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Association between parental history of *Helicobacter pylori* treatment failure and treatment failure in the offspring

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Abstract

Background and Aim: Both clarithromycin-resistant *Helicobacter pylori* and CYP2C19 polymorphisms may be passed down for generations and are known risk factors for the failure of *H. pylori* eradication therapy. However, no study has evaluated the risk of clarithromycin triple therapy failure in patients with a parental history of such failure. This study investigated the association between a history of clarithromycin triple therapy failure in parents and clarithromycin triple therapy failure in the offspring.
Methods: This cross-sectional study was conducted using a large administrative claims database of 3 100 000 insured individuals. We identified 404 patients who had both personal and parental records of prescriptions for first-line clarithromycin triple therapy between January 2005 and February 2018. Failure of clarithromycin triple therapy was defined as treatment with second-line therapy after having received first-line clarithromycin triple therapy. A parental history of clarithromycin triple therapy failure was defined as failure of clarithromycin triple therapy by either the father or the mother. Odds ratios were estimated using logistic regression models adjusted for age, sex, diabetes mellitus, and peptic ulcer.
Results: The incidence of clarithromycin triple therapy failure was 22.5% (91/404). Based on univariate analysis (odds ratio [95% confidence interval], 1.90 [1.10–3.29]) and multivariable analysis (odds ratio [95% confidence interval], 1.93 [1.10–3.39]), parental history of clarithromycin triple therapy failure was associated with failure of clarithromycin triple therapy in the offspring.
Conclusion: A parental history of clarithromycin triple therapy failure is a risk factor for failure of clarithromycin triple therapy in the offspring.

Introduction

Helicobacter pylori is a bacterium that affects 50% of the world population and is associated with a number of diseases, including chronic gastritis, peptic ulcer, idiopathic thrombocytopenic purpura, and gastric cancer.[1–6] Clinical practice guidelines recommend *H. pylori* eradication for patients with peptic ulcers and idiopathic thrombocytopenic purpura.[4–6] Moreover, recent randomized controlled trials and meta-analyses have demonstrated that *H. pylori* eradication reduces the risk of gastric cancer.[7–15]

Clarithromycin triple therapy, which consists of a proton-pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole, is the most common *H. pylori* eradication regimen worldwide.[5] However, the eradication rate of clarithromycin triple therapy has been declining with the rise in clarithromycin-resistant *H. pylori*.[16] Although the source of transmission of *H. pylori* infection is uncertain, there is increasing evidence supporting the notion of intrafamilial infection; *H. pylori* infection occurs in childhood, and deoxyribonucleic acid analysis has also suggested that clarithromycin-resistant *H. pylori* strain is transmitted among family members.[17–20] In addition, several meta-analyses have demonstrated that the eradication rate of clarithromycin triple therapy is affected by autosomal recessive cytochrome P450 (CYP) 2C19 polymorphisms, because most PPIs are metabolized by CYP2C19.[21–24]

We hypothesized that a parental history of treatment failure with clarithromycin triple therapy is associated with the failure of clarithromycin triple therapy in the offspring owing to the

transmission of clarithromycin-resistant *H. pylori* infections and CYP2C19 polymorphisms. However, no studies have evaluated whether a parental history of clarithromycin triple therapy failure is a risk factor for failure of clarithromycin triple therapy in the offspring. The present study aimed to investigate whether such an association exists.

Methods

Study design. A cross-sectional design was utilized to evaluate whether a parental history of clarithromycin triple therapy failure is a risk factor for failure of clarithromycin triple therapy in the offspring. Because the acquisition of *H. pylori* infections and inheritance of CYP2C19 polymorphisms are established by early childhood, it was unnecessary to restrict the study to patients whose parental *H. pylori* eradication treatment preceded their own treatment.[17–19,24]

Patients. We analyzed a large administrative claims data provided by JMDC Inc. (Tokyo, Japan). This database contains monthly claims from medical institutions and pharmacies submitted since January 2005 for roughly 3 100 000 insured Japanese individuals (approximately 4% of the entire population of Japan), composed primarily of company employees and their family members.[25] For each person, the JMDC database includes an encrypted personal identifier, family identifier, age, sex, diagnoses, medical services, and drugs provided. Encrypted personal identifiers were used to link claims data from different hospitals, clinics, and pharmacies.

In this study, patients who had both personal and parental records of prescriptions for first-line clarithromycin triple therapy (clarithromycin, amoxicillin, and a PPI) between January 1, 2005, and February 30, 2018, were included. Patients who were not the first of their siblings to receive clarithromycin triple therapy were excluded.

Failure of clarithromycin triple therapy against Helicobacter pylori. In Japan, the only first-line *H. pylori* eradication therapy covered by insurance consists of clarithromycin, amoxicillin, and a PPI. If patients fail first-line clarithromycin triple therapy, then second-line eradication therapy is covered by insurance; second-line therapy consists of metronidazole, amoxicillin, and a PPI. Because the results of tests for *H. pylori* infection could not be directly obtained from the database, we defined failure of clarithromycin triple therapy as the receipt of second-line therapy after completion of first-line clarithromycin triple therapy. The repetition of a course of first-line clarithromycin triple therapy was also defined as failure of clarithromycin triple therapy. Successful clarithromycin triple therapy was defined as the receipt of first-line clarithromycin triple therapy that did not require the repetition of first-line therapy or the use of second-line therapy.

Parental history of treatment failure with clarithromycin triple therapy. We used family identifiers to link the claims data of family members. A history of paternal or maternal clarithromycin triple therapy failure was defined as the receipt of second-line therapy after completion of first-line clarithromycin triple therapy—or the repetition of first-line clarithromycin triple therapy—by the father or mother, respectively. A parental history of clarithromycin triple therapy failure was defined as failure of clarithromycin triple therapy by either parent. A parental history of clarithromycin triple therapy success was defined as no history of clarithromycin triple therapy failure in parents who had received clarithromycin triple therapy. Based on parental history, patients were divided into the following two groups: the parental success group, those with a parental history of clarithromycin triple therapy success, and the parental failure group, those with a parental history of clarithromycin triple therapy failure. In this study, we assumed that fathers or mothers who did not receive clarithromycin triple therapy had not been infected with *H. pylori*.

Comorbidities. Comorbidities were defined based on the World Health Organization *International Classification of Diseases, 10th Revision*, or Japanese Standard Disease Names (JSDN): peptic ulcer (K25–K28), *Helicobacter pylori* gastritis (JSDN), idiopathic thrombocytopenic purpura (D693), diabetes mellitus (E10–E14), hypertension (I10–I13, I15), and dyslipidemia (E78).[26,27]

Statistical analysis. Patients' characteristics are expressed as means (standard deviation [SD]). The incidence of clarithromycin triple therapy failure in the parental failure group was compared with that in the parental success group. For the primary analysis, we used logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between a parental history of clarithromycin triple therapy failure and failure of such therapy in the offspring. Multivariable analysis was adjusted for age, sex, diabetes mellitus, and peptic ulcer. Potential confounders were selected based on known risk factors for eradication failure; that is, no statistical selection methods were used.

For the secondary analysis, eradication histories of the fathers and mothers were analyzed separately. We evaluated the association between a paternal history of clarithromycin triple therapy failure and failure of such therapy in the offspring and the association between a maternal history of clarithromycin triple therapy failure and failure of such therapy in the offspring. Multivariable analyses were adjusted for age, sex, diabetes mellitus, and peptic ulcer.

We conducted two sensitivity analyses to confirm the robustness of the primary analysis. First, to exclude patients who may have been lost to treatment follow-up, we restricted patients to those who had been tested for *H. pylori* infection at any time after completion of first-line clarithromycin triple therapy. Procedures or drug codes for the following were considered tests for the confirmation of *H. pylori* eradication: rapid urease test, microbial culture, urea breath test, antibody measurement, and stool antigen test. Second, instead of a cross-sectional study design, we used a cohort study design by restricting patients to those who underwent first-line clarithromycin triple therapy after their parent had received first-line clarithromycin triple therapy.

A P value < 0.05 was considered statistically significant. Stata/SE 15 (StataCorp, College Station, TX, USA) was used to

perform the statistical analyses. The analyses in this study were conducted with no missing data.

This study was approved by the ethics committee of Kyoto University.

Results

Patients' characteristics. A study flow diagram is shown in Figure 1. A total of 415 patients who received first-line clarithromycin triple therapy had a parental history of first-line clarithromycin triple therapy. After siblings were excluded (n = 11), 404 patients remained in the study. Table 1 shows characteristics of the study patients. The mean ages of the patients were 32.6 (SD 12.7) and 32.1 (SD 13.1) years, and the mean ages of the parents were 60.2 (SD 10.2) and 58.8 (SD 10.9) years in the parental success and parental failure groups, respectively.

Association between parental history of clarithromycin triple therapy failure and failure of clarithromycin triple therapy in the offspring (primary analysis). The overall incidence of treatment failure in patients taking clarithromycin triple therapy was 22.5% (91/404). The incidence of treatment failure was higher in the parental failure group, 32.5% (25/77), than in the parental success group, 20.2% (66/327). Based on univariate analysis (Table 2), a parental history of treatment failure with clarithromycin triple therapy was significantly associated with failure of clarithromycin triple therapy in the offspring; the crude OR was 1.90 (95% CI 1.10–3.29). After adjusting for potential confounders, the association remained significant; the adjusted multivariable OR was 1.93 (95% CI 1.10–3.39).

Association between paternal or maternal history of clarithromycin triple therapy failure and failure of clarithromycin triple therapy in the offspring (secondary analysis). Table 3 shows the ORs and 95% CIs for the association between a paternal or maternal history of clarithromycin triple therapy failure and failure of such therapy in the offspring. For the 146 patients who received first-line clarithromycin triple therapy and had a paternal history of such therapy, the overall incidence of treatment failure with clarithromycin triple therapy was 24.7% (36/146). The incidence of treatment failure with clarithromycin triple therapy was 57.1% (8/14) and 21.2% (28/132) in the paternal history of eradication failure group and paternal history of eradication success group, respectively. Based on multivariable analysis, the adjusted multivariable OR for the association between paternal history of clarithromycin triple therapy failure and failure of such therapy in the offspring was 5.23 (95% CI 1.56–17.6).

Table 1 Patients' characteristics

	Parental success group[†] (n = 327)	Parental failure group[‡] (n = 77)
Age (years)	32.6 ± 12.7	32.1 ± 13.1
Sex, men/women (n)	223/104	49/28
Peptic ulcer, n (%)	176 (53.8)	39 (50.7)
Helicobacter pylori gastritis, n (%)	95 (29.1)	26 (33.8)
ITP, n (%)	3 (0.92)	0 (0)
Diabetes mellitus, n (%)	16 (4.9)	4 (5.2)
Hypertension, n (%)	22 (6.7)	4 (5.2)
Dyslipidemia, n (%)	47 (14.4)	8 (10.4)
Year of *H. pylori* eradication[§]		
2005–2009, n (%)	15 (4.6)	3 (3.9)
2010–2013, n (%)	77 (23.5)	18 (23.4)
2014–, n (%)	235 (71.9)	56 (72.7)
Family history of *H. pylori* eradication[§]		
Father only, n (%)	107 (32.7)	6 (7.8)
Mother only, n (%)	203 (62.1)	55 (71.4)
Both, n (%)	17 (5.2)	16 (20.8)
Parental age (years)	60.2 ± 10.2	58.8 ± 10.9

Continuous data are expressed as means ± standard deviations.
[†]Parental success group, patients with a parental history of clarithromycin triple therapy (proton-pump inhibitor, clarithromycin, and amoxicillin) success.
[‡]Parental failure group, patients with a parental history of clarithromycin triple therapy failure.
[§]*H. pylori* eradication was defined as the receipt of clarithromycin triple therapy.
ITP, idiopathic thrombocytopenic purpura.

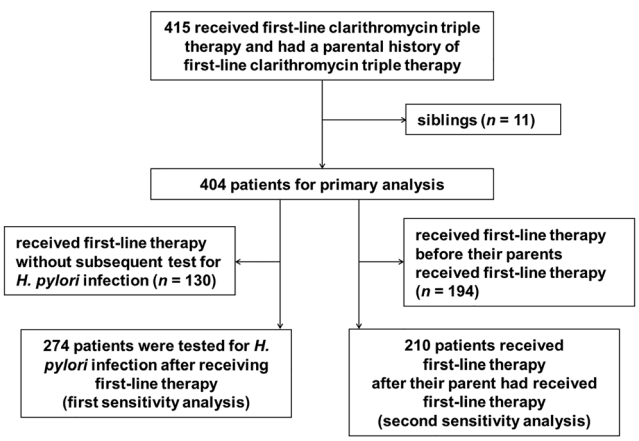

Figure 1 Study flow diagram. A total of 415 patients who received first-line clarithromycin triple therapy had a parental history of first-line clarithromycin triple therapy. After siblings were excluded (n = 11), 404 patients were eligible for primary analysis. Of those 404 patients, 274 patients who were tested for *H. pylori* infection after receiving first-line therapy were included in the first sensitivity analysis, and 210 patients who received first-line therapy after their parents had received first-line therapy were included in the second sensitivity analysis.

Table 2 Association between parental history of clarithromycin triple therapy failure and failure of clarithromycin triple therapy in the offspring

	Patients (n = 404)					
	Crude		Age and sex adjusted		Multivariable adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Parental history of clarithromycin triple therapy failure	1.90 (1.10–3.29)	0.022	1.90 (1.09–3.32)	0.024	1.93 (1.10–3.39)	0.022
Age (continuous)			0.97 (0.95–0.99)	0.003	0.97 (0.95–0.99)	0.002
Female			1.18 (0.71–1.94)	0.53	1.21 (0.73–2.03)	0.46
Diabetes mellitus					4.56 (1.78–11.7)	0.002
Peptic ulcer					1.02 (0.62–1.69)	0.93

Logistic regression models were used to estimate the ORs, 95% CIs, and P values.
CI, confidence interval; OR, odds ratio.

In contrast, 291 patients received first-line clarithromycin triple therapy and had a maternal history of such therapy; their overall incidence of treatment failure with clarithromycin triple therapy was 22.0% (64/291). The incidence of treatment failure with clarithromycin triple therapy was 29.0% (20/69) and 19.8% (44/222) in the maternal history of eradication failure group and maternal history of eradication success group, respectively. Based on the multivariable analysis, the adjusted multivariable OR for the association between a maternal history of clarithromycin triple therapy failure and failure of such therapy in the offspring was 1.61 (95% CI 0.85–3.03).

Sensitivity analyses. First, we restricted patients to those who were tested for *H. pylori* infection after receiving first-line clarithromycin triple therapy. Of the 274 patients who were eligible, the overall incidence of eradication failure was 27.0% (74/274). Based on multivariable analysis, a parental history of clarithromycin triple therapy failure was significantly associated with failure of such therapy in the offspring; the adjusted multivariable OR was 2.16 (95% CI 1.16–4.04). Second, instead of a cross-sectional study design, we used a cohort study design by restricting patients to those who received first-line clarithromycin triple therapy after their parent had received first-line clarithromycin triple therapy. Of the 210 patients who were eligible, the overall incidence of eradication failure was 17.1% (36/210). Based on multivariable analysis, a parental history of clarithromycin triple therapy failure was significantly associated with failure of such therapy in the offspring; the adjusted multivariable OR was 3.13 (95% CI 1.41–6.94).

Discussion

This is the first study to show that after adjusting for potential confounders, a parental history of clarithromycin triple therapy failure was independently associated with failure of clarithromycin triple therapy in the offspring. The robust association between a parental history of clarithromycin triple therapy failure and failure of such therapy in the offspring was confirmed using the following two sensitivity analyses: one in which patients were restricted to those who were tested for *H. pylori* infection after first-line clarithromycin triple therapy and the other in which patients were restricted to those who received first-line clarithromycin triple therapy after their parent had received first-line clarithromycin triple therapy.

It is known that the most important risk factor for failure of clarithromycin triple therapy is clarithromycin-resistant *H. pylori*, which can be transmitted from parents to their children.[4] Both epidemiological and biological evidence have suggested that intrafamilial transmission of *H. pylori* infection is the predominant mode of transmission.[18,28–33] Moreover, transmission of clarithromycin-resistant *H. pylori* strains among family members has been reported.[20] Another concern is CYP2C19 polymorphism. PPIs are primarily metabolized by CYP2C19, an enzyme known to have polymorphisms with three genotypes: homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers (PMs). Meta-analyses have shown that there is a

Table 3 Association between paternal or maternal history of clarithromycin triple therapy failure and failure of clarithromycin triple therapy in the offspring

	Patients with a paternal history of eradication failure (n = 146)		Patients with a maternal history of eradication failure (n = 291)	
	OR (95% CI)	P value	OR (95% CI)	P value
Parental history of clarithromycin triple therapy failure	5.23 (1.56–17.6)	0.007	1.61 (0.85–3.03)	0.14
Age (continuous)	0.96 (0.92–1.01)	0.11	0.97 (0.95–0.99)	0.02
Female	1.69 (0.72–3.96)	0.23	1.16 (0.63–2.14)	0.63
Diabetes mellitus	2.49 (0.10–61.4)	0.58	3.94 (1.49–10.4)	0.006
Peptic ulcer	0.75 (0.32–1.75)	0.51	0.97 (0.54–1.75)	0.93

Logistic regression models were used to estimate the ORs, 95% CIs, and P values.
CI, confidence interval; OR, odds ratio.

significant difference in the eradication rates between PM and heterozygous extensive metabolizer genotypes (OR 2.71, 95% CI 1.46–4.98) and between PM and homozygous extensive metabolizer genotypes (OR 1.90, 95% CI 1.38–2.60).[21–23] Because polymorphisms of CYP2C19 are inherited as autosomal recessive traits, such polymorphisms may cause eradication failure in the offspring.[24] However, we did not have data to determine which mechanism caused clarithromycin triple therapy failure in the offspring. Future studies with detailed information of clarithromycin-resistant *H. pylori* and CYP2C19 polymorphism are needed.

Several studies have indicated that having an *H. pylori*-infected mother is a more relevant risk factor for childhood infection than having an infected father, possibly because intimate contact plays an important role in transmission.[17,28–31] It follows that mothers are also expected to contribute more strongly than fathers to the transmission of clarithromycin-resistant *H. pylori* strains. However, our results showed that unlike a paternal history of clarithromycin triple therapy failure, a maternal history of clarithromycin triple therapy failure was not a significant risk factor for failure of such therapy in the offspring. This may be due to the small sample size used for individually evaluating the influence of paternal and maternal history of treatment failure. Thus, further studies are needed to evaluate the effect.

The present study has five limitations. First, the results of *H. pylori* infection tests were not obtained directly from the database. Failure of clarithromycin triple therapy was defined as receipt of second-line therapy after having received first-line clarithromycin triple therapy. This method may be prone to misclassification bias because those who had failed the first time but decided not to receive second-line therapy were regarded as successfully treated. Nevertheless, the eradication failure rate of the current study (22.5%) was consistent with that of previous studies: 14.9–32.0%.[5,34–36] Therefore, we believe that the eradication failure rate calculated in this study did not substantially differ from the true eradication failure rate. Second, because of the cross-sectional design, reverse causality could not be denied. To account for this possibility, we also used a cohort study design in which patients were restricted to those who received first-line clarithromycin triple therapy after their parent had received first-line clarithromycin triple therapy. By doing so, we confirmed the longitudinal association between a parental history of clarithromycin triple therapy failure and failure of clarithromycin triple therapy in the offspring. Third, we assumed that parents who had not received clarithromycin triple therapy had not been infected with *H. pylori*, because a parental history of clarithromycin triple therapy was available only if the parents had received clarithromycin triple therapy. Fourth, we were unable to adjust for some potential confounding factors, including smoking, body mass index, and medication adherence, and we did not check for CYP2C19 and the existence of clarithromycin-resistant *H. pylori* strains because this study was conducted using a claims database. Finally, mechanisms for the association confirmed in this study were believed to be clarithromycin-resistant *H. pylori* and CYP2C19 polymorphisms, which differ between Japan and other regions.[16,37,38] Further studies in populations with different ethnicities are needed to confirm our results.

In conclusion, this is the first study to demonstrate that a parental history of clarithromycin triple therapy failure is independently associated with failure of clarithromycin triple therapy in the offspring. To identify populations at risk of failure on clarithromycin triple therapy, it may be helpful for physicians to obtain information on the parental history of success or failure with such therapy.

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