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Original scientific paper

Helicobacter Pylori Infection and Acute Stroke

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ABSTRACT

The aim of this investigation was to determine whether Helicobacter pylori infection (HBPI) is an independent risk factor for acute noncardioembolic stroke, and also if there is a link between HBPI and other established and well-known risk factors for stroke, as well, to find if there is link between HBPI and severity of disease. In this prospective single centre study where enrolled 82 patients with acute stroke and control group was consistented 93 healthy individuals. The results of this study showed no difference between H.pylori seropositivity distribution in the investigate and control group (25.8 vs. 34.8%), additionally, there was no significant difference on the severity of the disease. Furthermore there was no evident association between acute stroke and HBPI in the patientes with three and more risk factors, but we found significant link between HBPI and carotid stenosis. Further studies are needed to clarify the possible causal relation between infection by this organism and stroke. It is necessary not only the elucidate of pathophysiology related to the association, but also to evaluate whether antibiotic treatment may result in clinical benefit of the patient.

Key words: *Helicobacter pylori infection, acute stroke*

Introduction

Stroke is amnog the most frequent causes of death and persisting disability in the world[1]. Classical risk factors cannot fully explain the clinical and epidemiological features of the disease[2]. There are several studies which showes that HBPI cause low grade infection which can lead to production vasoactive supstancies and can contribute to development of atherosclerosis and stroke[3]. Some mechanisms may play role in atherogenesis of HPBI: free radical formation and immune mediated mechanisms, direct influence on coagulation system. HPBI may cause prothrombotic status, could induce changes in coagulation with elevated serum levels of fibrinogen, prothrombin fragments, plasminogen-activating inhibitor-1 (PAI 1) and factor VII. Another possible mechanism linking HBPI and atherogenesis is lipid peroxidation due to an antioxidans loss or could be mediated by increasing cytokine levels[4-6]. There is potential that chronic bacterial infection may aggravate pre-existing plaque by enhancing T-cell activation as well as other inflammatory responses that may participate in the destabilization of the intimal cap resulting in plaque rupture, progression to acute ischemic syndromes, and ultimate enlargment of the atherosclerotic plaque[7]. Results on the association betweeen HBPI and stroke are controversial due to degree of studies pro[2,8-10] and many contra[11,12] that association. In this study we investigated a possible association between HPBI and acute stroke and the purpose was to determine whether HBPI is an indipendent risk factor for stroke, if there is a link between HBPI and severity of disease, find out is there relations between HBPI and established risk factors for stroke.

Material and Methods

In this prospective study were enrolled 82 patients consecutively admitted with acute stroke, but without known peptic ulcer disease or reciving therapy for *H. pylori* eradication in the last year. All subjects had given informed consent to inclusion in the study and research was carried out according with principles of Declaration of Helsinki. Control group consists of healthy subjects and they were excluded if they had history of peptic ulcer disease, received therapy for eradication *H. pylori* or received acid-suppresive drugs in last 12 months.

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All patients underwent cranial MSCT scaning, Duplex ultrasonography of the extracranial carotid arteries and transthoracic echocardiography to exclude patientis with cardioembolic stroke. Analyzed risk factors for stroke included hypertension, diabetes, hyperlipidemia, obesity, gender and cigarette smoking. Carotid stenosis is the possible cause of 1/3 patients with ischemic stroke**.** Abnormal findings of Duplex ultrasonography of the extracranial carotid arteries were further subdivided into groups according to the percent of stenosis. First degree of carotid stenosis (<50%), with middle stenosis (50-75%) and severe stenosis (>75%). Hypertension was considered in the patients with arterial pressure >140/90 mmHg, or were being treated with antihypertensive drugs or dietary modifications. Diabetic patients were considered to have diabetes if they have had fasting glucose >6.4 mmol/L, HbA1c>6.0% or were taking insulin, hypoglicemic agents or dietary modification to control the disease. Hyperlipidemia was considered in patients with serum cholesterol levels >5.2 mmol/L or receiving lipid lowering agents. Obesity status was defined followed by body mass index (BMI): subjects with BMI <24 were considered normal, BMI 25–29 were considered overweight and BMI >30 were considered obese. Smoking as risk factor was not considered in patients who had stopped smoking >20 years ago or who were <30 years of age when they stopped smoking. All subjects (patients with AMI and control group) underwent an enzyme-linked Immulite (chemiluminescent) analyzer IgG serologic test for H. pylori diagnosis (Diagnostic Products Corp., Los Angeles, CA, USA). The test had a sensitivity of 97% and a specificity of 98%.The severity of disease was present according to the National Institute of Health Stroke Scale (NIHSS). Statistical analysis was carried out by using SPSS software (Statistical Package for the Social Sciences, version 11,0, SPSS Inc., Chicago, IL, USA). For comparing differences between sets of results we used t–tests and for associations between variables correlation methods. Regression analysis was used for prediction of *H. pylori* seropositivity, χ^2 test was used to find out differences between frequency of risk factors. Results were shown by average values with standard deviations. A value of $p < 0.05$ was considered statistically significant.

Results

Investigate group was consisted of 83 patients with acute stroke consecutively admitted in stroke care unit. There was 32 men and 34 women, average age of 72.8 years. 20 (30.3%) had haemorrhagic stroke and 46 (69.7%) ischemic stroke. 16 patients were excluded because of cardioembolic stroke. The control group consists of 93 healthy individuals. (Table 1)

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF PATIENTS (N=66)

Characteristics	No (%)
Sex	
Male	32 (48.5)
Female	34 (51.5)
Age	
Mean±SD — yr	72.8±9.6
ICV	
Haemorrhagic	20 (30.3)
Ischemic	46 (69.7)
NIHSS*	
Minor	8 (12.1)
Moderate	50 (75.8)
Severe	8 (12.1)
Carotide stenosis	
No stenosis	14 (21.2)
First degree stenosis <50%	21 (31.8)
Mild stenosis 50-75%	24 (36.4)
Severe stenosis >75%	7 (10.6)
Hypertension	
No	13 (19.7)
Yes	53 (80.3)
Smoking	
No	52 (78.8)
Yes	14 (21.2)
Cholesterol	
Normal	29 (43.9)
High	37 (56.1)
Diabetes	
No	40 (60.6)
Yes	26 (39.4)
Obesity	
No	44 (66.7)
Yes	22 (33.3)
Leukocytes	
Normal	43 (65.2)
High	23 (34.8)
CRP	
Normal	28 (42.4)
High	38 (57.6)
Fibrinogen	
Normal	45 (68.2)
High	21 (31.8)
HBP test	
Negative	43 (65.2)
Positive	23 (34.8)

*National Institutes of Health Stroke Scale

There was 80.3% hypertonic patients in the investigate group, there was 39.4% diabetic patients. Dyslipidemia was present in the 56% patients. In the investigate group 33.3% patients were overweight, there were 21.2% smoking patients. On the carotid ultrasonography there were 20.2% with normal findings, 31.8% with first degree of carotid stenosis (<50%), 36.4% with middle stenosis (50-75%) and severe stenosis (>75%) 10.6% patientes. There was no significant differences between HBP seropositivity distribution in the investigate and control group (34.8% *vs* 25.8% Table 2), also there was no significant differences between men and women. (Table 2)

TABLE 2
DISTRIBUTION OF HBP IN THE INVESTIGATE AND CONTROL GROUP

	Control	Investigate	
Negative	69	43	112 (70.4%)
Positive	24	23	47 (29.6%)
	93 (58.5%)	66 (41.5%)	159

$\chi 2$=1.113, df=1, p=0.2914 There was no significant differences between HBP seropositivity distribution in the investigate and control group.

There were no significant diferrences between men and women in distribution of hypertension, obesity, diabetes, hyperlipidaemia, cigarette smoking. There was no significant differences on the severity of the disease according to the *H. pylori* seropositivity. Procalcitonin as a marker for infection was in normal levels in both patients and control group, independent of *H. pylori* seropositivity. There was no significant differences on the association of *H. pylori* infection with well known risk factors (hypertension, obesity, diabetes, hyperlipidaemia, cigarette smoking including gender) and we did not established HBPI as an independent risk factor for stroke (Tables 3-7).

TABLE 3
DISTRIBUTION OF HYPERTENSIVE PATIENTS ACCORDING INCIDENCE OF HBP

	HBP negative	HBP positive	
No	7	6	13 (19.7%)
Yes	36	17	53 (80.3%)
	43 (65.2%)	23 (34.8%)	66 (100%)

$\chi 2$=0.397, df=1, p=0.5286 There was no significant differences on the association of H. pylori infection with hypertension.

TABLE 4
DISTRIBUTION OF OBESITIVE PATIENTS ACCORDING INCIDENCE OF HBP

	HBP negative	HBP positive	
No	27	17	44 (66.7%)
Yes	16	6	22 (33.3%)
	43 (65.2%)	23 (34.8%)	66 (100%)

$\chi 2$=0.409, df=1, p=0.5225 There was no significant differences on the association of H. pylori infection with obesity.

TABLE 5
DISTRIBUTION OF DIABETIC PATIENTS ACCORDING INCIDENCE OF HBP

	HBP negative	HBP positive	
No	26	14	40 (60.6%)
Yes	17	9	26 (39.4%)
	43 (65.2%)	23 (34.8%)	66 (100%)

$\chi 2$=0,054, df=1, p=0,8612 There was no significant differences on the association of H. pylori infection with diabetes.

TABLE 6
DISTRIBUTION OF PATIENTS WITH HYPERLIPIDEMIC PATIENTS ACCORDING INCIDENCE OF HBP

	HBP negative	HBP positive	
Normal	19	10	29 (43.9%)
High	24	13	37 (56.1%)
	43 (65.2%)	23 (34.8%)	66 (100%)

$\chi 2$=0.042, df=1, p=0.8376 There was no significant differences on the association of H. pylori infection with cholesterol.

TABLE 7
DISTRIBUTION OF CIGARETTE-SMOKING PATIENTS ACCORDING INCIDENCE OF HBP

	HBP negative	HBP positive	
Non-smoker	32	20	52 (78.8%)
Smoker	11	3	14 (21.2%)
	43 (65.2%)	23 (34.8%)	66 (100%)

χ^2=0.759, df=1, p=0.3836 There was no significant differences on the association of *H. pylori* infection with cigarette smoking.

Measurement of CRP, fibrinogn and leukocyte was performed in all stroke patients. There was no significant diference between group with HBP seropositivity versus group with no seropositivity.There was no significant association between HBP seropositivity and acute stroke in the patients with 3 and more risk factors, but we found significant link between HBPI and carotid stenosis (Table 8). In summary our study shows no association between HBPI and stroke.

TABLE 8
DISTRIBUTION OF PATIENTS WITH CAROTIDE STENOSIS ACCORDING INCIDENCE OF HBP

	HBP positive	HBP negative	
No stenosis	2	12	14 (21.2%)
First degree stenosis <50%	9	12	21 (31.8%)
Mild stenosis 50-75%	12	12	24 (36.4%)
Severe stenosis >75%	0	7	7 (10.6%)
	23 (34.9%)	34 (65.1%)	66 (100%)

$\chi 2$=9.371, df=3, p=0.0247 There were significant differences between HBP positive and HBP negative according the carotide stenosis.

Discussion

Cardiovascular diseases are important cause of mortality. Classical risk factors cannot fully explain epidemiological variations of these disease. Helicobacter pylori are gram-negative bacteria which produce a chronic infection in humans associated with peptic ulcer disease, gastritis. *H. pylori* infection may increase risk for acute stroke through the changes in the lipid status with lower HDL cholesterol values and elevated serum trigliceride values, changes in the coagulation paremeters with elevated fibrinogen, prothrombin fragments, plasminogen-activating inhibitor 1 (PAI-1) and factor VII , increased concentrations of markers of inflammation as a tumor necrosis factor – α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) and others. J. Majka reported HPBI as an risk factor for stroke via an interaction of HP cytoxins or cytokines with atherosclerotic plaques in carotic arteries. It has been noticed possible direct effect on the stability of the atherosclerotic plaque. Most studies suggested that HBPI might be associated with stroke due to an increased prevalence of this organism in patientes with stroke. The pathophysiological mechanism underlying this association seems likely to be chronic inflamatory response to bacterial infection[13]. Since 1994 several studies have been performed on the correlation between HBPI and atherosclerosis. Despite all these studies there are still many controversies about the role of HBPI in stroke. Although most respective studies analyzed IgG antibodies against *H. pylori* in patientes with acute stroke and find association between HBP serpositivity and stroke, find HBPI as an independent risk factor for stroke of atherothrombotic origin[2,14]. The results of Sawayama suggest that chronic HBPI may be a triggering factor that increases the risk of acute ischemic stroke. Some prospective studies founded the strongly relation between HBPI and major cerebrovascular risk factors particulary cigarette smoking, diabetes, hypertension. With respect to stroke a nested case-control study with 137 patientes and 137 control subject found a trend to an increased risk by positive HBPI in adult with lower socioeconomic status and vascular risk factors[15]. *H. pylori* infection and cerebrovascular disease are associatted with lower socioeconomic status and their frequency is higher with older age[16]. In our study we faund 34.8% patients HBP seropositive patients with acute stroke *vs*. 25.8 seropositive healthy controls. There was not significant statistical difference (p=0.29) between these groups which sugest that HBPI is not independent risk factor for acute stroke. In our study there was significantly lower incidence of HBPI in both patients and controls, particulary due to exclusion criteria of all participants with known gastric disease, or reciving therapy for gastric disease or eradication for *H. pylori*, particulary for better socioeconomic conditions compare to postwar period in Croatia in recent studies[17]. Age of patientes in investigate group is not the limitation of the present study according to the results of Biagi P. who found the same prevalence of HBPI in group of hospitalized geriatric patients as in yonger group.

Our study investigated the relation between HBPI and carotid stenosis and found significant association. One study in Argentina guided by F. Ameriso demonstrated the presence of the microorganism in carotid lesions but they where unable to speculate on the role of HBPI[18]. Pasceri et al have demonstrated a higher prevalence of either *H. pylori* infection or Cag-A positive strains in 52% of the vascular disease patientes compared to 43% of controls. On the other site Sulewska A. found no DNA of HBP in atherosclerotis plaques, just like Stephen D. H. who reported no evidence for physical localization of HBP in carotid atherosclerotic plaques[19]. Just like F. Ameriso et al Michael R. Preuch supported the hypothesis of an association between infection CaG A-positive HBP strains and acute stroke. According to same recent studies and comparing the results of our patientes we noticed possible direct effect HBPI on the stability of the atherosclerotic plaque. Our prospective study does not provide evidence of any strong association between the HBPI and stroke. Further studies are are required to reveal the role HBPI as an risk factor cerebrovascular disease and to confirm our findings.

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INFEKCIJA HELIBACTER PYLORI I AKUTNI MOŽDANI UDAR

S A Ž E T A K

Cilj ovog istraživanja je bio odrediti da li infekcija *Helicobacter pylori* predstavlja neovisan faktor rizika za moždani udar, odrediti da li postoji povezanost težine kliničke slike oboljelog od moždanog udara s infekcijom *H. pylori*. U ovu prospektivnu studiju provedenu u jednom centru uključena su 82 bolesnika s akutnim moždanim udarom i 93 zdrava ispitanika u kontrolnoj skupini. Rezulati studije nisu pokazali značajnu razliku u distribuciji infekcije H. pylori u ispitanika i kontrolnoj skupini (34,8 vs. 25,8%) i nije nađena značajna razlika u težini bolesti prema seropozitivnosti na H. pylori. Značajna razlika uočena je između HBPI i oboljelih od stenoze karotide. Potrebne su veće multicentrične studije za određivanje precizne uloge *H. pylori* infekcije u nastanku akutnog moždanog udara.