

***Helicobacter pylori* Infection in Children with Idiopathic Thrombocytopenic Purpura and the Efficacy of Eradication Therapy**

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(Accepted Mar. 12, 2007)

Eradication of *Helicobacter pylori* (*H. pylori*) has been established as the first line treatment for *H. pylori*-positive chronic idiopathic thrombocytopenic purpura (ITP) in adults according to the results of a nationwide retrospective study in Japan, but it is unclear whether *H. pylori* infection is a precipitating cause of ITP in children. We investigated the prevalence of *H. pylori* infection in 25 children (15 boys and 10 girls), median age 2.8 years, who had been diagnosed with ITP during the six years from July 2000 to June 2006. The 11 patients with chronic ITP (44%) were significantly older than the 14 patients with acute ITP (56%), and female gender was significantly associated with higher prevalence of chronic ITP. Testing for *H. pylori* stool antigen, the ¹³C urea breath test, and/or testing for the presence of serum anti-*H. pylori* IgG antibody was performed in the 11 children with chronic ITP. *H. pylori* infection was diagnosed in three of them (1 boy and 2 girls), and eradication therapy was successful in all three of them. The platelet count in one of the cases increased after the eradication therapy.

In conclusion, *H. pylori* infection was present in 27% of the children with chronic ITP, and eradication therapy may be warranted for children with *H. pylori*-positive chronic ITP that is refractory to conventional therapy.

Key words: idiopathic thrombocytopenic purpura (ITP), *Helicobacter pylori* (*H. pylori*), eradication, child

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease caused by platelet antibodies¹⁾. About 80% of childhood ITP cases are cured within 6 months, and they are classified as the acute type. The other 20% are classified as the chronic type. The chronic type is usually treated with corticosteroids or immunosuppressive drugs, or by splenectomy, and occasionally patients are restricted from participation in sports to prevent serious bleeding²⁾.

In 1998, Gasbarrini et al reported that the platelet count of 8 patients with *H. pylori*-positive chronic ITP increased after eradication of *H. pylori*³⁾, and suggested the efficacy of *H. pylori* eradication in achieving platelet recovery in chronic ITP. In Japan, eradication therapy has been proposed as the first line of treatment in *H. pylori*-positive chronic ITP in adults⁴⁾.

By contrast, there have been few studies on the prevalence of *H. pylori* infection and the efficacy of

eradication in childhood ITP. In a report from Finland, none of 17 children with chronic ITP were diagnosed with *H. pylori* infection⁵⁾. In Taiwan, on the other hand, Jaing et al reported finding *H. pylori* infection in 9 of 22 chronic ITP patients and that the platelet count increased in 5 of them after successful eradication⁶⁾.

We investigated the prevalence of *H. pylori* infection and the effectiveness of eradication in childhood ITP patients diagnosed and treated in our hospital during past 6 years.

Patients and Methods

Between July 2000 and June 2006, 25 patients under 18 years of age were diagnosed with ITP at our hospital according to the criteria of the ITP Committee of the Japanese Society of Pediatric Hematology⁷⁾ and observed for 6 months or more.

An acute ITP group and a chronic ITP group were selected to retrospectively compare sex, age at diagnosis, history of preceding infection, platelet

Table 1 Comparison between the clinical and laboratory features of acute ITP and chronic ITP

	Acute ITP	Chronic ITP	Total	<i>p</i> -value
No. of cases	14	11	25	
	56%	44%	100%	
Sex				
Male	11	4	15	.048
Female	3	7	10	
Age at presentation (year)				
Median	2.1	8.0	2.8	.003
Range	(0.3 ~ 9.0)	(2.2 ~ 14.0)	(0.3 ~ 14.0)	
Preceding infection				
Positive	7	4	11	.688
Negative	7	7	14	
Platelet count at presentation ($\times 10^4/\mu\text{l}$)				
Median	1.7	1.7	1.7	.912
Range	(0.1 ~ 8.6)	(0.3 ~ 6.3)	(0.1 ~ 8.6)	
Minimum platelet count during the course ($\times 10^4/\mu\text{l}$)				
Median	1.2	1.4	1.2	.784
Range	(0.1 ~ 5.3)	(0.3 ~ 4.8)	(0.1 ~ 5.3)	

count at diagnosis, and minimum platelet count. *H. pylori* stool antigen (HpSA), the ^{13}C urea breath test (UBT), and/or testing for the presence of serum anti-*H. pylori* IgG antibody (HpAb) was performed in the children with chronic ITP. Two chronic ITP patients with anemia underwent endoscopy for a urease test and histologic examination and culture of *H. pylori*. Eradication was performed by triple eradication therapy in all of the *H. pylori*-positive ITP cases, and the platelet count response was observed. Triple eradication therapy consisted of a proton pump inhibitor (lansoprazole 1.5 mg/kg/day or omeprazole 1 mg/kg/day), amoxicillin (50 mg/kg/day), and clarithromycin (20 mg/kg/day)⁸⁾.

Informed consent for *H. pylori* testing, eradication and other treatments for ITP was obtained from the parents of the patients after a careful explanation of the study and the safety of treatments.

Fisher's exact probability test and Mann-Whitney's U test were used to perform the statistical analyses. *P* values < 0.05 were considered significant.

Results

There were 11 patients (44%) with acute ITP and 14 patients (56%) with chronic ITP. Seven (63%) of the chronic ITP patients were girls, as opposed to only three (21%) of the acute ITP patients, and thus

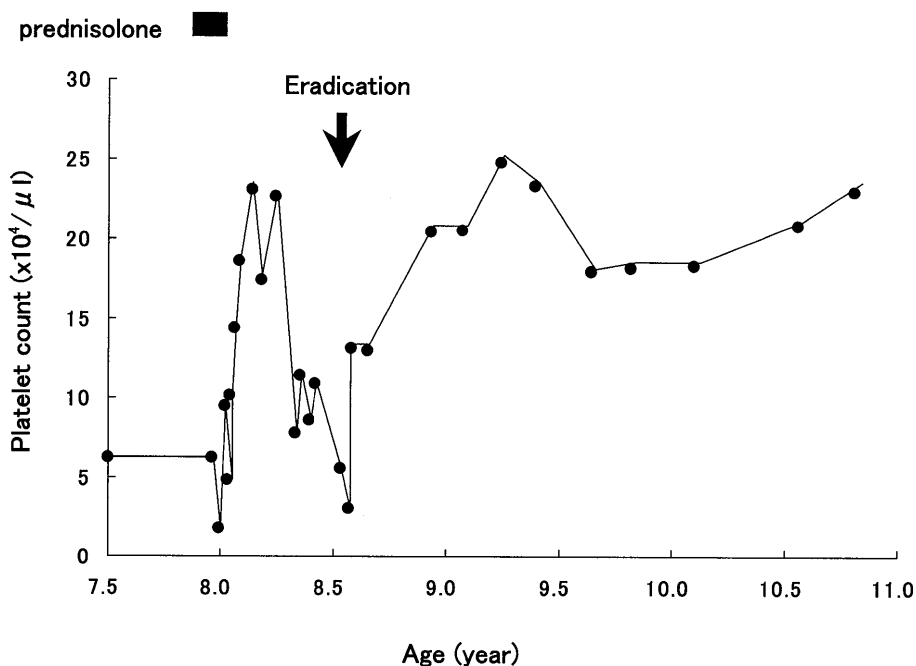
female gender was significantly associated with the development of chronic ITP ($p=0.048$). Median age at the time of diagnosis of ITP was 2.1 years in the acute ITP group and 6.0 years in the chronic ITP group. In other words, the patients with chronic ITP were significantly older than those with acute ITP ($p=0.003$). However, no differences in history of preceding infection, platelet count at diagnosis, or minimum platelet count were found between the acute group and chronic group (Table 1).

HpSA testing was performed in 8 of the chronic ITP cases, the UBT in 5 cases, HpAb testing in 2 cases, and HpSA and the UBT were positive in one case each, and the UBT and HpAb were both positive in one case. *H. pylori* infection was detected in three chronic ITP patients. Moreover, endoscopy was performed in two cases and the urease test was positive in both. In one case, pathological examination of a biopsy specimen revealed *H. pylori* infection (Table 2). Eradication was performed in all three cases that were positive for *H. pylori* infection and was successful in all of them. In one case, the normal platelet count continued without treatment for 12 months or more after eradication. The efficacy rate of platelet recovery after eradication in the children with chronic ITP was 33%.

Table 2 Clinical and laboratory characteristics of *H. pylori*-positive chronic ITP patients

Case	Age at Dx (Years)	Sex	Disease duration to eradication (Months)	Preceding infection	Minimum platelet count ($\times 10^4/\mu\text{l}$)	Previous treatment	Diagnostic tests for <i>H. pylori</i> infection
1	7.9	Female	11	Negative	1.8	prednisolone	UBT HpAb Endoscopy
2	2.8	Male	34	Positive	2.4	prednisolone cepharanthine	HpSA
3	10.6	Female	23	Negative	4.8	None	UBT Endoscopy

Dx: diagnosis, UBT: ^{13}C urea breath test, HpSA: *H. pylori* stool antigen, HpAb: anti-*H. pylori* IgG antibody.

**Fig. 1** Course of platelet counts during treatment in Case 1 over 3 years

Case Report (Fig. 1)

A 7-year-old girl was taken to an otolaryngologist complaining of frequent nosebleeds, and she was found to have thrombocytopenia (platelet count was $63,000/\mu\text{l}$). Five months later, the epistaxis recurred and her face was pale. After admission to our hospital, laboratory tests revealed a leukocyte count of $5,900/\mu\text{l}$, with 57% neutrophils, 1% eosinophils, 39% lymphocytes, and 2% monocytes. The hemoglobin concentration was 5.6 g/dl, and the platelet count was $63,000/\mu\text{l}$. Mean corpuscular volume (MCV) was 54.2 fL.

A diagnosis of ITP with iron-deficiency anemia was made based on these findings, and *H. pylori* infection was diagnosed based on a positive UBT

(12.4%) and positivity for HpAb 3.2 EV (EIA). The endoscopic finding of a positive urease test and pathological examination confirmed *H. pylori* infection. The platelet count declined to $18,000/\mu\text{l}$, and the patient was treated with prednisolone (2 mg/kg/day). After a transient increase in platelet count to $248,000/\mu\text{l}$, it decreased again to $56,000/\mu\text{l}$ after observation for 6 months.

Eradication was by treatment with three drugs: omeprazole 20 mg/day, amoxicillin 1,250 mg/day, and clarithromycin 500 mg/day, for 2 weeks. The platelet count gradually increased to $157,000/\mu\text{l}$ 3 months later, and the patient's serum converted to HpAb, and the UBT became negative. The patient's platelet count has remained within the normal

range for more than 2 years thus far.

Discussion

In 1998, Gasbarrini et al in Italy reported³⁾ observing that ITP regressed after the eradicating *H. pylori* in adult ITP patients with *H. pylori* infection. However, Jarque et al in Spain reported that testing for *H. pylori* should not be routinely included in the initial work-up for ITP, because there is no increase in platelet count after eradication of *H. pylori* infection in patients with chronic ITP⁹⁾. Emilia et al in Italy reported an overall response in 13 (50%) of 30 adult cases of *H. pylori*-positive ITP cases after eradication therapy¹⁰⁾, but there have been conflicting reports about the efficacy of eradication in regard to platelet recovery in adult chronic ITP from country to country.

According to a nationwide retrospective study in Japan, *H. pylori* infection was found in 70% of adult ITP cases, and a significant increase of platelet count was observed in 63% of the cases in which eradication was successful⁴⁾. These results suggested that eradication should be the first line of treatment for adult *H. pylori*-positive ITP patients.

There have been only a few studies on ITP associated with *H. pylori* infection in children. The prevalence of *H. pylori* infection in childhood ITP varies from country to country, the same as adult ITP^{5,6)}. In Japan, Sakai et al tested for HpAb, anti-*H. pylori* IgG antibody in urine, HpSA, and performed the UBT and verified *H. pylori* infection in only 2 (5%) of 40 patients under 15 years old diagnosed with chronic ITP¹¹⁾. Hayashi et al, on the other hand, reported diagnosing *H. pylori* infection in two of 10 subjects and that in the one in which eradication was performed, the platelet count increased¹²⁾. They concluded that eradication of *H. pylori* would also be valuable in children. The results of our study support their conclusion, because *H. pylori* infection was found in three of 11 cases of childhood chronic ITP, and there was a significant increase in platelet count in one of the three cases of successful eradication. We did not determine the prevalence of *H. pylori* infection in children with acute ITP. Jaing et al concluded that there were no indications for screening children with presumed acute ITP for *H. pylori*

infection based on a prospective cohort study showing no statistically significant relation between *H. pylori* infection and acute ITP¹³⁾.

The incidence of *H. pylori* infection in the general population in Japan is under 10% among those under than 10 years of age and 20% in those 10 years of age and over, and it increases to approximately 80% in those 40 years of age and over¹⁴⁾. The incidence of *H. pylori* infection in adult ITP patients does not appear to be different from the incidence in the general Japanese population⁴⁾. The incidence of *H. pylori* infection in the children with chronic ITP in our study was 27%, which may be no higher than the incidence (10-20%) of *H. pylori* infection Japanese children in the general population.

Serologic testing for *H. pylori* is unreliable, especially in young children¹⁵⁾. The lower incidence of *H. pylori* infection in childhood ITP reported by Sakai et al¹¹⁾ is probably due to diagnostic measurement with *H. pylori* serologic testing. The UBT is indicated for the initial diagnosis of infection in adults, but requires further validation in younger children. HpSA provide an alternative to UBT. It has sensitivity and specificity similar to the UBT, and it is suitable for diagnosis in children¹⁶⁾. Two patients with anemia in our study underwent endoscopy for the diagnosis of *H. pylori*. *H. pylori* culture and antibiotic sensitivity testing is useful for assessing resistance to antimicrobial agents, especially clarithromycin, but biopsy is sometimes contraindicated in chronic ITP because of a bleeding tendency. Eradication without endoscopy can be recommended for treatment of HpSA-positive or UBT-positive (older children) chronic ITP.

Spontaneous cures occur in 30% or more of children with chronic ITP¹⁾. Whether the increase in platelet count in this study was attributable to *H. pylori* eradication therapy or a spontaneous remission is unclear. Takahashi et al recently reported that platelet eluates from *H. pylori*-positive ITP patients reacted with *H. pylori* cytotoxic-associated gene A (CagA) protein and concluded that the molecular mimicry by CagA played a key role in the pathogenesis of *H. pylori*-positive ITP¹⁷⁾. An identification of the platelet antigen that shared an epitope

with CagA in future will be useful for the discrimination of the efficacy of *H. pylori* eradication therapy from a spontaneous remission.

Conclusion

The prevalence of *H. pylori* infection in childhood ITP was examined in 14 patients with chronic ITP in our hospital. Three patients (27% of the chronic ITP patients, 1 boy and 2 girls) had *H. pylori* infection, and eradication was successful. In one patient the platelet count increased after eradication, and complete remission was achieved. The results of this study suggested that eradication therapy is efficacious in treating childhood chronic ITP as well as adult ITP, and we concluded that eradication should be one of the treatments used in children with *H. pylori*-positive chronic ITP.

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小児特発性血小板減少性紫斑病における *Helicobacter pylori* 感染の関与と除菌療法の有効性についての検討

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特発性血小板減少性紫斑病（ITP）の成人例では、約 70% の症例で *Helicobacter pylori* (*H. pylori*) 感染を認め除菌成功例の半数以上で血小板が増加することから、ITP における除菌療法の有用性が確立されてきた。しかし、小児 ITP では、発症後 6 ヶ月以内に治癒する急性型の症例が多いこと、また *H. pylori* 感染の検査感度が低いため成人と比較し診断が困難であることなどから *H. pylori* の関与は明らかではない。今回われわれは、2000 年 7 月～2006 年 6 月までの 6 年間に当科で ITP と診断された 25 例、男児 15 例、女児 10 例、発症年齢中央値 2.8 歳（生後 3 ヶ月～14 歳）を対象に ITP における *H. pylori* の関与について検討を行った。急性型が 14 例（56%）、慢性型が 11 例（44%）、慢性型は急性型と比較し女児に多く発症年齢が年長である傾向を示した。慢性型 ITP に便中 *H. pylori* 抗原検査、尿素呼吸テスト、または血清抗 HPIgG 抗体検査を施行した。11 例中 3 例（27%、男児 1 例、女児 2 例）において *H. pylori* が陽性となり、*H. pylori* 陽性例の 3 例に対して amoxicillin, clarithromycin, proton-pump-inhibitor の 3 剤を 14 日間使用する除菌療法を行った。全例で除菌は成功し、1 例（慢性 ITP の 9%、ITP 症例中 4%）において血小板が増加し完全寛解となった。2 例では除菌療法の前後での血小板の変動は認められなかった。除菌療法の副作用は特に認められなかった。

今回の検討から、小児 ITP においても *H. pylori* が関与する症例があることから、一般的な治療に不応な慢性型小児 ITP 症例では除菌療法も考慮すべき治療法の一つであると思われた。