Research Square

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Helicobacter Pylori Infection is Associated with an Increased Stress Ulcer Risk in Brainstem Hemorrhage Patients with Robot-Aided Stereotactic Hematoma Aspiration

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Research article

Keywords: Helicobacter pylori infection, Stress ulcer, Brainstem Hemorrhage, Robot-aided, Stereotactic Hematoma Aspiration

Posted Date: August 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-772816/v1

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Abstract

Background: Whether *H. pylori* infection in brainstem hemorrhage patients is related to the occurrence of SU has not been reported. The purpose of this study is to explore the relationship between *H. pylori* infection and the occurrence of SU, and whether it is necessary to eradicate *H. pylori* infection during treatment.

Methods: This retrospective study was conducted in our patients in Neurocritical Care Unit (NICU), Intensive Care Unit (ICU), and Emergency Intensive Care Unit (EICU) between May, 2017-July, 2020. Patients were eligible for the study if they were admitted to a participating ICU for brainstem hemorrhage with gastrointestinal bleeding and with an ICU stay of at least 3 days. Patients were ineligible if their ICU stay was less than 72 hours, and patients with a previous history of gastric or duodenal ulcer were excluded from the study. All patients were performed with robot-aided stereotactic hematoma aspiration and gastric tube indwelling.

Results: In the study, 65 patients were enrolled. Of these, 7 patients were excluded because their ICU stay lasted less than 72 hours or because they had previous history of gastric or duodenal ulcer. A further 5 patients were excluded because they required blood transfusion for bleeding on admission. Thus, 53 patients constituted the study group.

Conclusions: This study showed brainstem hemorrhage patients infected by *H. pylori* were at increased risk of gastrointestinal bleeding, suggesting that *H. pylori* has a major role in the pathogenesis of acute SU in brainstem hemorrhage patients.

Background

Primary brainstem hemorrhage (PBSH) has the worst outcome among all types of spontaneous intracerebral hemorrhage (SICH) [1–3]. There was no standardized criteria to diagnose PBSH. Generally, the diagnosis of PBSH is based on the history of hypertension, the clinical and radiological features after excluding other bleeding etiologies such as aneurysm, arteriovenous malformation (AVM), cavernomas and tumor apoplexy within brainstem[3, 4]. The management of PBSH remains controversial[1, 2].

Stress ulcer (SU) caused by brain injury is also called Cushing ulcer, which was first reported by Cushing in 1932[5, 6]. SU is one of the common complications of patients with brain injury, with an incidence rate from 16–49%, as high as 40%-80% of patients with severe brain injury, increasing the mortality of patients[7]. William et al reported that endoscopic gastric mucosal injury after brain injury can appear within 24 hours, and 17% of patients can progress to clinically significant bleeding[8]. Although the incidence of upper gastrointestinal lesions in patients with brain injury is high, most of them are in the subclinical stage, and bleeding generally does not occur. However, once hemorrhage occurs, the condition can quickly deteriorate and severely affect the prognosis. It can also directly lead to death due to hemorrhagic shock. It is generally believed that the occurrence of SU after PBSH is due to various factors such as increased sympathetic nerve excitability under stress[9–13].

Helicobacter pylori (H. pylori) is a spiral-shaped G-bacterium that lives in the human stomach and duodenum. The infection rate of *H. pylori* in the population is related to the socio-economic development of the country or region where the patient lives. The infection rate within 10 years in developed countries is between 25%-50%, however, more than 90% people are infected with *H. pylori* in developing countries[14]. The *H. pylori* infection rate in the Chinese population is close to the world average which ranging from 42–84% in different regions in China. Studies have shown that aggravated *H. pylori* infection can directly lead to stress gastrointestinal mucosal lesions[15, 16]. Conversely, other studies have shown that there was no relationship between *H. pylori* seropositivity and gastric bleeding[17–19].

Whether *H. pylori* infection in PBSH patients is related to the occurrence of SU has not been reported. The purpose of this study is to explore the relationship between *H. pylori* infection and the occurrence of SU, and whether it is necessary to eradicate *H. pylori* infection during treatment.

Methods

This retrospective study was conducted in our patients in Neurocritical Care Unit (NICU), Intensive Care Unit (ICU), and Emergency Intensive Care Unit (EICU) between May, 2017-July, 2020. Patients were eligible for the study if they were admitted to a participating ICU for PBSH with gastrointestinal bleeding and with an ICU stay of at least 3 days. Patients were ineligible if their ICU stay was less than 72 hours, and patients with a previous history of gastric or duodenal ulcer were excluded from the study. Because the aim of the study was to analyze the potential role of *H. pylori* infection for SU occurring in PBSH patients during treatments, patients who had hemorrhagic shock on admission or who received more than two units of red blood cell transfusion before or during the first 72 hours after admission to the ICU were also excluded from the study. Blood sample for serum *H. pylori* urease antibody detection was done within 6 hours after admission. All patients were performed with robot-aided stereotactic hematoma aspiration (Fig. 1) and gastric tube indwelling.

Clinical data

The following clinical characteristics were recorded: age, gender, previous significant disease, history of upper gastrointestinal bleeding. Upper gastrointestinal bleeding was suspected at 1, 3, and 7 days after operation.

Detection of H. pylori **antigen**

Serological antibody detection uses the colloidal gold method *H. pylori* urease antibody detection kit (Beijing Kangmei Tianhong Biotechnology Co., Ltd.). The blood sample was collected at 12 hours after admission.

Detection of gastric occult blood test

Gastric occult blood (OB) gold gel stripe is used. The gastric juice specimens were collected with sterile plastic tubes, and were collected three times at 1, 3, and 7 days after operation, and were submitted for

inspection and completed within 1 hour after collection. Immunoassay hemoglobin colloidal gold test strip: product of Wanhua Bioengineering Co., Ltd., batch number 20407002, detection range 0.2–2000μg/ml. A red positive reaction line was showed within 5 minutes a red reaction line is positive.

Statistical analysis

All the data were presented as mean ± standard deviation (SD). Comparisons between data groups were performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Qualitative values were compared by using the χ2 test or Fisher's exact test, as appropriate. Chi-square tests of independence for categorical variables and two-sample t-tests for continuous variables were used to compare unadjusted data; Mann–Whitney U-tests were used for continuous variables that were not normally distributed. P-value of less than 0.05 was considered to indicate statistical significance.

Results

In the study, 65 patients were enrolled. Of these, 7 patients were excluded because their ICU stay lasted less than 72 hours or because they had previous history of gastric or duodenal ulcer. A further 5 patients were excluded because they required blood transfusion for bleeding on admission. Thus, 53 patients constituted the study group. The clinical characteristics of the patients are summarized in Table 1.

Table 1
Clinical characteristics of the 53 brainstem patients

Characteristic Value	
Age in years, mean ± SD (range)	56.09 ± 16.07 (18–83)
Male sex (%)	67.9
Blood Type	
A	18
B	16
ABO	17
O	2

Serology and OB test

Tests for *H. pylori* urease antibodies were performed in 53 PBSH patients. The results were negative in 35 patients (66.04%) and positive in 18 patients (33.96%). The SU was detected with OB test positive and the incidence of OB positive was 25 patients in total (47.17%). The incidence of seropositive in digestive gastrointestinal hemorrhage was 68.0%. OB test positivity was associated with male sex ($p < 0.05$), *H. pylori* urease antibody positivity ($p < 0.05$) and blood type ($p < 0.05$). The other clinical characteristics did not differ according to *H. pylori* status (Table 2). *H. pylori* urease antibody was detected in 33.96% of

patients. *H. pylori* urease antibody positivity was associated with male sex ($p < 0.05$) and OB test positivity ($p < 0.05$). The other clinical characteristics did not differ according to *H. pylori* status (Table 3).

Table 2
Clinical characteristics of Brainstem Hemorrhage patients with negative and positive OB test detection

	OB^+ (n = 25)	OB^- (n = 28)	$t/z/x^2$	P
Age (years)	58.75 ± 17.043	53.86 ± 15.259	-1.527	0.276
Male	21	15	0.616	**0.013**
Positivity of *H. pylori*	17	0	30.242	**0.000**
Blood Type				
A	10	8	7.82	**0.031**
B	4	12		
AB	0	2		
O	11	6		

Table 3
Clinical characteristics of Brainstem Hemorrhage patients with negative and positive H. pylori detection

	HP^+ (n = 18)	HP^- (n = 35)	$t/z/x^2$	P
Age (years)	61.06 ± 14.69	53.72 ± 16.42	1.568	0.123
Male	15	21	4.739	**0.029**
Positivity of OB	17	0	30.242	**0.000**
Blood Type				
A	8	10	6.496	0.087
B	2	14		
AB	0	2		
O	8	9		

Discussion

We found the correlation between *H. pylori* infection diagnosed by serum *H. pylori* urease antibody detection and the occurrence of upper gastrointestinal bleeding in PBSH patients.

PBSH has been confirmed that it was associated with increased gastric acid secretion and the risk of SU. Both proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2) have been shown to reduce the incidence of upper gastrointestinal bleeding the similar as that in brainstem patients[1, 2, 20, 21].

The infection rate of *H. pylori* in China is relatively high, but not all infected patients have the same clinical outcome. In 1983, Australian scholars successfully isolated H. pylori from gastric mucosal tissue for the first time. The concept of "sterile zone in the stomach" in the past of mankind. Since then, a large number of studies have shown that *H. pylori* has serious pathogenicity, and its infection is closely related to a variety of upper gastrointestinal diseases [22]. *H. pylori* is a spiral, microaerobe bacterium that shuttles through flagella and spiral structures and colonizes between the surface and mucosal layers of the gastric mucosa. *H. pylori* infection is globally distributed, and there are differences in the infection rate in various regions; the infection rate in my country is about 50%, of which the infection rate in rural population is about 66%, and the infection rate in urban population is about 47% [22]. At present, *H. pylori* has been recognized as the main pathogenic factor of chronic gastritis, atrophic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. However, not all people infected with *H. pylori* have clinical symptoms.

The pathogenicity of *H. pylori* depends on colonization factors (flagella and helical structure) and virulence factors urease (Ure), adhesin, lipopolysaccharide, cytotoxin-related protein and cell vacuolar toxin (VacA). Colonization, inflammation and immune response damage the gastric mucosa, leading to disease [23]. At present, *H. pylori* has been rated as "the first type of carcinogen" and is an important pathogen causing gastric diseases [22], and many studies have shown that *H. pylori* positive and peptic ulcer, chronic Gastrointestinal diseases such as gastritis and gastric cancer have a strong correlation[23, 24]. Data show that 40% of the population in China has been infected with *H. pylori*, which is the main cause of gastric disease. In order to implement effective treatment for patients with gastric disease as soon as possible, it is necessary to diagnose the cause as soon as possible [24].

Bacterial culture method is currently recognized as the gold standard for the diagnosis of *H. pylori* infection, but the operation of bacterial culture method is very complicated, the detection time is relatively long, and the method is susceptible to external factors, which brings a large workload to clinical testing. The efficiency is low, so it is necessary to find a quick and easy detection method [25]. 14-urea breath test method (14C-UBT), serum *H. pylori* urease antibody enzyme-linked immunosorbent assay (ELISA), and silver staining method are currently commonly used methods for detecting *H. pylori* infection. The first two are non-invasive methods and the latter one is invasive. Studies have shown that the serum *H. pylori* urease antibody ELISA detection method can achieve a similar effect to the silver staining method, and has a better effect than the 14C-UBT detection. Therefore, for coma patients, we choose serum *H. pylori* urease antibody test to assess *H. pylori* infection. Robert et al performed one large clinical study in 2006 and reported a small percentage of *H. pylori* infection detected with rectal swab sampling in ICU patients and showed that the patients infected with *H. pylori* had no additional risk of gastrointestinal bleeding, thus *H. pylori* does not seem to have a major role in the pathogenesis of acute stress ulcer in ICU patients [19]. However, the detection of *H. pylori* infection with rectal swab sampling was not reliable.

In recent years, *H. pylori* infection has been confirmed as an independent risk factor for cardiovascular and cerebrovascular diseases [26]. The possible mechanism is blood lipid metabolism disorder, blood oxygen free radical levels significantly increase, affect the immune system, and make vascular endothelium hyperplasia, injury, changes in blood composition, atherosclerotic plaque formation, and at the same time can increase the concentration of TNF-α and IL-6 in plasma. In recent years, some studies have discussed the relationship between *H. pylori* and SU, and the results are not consistent, and even many experimental results are completely opposite. Comparison of the positive rate of plasma *H. pylori*-IgG antibody in ischemic stroke patients and plasma IgG antibody concentration to verify whether *H. pylori* increases the occurrence of SU[26].

Conclusion

This study showed PBSH patients infected by *H. pylori* were at increased risk of gastrointestinal bleeding, suggesting that *H. pylori* has a major role in the pathogenesis of acute SU in PBSH patients, maybe it is necessary to eradicate *H. pylori* infection during treatment.

Limitation

The number of cases was small, and non-invasive detection methods have false positives or false negatives. Subsequent clinical sample size needs to be expanded in the future.

Abbreviations

PBSH
primary brainstem hemorrhage; SICH:spontaneous intracerebral hemorrhage; AVM:arteriovenous malformation; SU:Stress ulcer; *H. pylori*:Helicobacter pylori; NICU:Neurocritical Care Unit; ICU:Intensive Care Unit; EICU:Emergency Intensive Care Unit; OB:occult blood; SD:standard deviation; PPI:proton pump inhibitors; H2:histamine-2 receptor antagonists; MALT:mucosa-associated lymphoid tissue; Ure:urease ; VacA:vacuolar toxin; 14C-UBT:14-urea breath test; ELISA:enzyme-linked immunosorbent assay

Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the the First Affiliatted Hospital of Anhui Medical University research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was funded by Beijing Postdoctoral Foundation (2020-ZZ-008), Returned overseas students from Anhui Province in 2020 Innovation and Entrepreneurship Support Plan Project (2020LCX016), Funding of the Anhui Universal Natural Science Foundation (KJ2020A0172) and Cultivate Funding of the National Natural Science Foundation of China (2016KJ12).

Authors' contributions: XM, GC and LY analyzed and interpreted the patient data. XM, HC and BL were a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements: Not applicable

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Figures

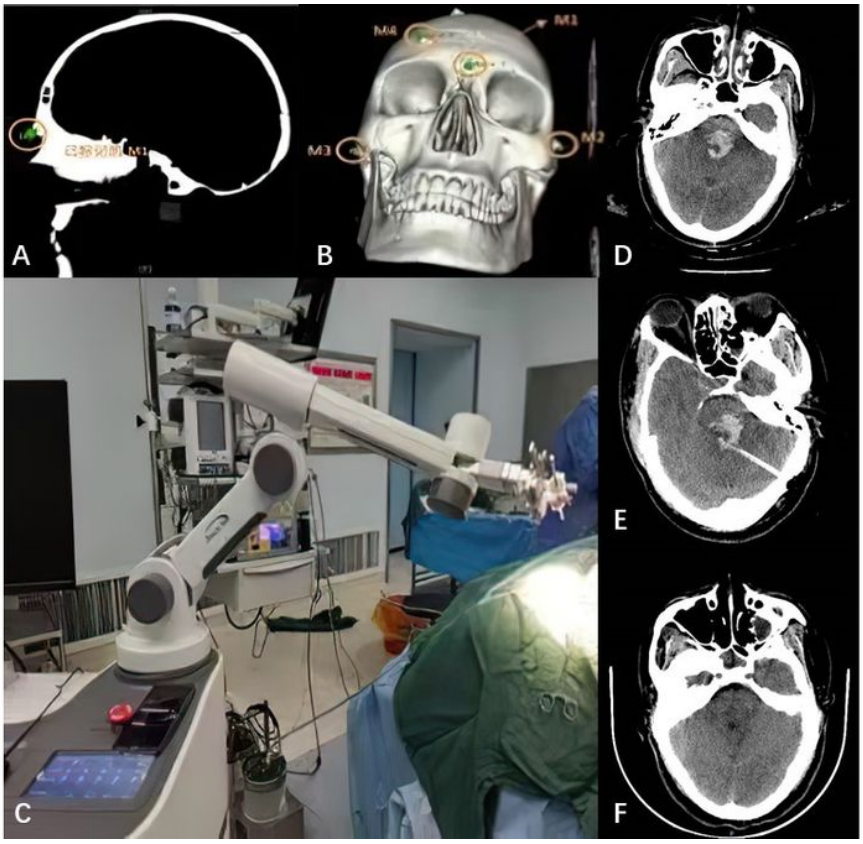

Figure 1

All patients were performed with robot-aided stereotactic hematoma aspiration