis of *H. pylori*-associated ITP (2). Proposed mechanisms include molecular mimicry, platelet aggregation induced by *H. pylori*, and possibly immunomodulatory effects of triple eradication therapy (11). We also investigated whether *H. pylori* presence increases mortality in these patients as *H. pylori* itself is proposed to induce platelet aggregation, and thrombocytopenia is known to be among the severity criteria for CCHF according to different studies. Recently, Yılmaz et al. (4) found in their study that platelet count, Hb, INR, AST, and CRP values were independent risk factors indicating the severity of CCHF. We used their cut-off values in our study and could not find any difference between *H. pylori*-positive and -negative groups with respect to severity.

We conclude that the presence of *H. pylori* does not increase the severity in dyspeptic CCHF patients. The major pitfall of our study is that there was only one patient with upper gastrointestinal bleeding, and he was in the *H. pylori*-positive group. Further studies including a larger number of CCHF patients with upper gastrointestinal system bleeding are necessary to recommend *H. pylori* screening and eradication in CCHF.

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