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RANDOMIZED CONTROLLED TRIAL

Helicobacter pylori infection in Mongolian gerbils does not initiate hematological diseases

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Abstract

AIM: To investigate whether *Helicobacter pylori* (*H. pylori*) infection contributes to idiopathic thrombocytopenic purpura (ITP) or iron-deficiency anemia (IDA) onset in gerbils.

METHODS: A total of 135 Mongolian gerbils were randomly divided into two groups: an *H. pylori* infection group and a control group. Both groups were fed the same diet and the same amount of food. Each group was then divided into three subgroups, which were sacrificed at 6, 12, or 18 mo for analysis. At each time point, arterial blood was collected from the abdominal aorta and a complete blood cell count was analyzed in the clinical laboratory in the First Affiliated Hospital of Nanchang University.

RESULTS: There were no significant differences in platelet counts (938.00 ± 270.27/L *vs* 962.95 ± 162.56 × 10^9/L), red blood cell counts (8.11 ± 1.25/L *vs* 8.44 ± 1.48 × 10^{12}/L), or hemoglobin levels (136.9 ± 8.76 g/L *vs* 123.21 ± 18.42 g/L) between the control and the *H. pylori* groups, respectively, at 18 mo. With the exception of the mean corpuscular volume (MCV), all other indicators, including white blood cell counts, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, mean platelet volume, platelet distribution width, lymphocyte count, and lymphocyte count percentage, showed no significant differences between the control and *H. pylori* infection groups at each time point. The MCV in the *H. pylori* infection group (52.32 f/L ± 2.86 f/L) was significantly lower than the control group (55.63 ± 1.89 f/L) at 18 mo (P = 0.005), though no significant differences were observed at 6 (54.40 ± 2.44 f/L *vs* 53.30 ± 1.86 f/L) or 12 mo (53.73 ± 2.31 f/L *vs* 54.80 ± 3.34 f/L).

CONCLUSION: A single *H. pylori* infection is insufficient to cause onset of ITP or IDA and other factors may be required for disease onset.

Key words: *Helicobacter pylori*; Extragastric diseases; Idiopathic thrombocytopenic purpura; Iron-deficiency anemia; Chronic inflammation

Core tip: This is the first study designed to investigate the relationship between *Helicobacter pylori* (*H. pylori*) infection and idiopathic thrombocytopenic purpura (ITP) and iron-deficiency anemia (IDA) hematological diseases in a Mongolian gerbil model. Although there were no significant differences between the *H. pylori* infection and control groups, this study may help us better understand the relationships between *H. pylori* and extragastric diseases. While a single *H. pylori* infection is not sufficient to cause ITP or IDA, the precise role of *H. pylori* infection in extragastric disease pathogenesis

remains to be further elucidated.

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INTRODUCTION

Recently, several studies have demonstrated a close association between *Helicobacter pylori* (*H. pylori*) infection and hematological diseases, such as idiopathic thrombocytopenic purpura (ITP) and iron-deficiency anemia (IDA)[1]. In 1998, Gasbarrini *et al*[2] were the first to demonstrate that eradication of *H. pylori* may promote regression of ITP. Since that seminal study, many clinical studies have sought to identify the relationship between *H. pylori* and ITP. It is currently hypothesized that *H. pylori* may be involved in the pathogenesis of ITP[3], and ITP is listed as one of the indications for *H. pylori* eradication[4-6]. IDA, another hematological disease, also shows a close association *H. pylori* infection[7].

Although *H. pylori* infection appears to have a close association with both ITP and IDA, there are still many obstacles that exist in clinical practice. For example, exactly how *H. pylori* pathogenesis influences the onset of these diseases remains unclear. Moreover, eradication of *H. pylori* infection is not beneficial for all ITP and IDA patients[8-10]. Mongolian gerbils have been frequently used to study the pathogenesis of *H. pylori* infection as they are susceptible to colonization and develop gastric diseases as a result of infection[11,12]. To further investigate whether *H. pylori* infection is a contributing factor in the initiation of ITP and IDA, this study was designed to evaluate *H. pylori* infection in a Mongolian gerbil model.

MATERIALS AND METHODS

Animal and bacterial strains

A total of 135 Mongolian gerbils obtained from the Zhejiang Institute of Medical Sciences were randomly assigned to one of two groups: the control group (n = 45) or the *H. pylori* group (n = 90). Animals were individually housed in air isolation cages (IVC-Ⅱ Suzhou Fengshi Animal Equipment Co., Suzhou, China). Gerbils in the *H. pylori* group were intragastrically administered a suspension of *H. pylori*, strain ATCC43504 (CagA+, VacA+; Chinese Center for Disease Control and Prevention, Beijing, China). The control group was administered *Brucella* broth. Each group was then divided into three subgroups, which were sacrificed at 6, 12, or 18 mo. Each control subgroup contained 15 Mongolian gerbils while each *H. pylori* subgroup contained 30 Mongolian gerbils. All Mongolian gerbils were fed the exact same diet and the same amount of food, and procedures were approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

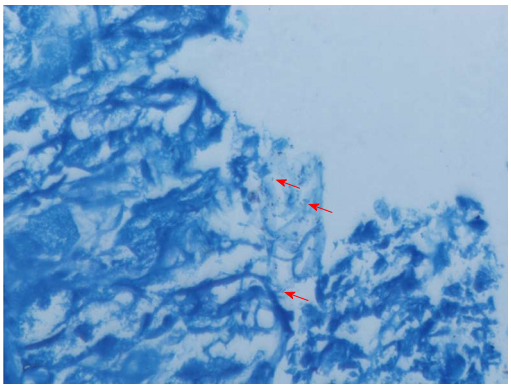

Figure 1 Giemsa staining of Mongolian gerbil gastric mucosa at 18 mo. Red arrows indicate colonization by *Helicobacter pylori* infection (Magnification: × 200).

Confirmation of H. pylori infection

All gastric tissues were harvested from the gastric antrum of the Mongolian gerbils. The tissues were then fixed in 10% formaldehyde overnight at 4 ℃ prior to paraffin embedding. Paraffin sections, 4 μm thick, were cut with a microtome and stored at room temperature. *H. pylori* infection was confirmed by Giemsa staining[13]. Each biopsy was assessed and diagnosed by two veteran pathologists.

Blood cell counts

Arterial blood was collected from the abdominal aorta at 6, 12, or 18 mo, and a complete blood count was obtained for each specimen in the clinical laboratory at the First Affiliated Hospital of Nanchang University.

Statistical analysis

All data are presented as mean ± SD. Statistical significance was evaluated using an unpaired Student's t-test. Statistical analyses were performed with SPSS statistical software, version 19.0 (IBM, Chicago, IL, United States). A P value of < 0.05 was set as the threshold for statistical significance.

RESULTS

Due to a malfunction in the air supply system, 11 Mongolian gerbils from the 12-mo subgroup (*H. pylori* group: n = 8; control group: n = 6) and 14 Mongolian gerbils from the 18-mo subgroup (*H. pylori* group: n = 12; control group: n = 7) died. The remaining Mongolian gerbils were successfully infected with *H. pylori*, which was confirmed by pathology detection (Figure 1).

All of the blood cell count data are listed in Table 1. Platelet counts, which address the presence of ITP, were first analyzed. There were no significant differences observed between the control and *H. pylori* groups at any time point. Next, red blood cell counts and hemoglobin levels were assessed to determine the presence of IDA.

Table 1 Blood cell counts from *Helicobacter pylori* infected and control Mongolian Gerbils at different time points

Group	WBC (× 10^9/L)	RBC (× 10^{12}/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW-SD (fL)	PLT (× 10^9/L)	MPV (fL)	PDW (%)	LYM (× 10^9/L)	LYM%
6 mo													
Control (n = 15)	3.92 ± 1.92	8.63 ± 0.68	136.9 ± 8.76	0.47 ± 0.03	53.30 ± 1.86	15.43 ± 0.81	276.78 ± 6.45	30.31 ± 1.43	1071.50 ± 246.91	6.82 ± 0.36	7.77 ± 0.47	1.97 ± 1.27	50.46 ± 19.10
H. pylori (n = 30)	4.43 ± 2.21	8.88 ± 0.59	131.9 ± 9.42	0.48 ± 0.03	54.40 ± 2.44	15.31 ± 0.47	283.68 ± 8.12	29.61 ± 1.07	962.95 ± 162.56	7.04 ± 0.32	7.63 ± 0.49	1.84 ± 0.88	43.29 ± 16.75
12 mo													
Control (n = 9)	3.67 ± 1.82	8.25 ± 1.11	122.22 ± 10.16	0.43 ± 0.03	54.80 ± 3.34	15.47 ± 1.17	282.44 ± 4.90	29.95 ± 0.88	897.33 ± 157.61	7.30 ± 0.26	8.67 ± 0.31	1.98 ± 0.98	65.60 ± 10.35
H. pylori (n = 27)	2.93 ± 1.80	7.92 ± 0.78	124.61 ± 16.73	0.44 ± 0.06	53.73 ± 2.31	15.13 ± 0.97	281.23 ± 7.27	30.22 ± 2.21	1048.46 ± 289.42	7.19 ± 0.41	8.66 ± 0.84	1.81 ± 0.82	61.00 ± 13.38
18 mo													
Control (n = 8)	2.60 ± 1.23	8.11 ± 1.25	136.50 ± 22.99	0.46 ± 0.07	55.63 ± 1.89	16.21 ± 0.84	291.37 ± 7.61	30.71 ± 1.31	938.00 ± 270.27	7.16 ± 0.37	8.60 ± 0.63	1.44 ± 0.57	52.97 ± 11.32
H. pylori (n = 23)	2.90 ± 2.08	8.44 ± 1.48	123.21 ± 18.42	0.42 ± 0.07	52.32 ± 2.86[a]	15.24 ± 1.04	291.21 ± 12.24	29.18 ± 6.62	1011.43 ± 227.14	6.88 ± 1.55	8.42 ± 2.01	1.47 ± 0.76	51.14 ± 12.79

[a]P < 0.05 *vs* control group. *H. pylori*: *Helicobacter pylori*; HCT: Hematocrit; HGB: Hemoglobin; LYM: Lymphocyte; LYM%: Percentage of lymphocytes; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; MPV: Mean platelet volume; PDW: Platelet distribution width; PLT: Platelet; RBC: Red blood cell; RDW-SD: Red cell distribution width-standard deviation; WBC: White blood cell.

Again, no significant differences were observed between the control and *H. pylori* groups. Leukocyte counts, hematocrits, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume (MCV), red blood cell distribution width, mean platelet volume, platelet distribution width, lymphocyte count, and percentage of lymphocytes were also quantified. No significant differences were observed, with the exception of the MCV, which was significantly lower in the *H. pylori* group in comparison to the control group at 18 mo (52.32 ± 2.86 *vs* 55.63 ± 1.89 fL).

DISCUSSION

A majority of the studies on extragastric manifestations and *H. pylori* have predominantly focused on the epidemiology and clinical outcome after *H. pylori* eradication. It is currently believed that the prevalence of *H. pylori* infection in patients with ITP is significantly higher than that in healthy individuals, though *H. pylori* infection has not been attributed to severe forms of thrombocytopenia[14,15]. Previous research and systematic reviews have demonstrated that *H. pylori* eradication can increase the platelet count in adult ITP patients, especially in mild cases[16,17]. The cytotoxin-associated gene A (CagA), a virulence factor from *H. pylori*, has specifically been implicated in the pathogenesis of ITP[18,19]. Few studies, however, have focused on whether *H. pylori* infection is an initiating factor in ITP. Several hypotheses have been proposed to address how *H. pylori* may contribute to ITP disease onset, including molecular mimicry between *H. pylori* antigens and platelet glycoproteins, platelet aggregation, downregulation of the reticuloendothelial system, and induction of a Th1-mediated immune response[1,20-22].

Studies have also revealed that *H. pylori* infection is closely associated with IDA in both adults and children[23]. Active *H. pylori* infection has been detected in over 50% of patients with unexplained refractory IDA, and 64%-75% of such patients are permanently cured after *H. pylori* eradication[24]. A recent study conducted by Xia *et al*[25] showed that IDA is strongly correlated with *H. pylori* infection and that eradication promoted a more rapid response to oral iron therapy. Similarly, another study demonstrated that eradication of *H. pylori* increased the treatment efficacy in severe refractory IDA[26]. It is currently thought that *H. pylori* causes IDA by an increased iron loss through reduced iron absorption due to bacterial utilization of the iron[1,23].

Most of the previous studies were retrospective in nature, and carried out in a human patient population. Due to inherent individual differences between human subjects, the results from human studies have been difficult to interpret. Very few studies have used animal models to address the relationship between *H. pylori* and extragastric diseases. Huang *et al*[27] investigated the pathological changes occurring in the liver and gall bladder of *H. pylori*-colonized C57BL/6 mice over an eight-month period. Higgins and colleagues analyzed the influence of *H. pylori* infection on colitis and immune response in a mouse model[28].

In this study, a Mongolian gerbil animal model was used to study the association between *H. pylori* infection and ITP and IDA onset to eliminate many of the confounding factors present in human studies. Using this animal model, *H. pylori* infection was allowed to persist for up to 18 mo, a duration significantly longer than other comparable stud-

ies. No significant differences were observed between the *H. pylori* and control groups, with the exception of MCV levels, which were significantly lower in the *H. pylori* group. However, these lower MCV levels may be attributed to the small sample size. The results suggest that a single *H. pylori* infection is insufficient to cause either ITP or IDA. Thus, *H. pylori* may play an auxiliary role in ITP or IDA pathogenesis, but does not serve as an initiating factor.

This study also has some limitations. Only one bacterial strain of *H. pylori* was used in this study, which does not comprehensively account for the range of *H. pylori* infections that can occur. Relatively straightforward parameters were measured, which may not have detected more subtle changes in the immune system occurring before the appearance of abnormal blood cell counts. Furthermore, Mongolian gerbils may not acquire hematological diseases easily whereas mouse strains, which are prone to developing ITP or IDA, should be considered as an alternate model in the future[29,30].

In conclusion, *H. pylori* infection may require other pathogenic factors to contribute to ITP and IDA onset. Factors such as host polymorphisms may also contribute to disease development, a feature that should be examined in future studies.

COMMENTS

Background

Increasing evidence has demonstrated a strong correlation between *Helicobacter pylori* (*H. pylori*) infection and extragastric diseases, including hematological, cardiovascular, and nervous system diseases. Two diseases that show a robust association with *H. pylori* infection are idiopathic thrombocytopenic purpura (ITP) and unexplained iron-deficiency anemia (IDA).

Research frontiers

Several epidemiological studies have demonstrated a higher rate of *H. pylori* infection in ITP and IDA patient populations in comparison to controls. Moreover, infection eradication is beneficial in most cases. The precise role of *H. pylori* in ITP and IDA disease onset, however, is still not understood and whether infection eradication is beneficial or necessary for all ITP or IDA patients remains controversial. This study was designed to evaluate whether a single *H. pylori* infection can trigger ITP or IDA onset.

Innovations and breakthroughs

Previous studies examining the role of *H. pylori* infection in ITP and IDA in patient populations were retrospective in nature, with several confounding factors affecting interpretation of study results. In the present study, Mongolian gerbils were used as an animal model of *H. pylori* infection to exclude many of the confounding factors present in the previous studies.

Applications

This study will further elucidate the roles played by *H. pylori* infection in the pathogenesis of hematological and other extragastric diseases.

Terminology

Idiopathic thrombocytopenic purpura is an autoimmune hemorrhagic syndrome that manifests as isolated low platelet count due to immune destruction. Iron-deficiency anemia is a common form of anemia caused by iron deficiency due to several different factors, and may affect hemoglobin synthesis in blood cells.

Peer review

This research report is an *in vivo* study evaluating the effect of *H. pylori* infection on ITP and IDA onset in a Mongolian gerbil model. Infection in gerbils is a suitable system to model human infection and the results obtained in this paper justify the conclusions drawn. The results of this study are clinically relevant and applicable to a broad audience.

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