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How We Eradicate *H. pylori*

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The progress of gastric cancer treatment started with efforts to improve diagnostic techniques for detecting early stage cancers that could be cured surgically. This ability for early detection of gastric cancer was realized by the development of double contrast radiography, the widespread use of panendoscopy utilizing small-diameter endoscopes, and the establishment of screening systems in local communities and workplaces. Gastric cancer screening using photofluorography is performed in the majority of people at regular intervals, based on the assumption that the likelihood of gastric cancer development is similar in all individuals. However, a negative result from the screening in one year does not predict the status in the next year, and there is a concern that the detection of advanced cancer may increase when people undergo screening at longer intervals.

On the other hand, there is an association between atrophic gastritis and gastric cancer known before the discovery of *Helicobacter pylori* and the concept of a high-risk group for gastric cancer has been suggested. This concept may lead to efficient detection of gastric cancer based on the assumption that there are individual variations in the likelihood of gastric cancer development.

Following the discovery of *H. pylori*, it was demonstrated that *H. pylori* infection was responsible for most cases of atrophic gastritis, and reports from many facilities showed that eradication of *H. pylori* improved atrophic gastritis. These findings suggest the possibility that *H. pylori*-negative individuals might be excluded from the high-risk group for gastric cancer. However, *H. pylori*-positive individuals may further be divided into two types: Those in one type do not show progression of atrophy, but may develop duodenal ulcers while remaining in a high-acid condition. The other type shows progression from atrophic gastritis to intestinal metaplasia and gastric cancer. It is impossible to discriminate between these two types based on serum antibody titers, urea breath test, etc., and invasive endoscopy is needed for accurate assessment. The paper by Seto presented here also demonstrates a high rate of *H. pylori* infection among patients with atrophic gastritis.

Before the discovery of *H. pylori*, we reported that serum pepsinogen (PG) values, in particular the PG 1/2 ratio, highly correlated with the extent of atrophic gastritis. We developed the serum PG method for identifying the high-risk group in gastric cancer screening, and the performance of this method so far has been satisfactory.

A further step forward has been the attempt to provide active treatment to the patients with atrophic gastritis who were found to be high risk for gastric cancer, and to help the patients move out of the high-risk group. Seto's paper emphasizes that eradication at a young age is desirable for the purpose of preventing gastric cancer development, and this point is also elaborated in Suzuki's paper. At the present, there is a controversy regarding the effectiveness of eradication in improving the cases with intestinal metaplasia developing from atrophic gastritis. From the standpoint of gastric cancer prevention, it is important that *H. pylori*-positive individuals undergo eradication before the progression of atrophic gastritis takes place. Because *H. pylori* eradication is not covered by the health insurance, it is difficult to perform this procedure in cases with atrophic gastritis. However, people are taking more interest in *H. pylori* infection, and many patients are now visiting hospitals to receive eradication. The benefit of eradication is considered to surpass the cost.

After the turn of the century, the clinical practice for gastric cancer has been undergoing a major shift in focus from early detection and treatment to the prevention of cancer development. At this point in time, the award of the Nobel Prize to Marshall and Warren for the discovery of *H. pylori* has just been announced. I wish to congratulate them, like my colleagues engaged in the study of gastritis and gastric cancer.

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Prevalence of *Helicobacter pylori* Infection, Eradication Therapy, and Effectiveness of Eradication in Cancer Suppression or Prevention

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Abstract

Since April 1993, we have been examining the *H. pylori* infection status of patients who received upper gastrointestinal endoscopy at our clinic and wished to receive infection tests. We have also been conducting *H. pylori* eradication in the patients with *H. pylori*-positive chronic gastritis since April 1994. Development of gastric cancer was observed in 5 of the 305 patients who received successful eradication. The cancer incidence rate was as low as 1.6%, and the mean age of the patients developing cancer was as high as 68 years old at the time of eradication. Development of gastric cancer after eradication in *H. pylori*-positive ulcers was noted only in 1 of the 360 cases of successful eradication. The cancer incidence rate was 0.27%, and the patient was 67 years of age. These observations indicate that eradication in younger patients is more likely to result in the suppression or prevention of carcinogenesis in the gastric mucosa.

Key words *Helicobacter pylori*, Eradication therapy, Suppression or prevention of carcinogenesis

Introduction

More than 20 years have passed since *Helicobacter pylori* was first isolated from human gastric mucosa.[1] Since the discovery, studies have confirmed that *H. pylori* is found frequently in gastric mucosa from patients with chronic active gastritis and digestive ulcer, patients with gastric carcinoma are frequently positive for *H. pylori* antigens in serum,[2] *H. pylori* is an important factor leading to the recurrence of digestive ulcer,[3,4] and eradication of the bacteria almost completely prevents recurrence.[5–11] In 1994, the National Institute of Health (NIH) in the U.S. recommended eradication of *H. pylori* as a treatment for digestive ulcer,[12] and the World Health Organization (WHO) in the same year specified *H. pylori* as a confirmed carcinogenic factor.[13] Although the most widely recognized meaning of eradication is related to the prevention of recurrence of digestive ulcer, it also causes endoscopic and histological improvement of atrophic gastritis and intestinal metaplasia of gastric mucosa, suggesting that eradication may be effective in preventing gastric cancer. If such prevention is possible, this method is considered to have major clinical significance.

Since April 1993, we have been evaluating the prevalence of *H. pylori* infection and the use of eradication therapy for a period of more than 10 years. This paper presents the results and some discussion concerning the effectiveness of eradication in suppressing or preventing carcinogenesis.

Subjects and Methods

Prevalence of *H. pylori* infection

The subjects were 2,109 patients who received

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upper gastrointestinal endoscopy because of such subjective symptoms as hunger pain, discomfort, and marked acid symptoms during the period from April 1993 to April 2004 and wished to receive infection screening. They included 1,085 males and 1,024 females. The age of the subjects ranged from 12 to 90 years with the mean age of 52.2 years (51.7 for males and 52.6 for females).

The methods used for the detection of *H. pylori* infection were a rapid urease test and microscopy. A patient was considered to have no infection if the results from both methods were negative. The specimens for the rapid urease test, microscopy, and biopsy were taken from 2 locations: the pyloric antrum and the greater curvature of the stomach. The infection rate was analyzed by age group and by disease classification. In the analysis by disease classification, patients with gastritis were classified into the following groups: superficial gastritis with mild endoscopic findings such as linear reddening and histologically slight congestion; erosive gastritis with marked endoscopic observation of erosive changes (including multiple changes) and histological observation of edema and slight lymphocyte infiltration, including cases with small hemorrhage; and atrophic gastritis with extensive mucus adhesion, marked coarse folds, endoscopic evidence of intestinal metaplasia, histologically confirmed infiltration of inflammation cells consisting of neutrophils, atrophied mucosa, and marked decrease in proper gastric glands. Patients showing coexistence of different types of gastritis were classified under the most prominent type. Patients with gastric polyps were classified into hyperplastic polyps, fundic gland polyps, and polyps complicated with gastritis. Patients with gastric cancer were classified into early cancer and advanced cancer.

H. pylori eradication therapy

The subjects were 811 patients who received eradication in the period from April 1994 to June 2004. They included 242 cases of gastric ulcer, 148 cases of duodenal ulcer, 57 cases with concomitance of gastric and duodenal ulcers, 358 cases of chronic gastritis, and 6 cases of gastric cancer. In the case of chronic gastritis, only the patients with subjective symptoms, positive *H. pylori* tests, endoscopic findings, and histological evidence of infection were included in the subjects. The subjects included 470 males and 341 females. The age of the subjects ranged from 12 to 85 years, with the mean age of 54.0 years (52.5 for males and 56.1 for females).

Five methods of treatment were used according to the changing practice in our clinic as follows:

Method 1: Two-Drug Combination of PPI + AM: Daily doses were PPI (lansoprazole 30 mg or omeprazole 20 mg) after breakfast and amoxicillin 750 mg, divided into 3 equal doses after meals. Medication was continued for 4 weeks. This method was used for 1 year from April 1994.

Method 2: Three-Drug Combination of PPI + AM + Defensive Agent (other than ECA): A daily dose of either sofalcone 60 mg, plaunotol 240 mg, polaprezinc 150 mg, rebamipide 300 mg, or cetraxate hydrochloride 1.5 g, divided into 3 equal doses after meals, was added to the regimen of Method 1. Medication was also continued for 4 weeks. This method was used for 1 year from April 1995.

Method 3: Three-Drug Combination of PPI + AM + ECA. A daily dose of ecabet sodium 3 g, divided into 2 equal doses after breakfast and supper, was added to the regimen of Method 1. Medication was also continued for 4 weeks. This method was used for about 6 years from 1995.

Method 4: Three-Drug Combination of PPI + AM + CAM: Daily doses were PPI (lansoprazole 60 mg or omeprazole 40 mg), amoxicillin 1,500 mg, and clarithromycin 200 mg or 400 mg, divided into 2 equal doses after breakfast and supper. Medication was continued for 1 week. This method was used from November 2001 to the present.

Method 5: Four-Drug Combination of PPI + AM + ECA + MNZ: Daily doses were PPI (lansoprazole 60 mg, omeprazole 40 mg, or rabeprazole 20 mg), amoxicillin 1,500 mg, ecabet sodium 3 g, and metronidazole 500 mg, divided into 2 equal doses after breakfast and supper. Medication was continued for 2 weeks. This method was used from about 2001 to the present, mainly for the patients with *H. pylori*-positive chronic gastritis and the cases in which eradication failed.

The result of eradication was assessed basically 4 weeks or more after the completion of eradication treatment. Until 2000, eradication was considered successful if both microscopy and culture tests were negative. Urea breath tests

were added in and after 2001.

The success rate of re-eradication was also evaluated in the cases receiving repeated eradication after an episode of unsuccessful eradication or re-infection following successful eradication. Patients who became positive for *H. pylori* 3 years or more after successful eradication were considered to have had re-infection, while those who became positive within 3 years were counted as relapse.

Cancer rate after *H. pylori* eradication

The cancer rate was studied in 670 patients who received successful eradication. Endoscopy was performed basically once a year and at any time when changes in subjective symptoms were noted.

Results

Prevalence of *H. pylori* infection

As shown in Table 1, 1,327 (62.9%) of the 2,109 subjects were positive for *H. pylori* infection. The infection rate among males was 69.2%, which was significantly higher than 56.3% among females (χ^2 test: $P<0.001$).

Among the age groups (Fig. 1), the infection rate was highest in the patients aged 50–59 years (74.4%), followed by the 60–69 and 70–79 age groups. Infection was twice more prevalent in males than in females in the 20–29 and 30–39 age groups.

Infection rates by disease classification were as shown in Table 2. Among the types of gastritis, the patients with atrophic gastritis showed a high infection rate of 87.8%, in contrast to the lower rates associated with superficial gastritis and erosive gastritis. Patients with ulcers showed high rates, which were 84% in the patients with gastric ulcer and those with duodenal ulcer and 92.4% in those with concomitant gastric and duodenal ulcers (highest of all disease groups). The number of male patients with ulcers was 2.25 times higher than females. In the patients with gastric polyps, the infection rate was 2.9% in fundic gland

Table 1 *H. pylori* infection rate

Patients examined	2,109
Males	1,085
Females	1,024
H. pylori-positive patients	1,327
H. pylori-negative patients	782
Infection rate	62.9%
Males	751 (69.2%)
Females	576 (56.3%)

Test methods: Rapid urease test and microscopy (1993–2004)

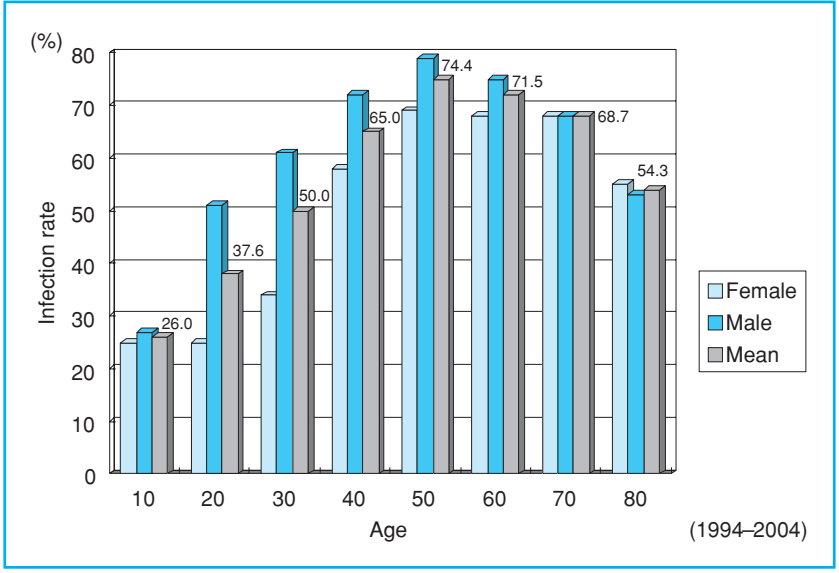

Fig. 1 *H. pylori* infection rate among patients with gastric disease by age group

Table 2 *H.pylori* infection rate by disease classification

	Disease	Gastritis			Ulcers			Gastric polyps			Gastric cancer		Sub-mucosal tumor	Total
		Superficial	Erosive	Atrophic	Gastric	Duodenal	Gastric & duodenal	Hyperplastic	Fundic gland	With gastritis	Early	Advanced		
Male	+	3	149	131	227	140	55	6	0	18	7	15	0	751
	−	32	166	22	48	25	5	7	17	4	0	5	3	334
	Total number	35	315	153	275	165	60	13	17	22	7	20	3	1,085
	Infection rate (%)	8.6	47.3	85.6	82.5	84.8	91.7	46.2	0	81.8	100	75.0	0	69.2
Female	+	6	155	158	111	65	18	9	3	32	4	13	2	576
	−	70	207	19	15	12	1	17	84	17	0	1	5	448
	Total number	76	362	177	126	77	19	26	87	49	4	14	7	1,024
	Infection rate (%)	7.9	42.8	89.3	88.1	84.4	94.7	34.6	3.4	65.3	100	92.9	28.6	56.3
All patients	+	9	304	289	338	205	73	15	3	50	11	28	2	1,327
	−	102	373	41	63	37	6	24	101	21	0	6	8	782
	Total number	111	677	330	401	242	79	39	104	71	11	34	10	2,109
	Infection rate (%)	8.1	44.9	87.8	84.3	84.7	92.4	38.5	2.9	70.4	100	82.4	20.0	62.9

(1994–2004)

Table 3 Number and success rate of *H.pylori* eradication (by disease and by method)

Method of eradication \ Disease		Gastric ulcers	Duodenal ulcers	Gastric & duodenal ulcers	Chronic gastritis	Gastric cancer	Total
PPI + AM	Success	16	13	3	32		64
	Failure	2	1		2		5
	Undetermined		2		2		4
	Success rate (%)						92.8
PPI + AM + Defensive agent other than ECA	Success	12	5	6	15		38
	Failure	3	4		4		11
	Undetermined				1		1
	Success rate (%)						77.6
PPI + AM + ECA	Success	102	50	16	155	4	327
	Failure	2	3	3	9		17
	Undetermined	9	4	2	5		20
	Success rate (%)						95.1
PPI + AM + CAM	Success	69	36	17	51	0	173
	Failure	3	9	3	9	0	24
	Undetermined	13	14	5	5	1	38
	Success rate (%)						87.8
PPI + AM + ECA + MNZ	Success	9	4	2	52	1	68
	Failure	0	0	0	3	0	3
	Undetermined	2	3	0	13	0	18
	Success rate (%)						95.8
Total	Success	208	108	44	305	5	670
	Failure	10	17	6	27	0	60
	Undetermined	24	23	7	26	1	81
	Total	242	148	57	358	6	811
	Success rate (%)	95.4	86.4	88.0	91.9	100	91.8

PPI: proton pump inhibitor, AM: amoxicillin, ECA: ecabet sodium, CAM: clarithromycin, MNZ: metronidazole,
Defensive agent other than ECA — SOF: sofalcone, PLA: plaunotol, POL: polaprezinc, REB: rebamipide, or CET: cetraxate hydrochloride
(1994.4–2005.6)

Table 4 Cases of gastric cancer after eradication in chronic gastritis

Case	1	2	3	4	5
Age at eradication, sex	80.M	65.M	66.F	53.F	78.F
Method of eradication	PPI AM ECA	PPI AM SOF	PPI AM SOF	PPI AM ECA	PPI AM ECA
Years from eradication to cancer development	3	5	7	3	3
H. pylori infection at the time of cancer detection	(−)	(−)	(−)	(−)	(−)
Classification of early gastric cancer	IIb	IIb + IIc	III + IIc	IIb + IIc	IIc
Tumor size (cm)	0.3×0.3	0.5×0.2	2.5×2.5	3.5×1.0	2.0×1.0
Method of resection	EMR	Op	Op	Op	EMR→OP
Metastasis & invasion	(−)	(−)	(−)	(−)	(−)
Histological diagnosis	Well-differentiated tubular adenocarcinoma	Well-differentiated tubular adenocarcinoma	Moderately-differentiated tubular adenocarcinoma	Well-differentiated tubular adenocarcinoma (moderately-differentiated in part)	Signet ring cell carcinoma

PPI: proton pump inhibitor, AM: amoxicillin, ECA: ecabet sodium, SOF: sofalcone

polyps (lowest of all disease groups), 38.5% in hyperplastic polyps, and as high as 70.4% in polyps complicated with gastritis. Contrary to ulcers, the number of female patients with polyps was more than 3 times higher than males. Among the types of gastric cancer, the infection rate was 100% in early cancer and 82.4% in advanced cancer. It was as low as 20% in submucosal tumor.

H. pylori eradication therapy

Of the 811 cases receiving eradication therapy, the result was successful in 670 cases, unsuccessful in 60 cases, and undetermined in 81 cases, as shown in Table 3. The total success rate was 91.8%. As seen by disease classification, the success rate was highest in the patients with gastric ulcer (95.4%), followed by chronic gastritis (91.9%). It was lowest in the patients with duodenal ulcer (86.4%). Among the 5 methods of treatment, Method 1 resulted in an eradication success rate of 92.8%. The addition of defensive agents during the 2nd year caused an increase in unsuccessful results, reducing the success rate to 77.6%. An exception was Method 3 (3-drug combination including ECA), which showed improved eradication efficiency, and the use of this method was continued for 6 years. While this method was used in nearly a half of all cases, it resulted in a high success rate of 95.1%. The success rate of Method 4 was somewhat lower (87.8%) because of the problem related to the CAM resistance in the Japanese population. Method 5 was used in the cases of unsuccessful eradication or re-infection, as well as in the patients with *H. pylori*-positive chronic gastritis who were young or had a family history of gastric cancer. This method has been used since about 2001 up to the present, and the success rate has been as high as 95.8%.

Re-eradication was successful in 45 cases (including 13 cases of re-infection), undetermined in 13 cases, and unsuccessful in 6 cases. The success rate was 88.2%.

Cancer rate after *H. pylori* eradication

Our clinic has a record of successful eradication in 305 cases of chronic gastritis, including 3 cases of superficial gastritis, 115 cases of erosive gastritis, and 187 cases of atrophic gastritis. Development of gastric cancer was observed in 5 of these cases, and was totally developed in the patients who had atrophic gastritis. As shown in Table 4, these included 2 males and 3 females.

The age at the time of eradication was as high as 68 years on average. The mean time from eradication to cancer development was 4.2 years, and all cases were detected in the stage of early cancer. Thus, the rate of cancer development after eradication was 1.6%. No cases of gastric cancer developed in the patients receiving eradication at ages of 52 years or less.

Of the 360 cases of *H. pylori*-positive ulcers receiving successful eradication at our clinic, only 1 developed gastric cancer after eradication. This patient was a male aged 67 years, and the rate of cancer development after eradication was 0.27%.

Discussion

Prevalence of *H. pylori* infection

We have been examining the *H. pylori* infection status of patients visiting our clinic since April 1993. The results in 1998[15] showed that the infection rate among the more than 1,000 cases examined in 5 years was 66.9%. In contrast, the present study revealed that the infection rate decreased to 62.9%, while the total number of cases increased to exceed 2,000. This decrease in the infection rate may be explained by the improvement and expanding coverage of water supply and sewerage systems. The analysis by age group indicated that the infection rate among patients younger than 40 years old decreased to less than 50%, lower than the rate reported 5 years ago by about 10%, probably because of the same reason. The analysis by disease classification showed that all types of ulcers were associated with an 84% or higher infection rate, indicating that nearly 90% of ulcers involved *H. pylori* infection. In contrast, infection was detected in only 3 of 104 patients with fundic gland polyps, which were mostly presented as multiple polyps.

H. pylori eradication therapy

Five different methods of eradication were used in the period from 1994 to the present day. The 3-drug combination of PPI + AM + ECA (Method 3) was the method providing the highest eradiation efficiency until recently. ECA is considered to improve the eradication rate through its prolonged retention in the gastric mucosa, activity to inhibit urease,[20] activity to prevent the survival and adhesion of *H. pylori*,[21,22] and ability to reduce side effects of concomitant drugs. Because of this reason, ECA was also added to the eradication regimen in Method 5. One problem was that medication in Method 3 was continued for 4 weeks, because we limited the daily dose of AM to 750 mg considering the possibility of side effects. The long period of medication might be a disadvantage of this method. The regimen in Method 5 included metronidazole, which is expected to remain highly effective for some time in the future, because the use of this agent has not been popular in Japan.

The success of eradication was evaluated 4 weeks or more after eradication treatment at our clinic. Most patients were re-examined by endoscopy, as well as the rapid urease tests and microscopy, 1 year after treatment, and were found to be negative in all cases. This indicated that evaluation conducted 4 weeks or more after treatment provides correct results. Evaluation at later timing may result in an increase in undetermined cases. There is a possibility that the addition of urea breath tests may lower the success rate in the future, and we need to look carefully at the effect of this alteration of the evaluation method. In any case, the key to successful eradication is ensuring the compliance of patients with eradication regimens. In this sense, practical physicians are expected to achieve a better eradication rate. With respect to re-eradication, we performed re-eradication in the patients who desired it and achieved a success rate of as high as 88.2%. We consider persistent repeat treatment using a different method more important than pursuing the cause of failure.

Finally, there is a problem with the undetermined cases, which represented about 10% of all cases receiving eradication (81 of 811 cases). Although we repeatedly prompted them, some patients did not receive evaluation tests because their symptoms disappeared. These are considered to have included many successful cases. Unfortunately, solution to this problem seems difficult.

Cancer rate after *H. pylori* eradication

Gastric cancer developed in 5 patients with chronic gastritis after eradication (cancer incidence rate 1.6%). All cases developed in the patients with atrophic gastritis, and the mean age of these patients at the time of eradication was as high as 68 years old. No cancer developed in

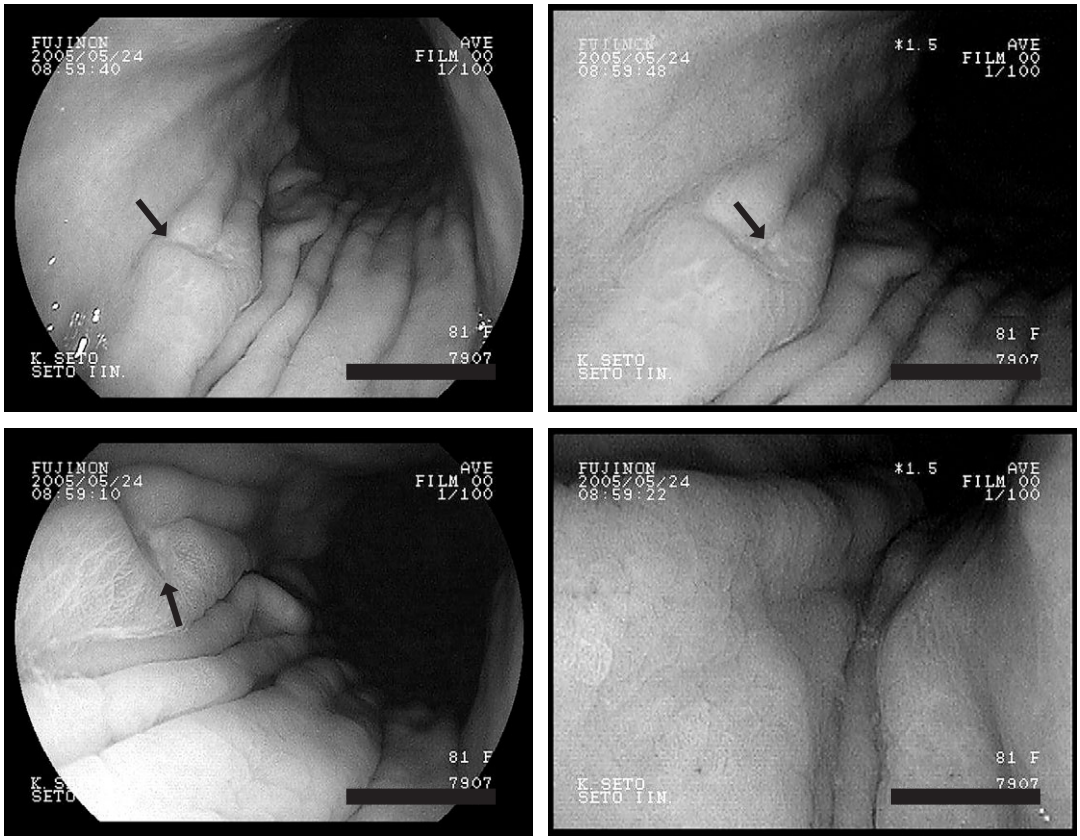

Fig. 2 Gastric cancer after *H. pylori* eradication in chronic gastritis, case No. 5

the patients younger than 52 years old. The earlier 4 cases of gastric cancer were described in our report "Development of gastric cancer after eradication in *H. pylori*-positive chronic gastritis" in March 2004. The 5th case was detected in May of this year 3 years after the 4th case. This patient was an 81-year-old female who received eradication using PPI + AM + ECA 3 years ago. While she was receiving outpatient treatment for hepatitis C, endoscopy was performed because of slight subjective symptoms, and an IIC-like lesion was found in a part of the greater curvature, where atrophic changes were prominent. Histopathological study confirmed group V signet ring cell carcinoma, and surgery was performed on the patient (Fig. 2). Despite this addition of a new case, the cancer incidence rate decreased from 1.8% to 1.6%. Furthermore, only 1 case of gastric cancer developed after eradication in the patients with ulcers (cancer incidence rate 0.27%). This patient was a 67-year-old male who had ulcers in the lesser curvature of the gastric angle and was positive for *H. pylori* infection. Eradication using PPI + AM + ECA was performed successfully and ulcers disappeared, but a protruded lesion with central ulceration was found in the same area after 5 and a half years. Biopsy proved group V adenocarcinoma, and surgery was performed on the patient. The experience with these cases suggests that eradication in younger patients and patients lacking atrophy is more likely to achieve normalization of the gastric mucosa, which may lead to the suppression or prevention of cancer development.

Naomi Uemura et al. reported their results suggesting the possibility that eradication may suppress the development or growth of metachronous gastric cancer.[17] In agreement with their finding, we also performed eradication in the 6 cases of *H. pylori*-positive gastric cancer before or after surgery, and observed no relapse

of cancer up to the present day.

With respect to the effect of eradication on residual gastric mucosa after endoscopic mucosal resection (EMR), Uemura et al. discussed that eradication morphologically improved inflammatory cell infiltration in infected gastric mucosa, functionally suppressed the production of various cytokines, endoscopically improved coarse folds in the greater curvature of the gastric corpus, and improved gastric acid secretion, improving visibility in endoscopic observation and potentially contributing to the early detection of gastric cancer.[18] These remarks agreed with our experience that early-stage gastric cancers after eradication were detected in clean surfaces of the mucosa.

In the study published in 2004, Wong et al. followed 1,630 *H. pylori*-positive patients in Fujian Province, China, with and without eradication for 7.5 years.[19] While the follow-up of all patients revealed no significant difference between groups with and without eradication, the timing of carcinogenesis was clearly later in the eradication group than in the non-eradication group. This result suggests the effectiveness of eradication in suppressing carcinogenesis. On the other hand, the subgroup analysis of patients lacking atrophy, intestinal metaplasia, or dysplasia revealed a significantly lower rate in the eradication group, which included no patient developing gastric cancer, than in the non-eradication group. This result is considered to have the same implication as observation that eradication is more likely to suppress or prevent cancer in younger patients.

Conclusion

1) Of the total 2,109 patients examined, 1,327 were positive and 782 were negative for *H. pylori* infection. The prevalence of infection was 62.9%.
2) High infection rates were associated with ulcers and atrophic gastritis. Among the types of gastric polyps, fundic gland polyps were associated with the lowest infection rate, while the cases complicated with gastritis showed considerably high infection rates.
3) *H. pylori* eradication therapy was performed using 5 different methods. The result of eradication in 811 patients was successful in 670 cases, undetermined in 81 cases, and unsuccessful in 60 cases. The success rate was 91.8%. The 5th method has been used in the cases of unsuccessful eradication or re-infection, as well as in the patients with *H. pylori*-positive chronic gastritis who were young or had a family history of gastric cancer. This method has been recording a success rate of as high as 95.8%, and future developments are expected. Re-eradication was successful in 88.2% of cases. Persistent attempts at eradication should be continued with careful selection of the treatment method.
4) Development of gastric cancer after eradication in *H. pylori*-positive chronic gastritis was detected in 5 of the 305 cases of successful eradication (cancer incidence rate 1.6%). The mean age of the patients developing cancer was as high as 68 years old. No cases of gastric cancer developed in the patients aged 52 years or less. Development of gastric cancer after eradication in *H. pylori*-positive ulcers was noted in 1 of the 360 cases of successful eradication (cancer incidence rate 0.27%, age 67 years old). These important observations indicate that eradication in younger patients is more likely to result in suppression or prevention of carcinogenesis in the gastric mucosa.

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Original Article

Health-related Quality of Life among Community-dwelling Elderly People in the General Populations of the US and Japan

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Abstract

Background Japanese live longer than Americans, but whether elderly Japanese enjoy better health-related quality of life (HRQOL) than elderly Americans is unknown.

Objective To compare HRQOL between community-dwelling elderly Japanese and Americans using population data.

Design, Setting, and Participants Retrospective, cross-sectional study using nationwide survey data of 706 US and 491 Japanese subjects aged 65 years or above.

Main outcome measures The 36-Item Short-Form Health Survey.

Results Elderly Japanese had higher physical-related HRQOL scores (physical functioning, role-physical, bodily pain, vitality) and social functioning than elderly Americans. The disparity of physical functioning scores between the two populations was greater in the higher-aged groups. Medical conditions were surveyed using a self-report questionnaire. More than 76% of elderly Americans reported having two or more medical conditions compared with 39% of Japanese. Only 8.3% of elderly Americans reported having no medical condition, compared with 28% of Japanese. Multivariate analyses suggest that the number of medical conditions is the most important independent predictor for physical functioning scores. In addition, mental health-related HRQOL scores (mental health, general health perceptions, and role-emotional) were lower in Japanese than in the Americans.

Conclusions Community-dwelling elderly Americans had lower physical functioning and more comorbid conditions than similarly aged Japanese.

Key words Health-related quality of life, The United States, Japan, Elderly, SF-36

Introduction

The populations of economically developed countries such as the United States (US) and Japan are ageing. At age 65, life expectancy in the US was 16.6 years for US men and 19.5 years for women in 2002,[1] compared with 18.21 years for Japanese men with 23.28 years for Japanese women in 2004.[2] However, whether elderly

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Japanese enjoy a higher quality of life than elderly Americans is unclear. No previous study has assessed differences in health-related quality of life (HRQOL) between representative samples of the general populations of both the US and Japan using comparable measures. We looked for differences in HRQOL between community-dwelling elderly people in the US and Japan, using the 36-Item Short-Form Health Survey (SF-36).[3] We hypothesized that community-dwelling elderly Japanese would report better HRQOL compared with similarly aged elderly Americans.

Methods

Study design

A retrospective, cross-sectional design was employed.

Samples and data collection

Data for the US population were derived from the 1990 National Survey of Functional Health Status (NSFHS), a cross-sectional survey to collect national normative data for the SF-36 Health Survey.[4] The sampling frame was 2,909 households from the General Social Survey.[5] From this sample, 3,251 non-institutionalized subjects aged 18 years or older were selected, and data were available from 2,474 (76.1%) of these individuals. The response rate of those aged 65 years or older was more than 80%. The questionnaire was self-reported and administrated by mail or telephone.

Japanese data were derived from a 1995 cross-sectional survey designed to obtain national normative data for the Japanese version of the SF-36 Health Survey.[6] A two-stage stratified random sampling frame was constructed to select non-institutionalized subjects aged 16 and older from the Japanese population. A total of 300 districts were randomly selected from 50 strata, consisting of 10 major regions of Japan and five city sizes. Within each of the 300 districts, 15 respondents were randomly selected. Of 4,500 eligible subjects selected, data were available from 3,395 individuals (75.4%). The self-reported questionnaire was hand-delivered to participants by a trained data collector who collected the completed questionnaire one week later. The questionnaires were hand-delivered to 617 persons aged 65 years or older, and were returned by 491 (79.6%). We analyzed data from 706 US and 491 Japanese subjects aged 65 years or older.

Questionnaire content

The NSFHS survey contained questions regarding HRQOL, social factors related to HRQOL, demographic and other characteristics. HRQOL was measured using the SF-36. This generic instrument comprises eight scales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH).[7] Scores on all eight scales are transformed to a 0 to 100 scale using the Medical Outcomes Study algorithm.[7] Higher scores are associated with better status. Chronic medical conditions were measured using a checklist of fourteen conditions (hypertension, myocardial infarction, congestive heart failure, diabetes, angina, cancer, chronic allergies or sinus trouble, arthritis of any kind or rheumatism, sciatica or chronic back problems, blindness or other trouble seeing, chronic lung disease, dermatitis or other chronic skin rash, deafness or trouble hearing, and limitation in the use of an arm or leg). The subjects were asked whether or not they had been given a diagnosis of hypertension, myocardial infarction, congestive heart failure, diabetes, or cancer. For the other nine conditions, the subjects were asked whether or not they thought they had the condition.

The Japanese questionnaire included similar items regarding HRQOL, social factors related to HRQOL and demographic and other characteristics including weight and height. The Japanese language version of the SF-36 was used to measure HRQOL. This was developed in accordance with the protocol recommended by the International Quality of Life Assessment Project,[8] and has been shown to be reliable and valid.[9] The scoring algorithm of the Japanese-language version of the SF-36 is the same as the Medical Outcomes Study algorithm.[10] Chronic medical conditions were measured using a checklist of thirteen conditions comparable to those in the NSFHS survey (hypertension, myocardial infarction, congestive heart failure, diabetes, angina, chronic allergies or sinus trouble, arthritis of any kind or rheumatism, sciatica or chronic back problems, blindness or other trouble seeing, chronic lung disease, dermatitis or other chronic skin rash, deafness or trouble hearing, and

limitation in the use of an arm or leg) and cerebrovascular diseases. Unfortunately, the US subjects were not asked about cerebrovascular diseases, nor were the Japanese subjects asked whether or not they had cancer.

Statistical analyses

SAS version 8.2 was used to analyze the data. Continuous variables were compared using Student's t-test (for normally distributed data) or the rank-sum test (for non-normally distributed data). We used the chi-square test or Fisher's exact probability test for comparison of categorical variables. Body Mass Index (BMI) for the Japanese subjects was calculated as weight in kilograms divided by height in meters, squared.

We compared scores on the eight scales of the SF-36 between the US elderly and Japanese elderly subjects with scores for males and females combined. We also evaluated mean scores on the PF for seven different age groups (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75 years or older). We then compared PF scores between elderly Americans and elderly Japanese by gender-age (65–69, 70–74, 75–79, 80 years or older) groups.

The associations between the subject's location (US or Japan) and scores on the PF were estimated using multiple linear regression models. The dependent variable was the continuous score on the PF. Independent variables were the subject's location, age, gender, number of medical conditions, marital status (married or not), and education (more than twelve years of education or not). Age and number of comorbid conditions were entered into the model as continuous variables; other factors were entered as categorical variables.

Results

Characteristics of the samples

Table 1 shows the demographic characteristics of the samples. The elderly Americans on average were older, had more years of education, and were more likely to be female. Compared to the Americans, the Japanese were more likely to be married. Twenty-eight percent of the Japanese elderly subjects reported none of the comorbid conditions listed, compared with only 8.3% of

Table 1 Study sample characteristic

	US (n=706)	Japan (n=491)	P-value
Age (Mean±SD)	73.4±6.2	71.2±5.8	<0.0001
Gender-no. (%)			
Male	293 (41.5)	266 (54.2)	
Female	413 (58.5)	225 (46.8)	<0.0001
Education-no. (%)			
12 years or less	480 (69.2)	411 (85.6)	
more than 12 years	214 (30.8)	69 (14.4)	<0.0001
Marital status-no. (%)			
Never married	30 (4.3)	4 (0.8)	0.0004
Married	415 (59.1)	373 (76.4)	<0.0001
Divorced	37 (5.3)	8 (1.6)	0.0012
Separated	5 (0.7)	5 (1.0)	0.5620
Widowed	215 (30.6)	98 (20.2)	<0.0001
Body weight (kg)	no data	Male: 58.5±8.8 Female: 50.2±7.9	not available
Height (cm)	no data	Male: 161.4±6.5 Female: 149.8±6.3	not available
Prevalence of overweight (%) (25≦Body Mass Index)	no data	Male: 16.3 Female: 18.9	not available

the Americans (Table 2). The prevalence of 11 medical conditions was significantly higher in the Americans than in the Japanese; the prevalence of myocardial infarction and diabetes was similar between the two groups. Fewer than 20% of the Japanese subjects were overweight or obese (defined as a BMI of 25 kg/m^2 or more, Table 1). Although in this study, height and weight were self-reported, this finding is generally consistent with that of a survey in which height and weight were measured directly, which was published by the Japanese Ministry of Health and Welfare.[11]

SF-36 scores in the US and Japan

Table 3 shows the SF-36 scores of the elderly subjects in the US and Japan. The Japanese elderly subjects had higher scores on the PF, RP, BP, VT, and SF scales. The largest differences

Table 2 Prevalence of medical conditions

	US (n = 706) no. (%)	Japan (n = 491) no. (%)	P-value
Number of medical conditions			
0	54 (8.3)	137 (28.0)	<0.0001
1	96 (14.8)	162 (33.0)	<0.0001
2 or more	497 (76.8)	192 (39.0)	<0.0001
Medical conditions			
Hypertension	344 (49.7)	185 (37.7)	<0.0001
Congestive heart failure	60 (8.8)	18 (3.7)	0.0005
Myocardial infarction	42 (6.1)	20 (4.1)	0.1262
Angina	74 (10.8)	33 (6.7)	0.0157
Diabetes	87 (12.6)	49 (10.0)	0.1630
Chronic allergies or sinus trouble	243 (35.3)	25 (5.1)	<0.0001
Arthritis or rheumatism	436 (63.0)	49 (10.0)	<0.0001
Sciatica or chronic back problems	202 (29.3)	101 (20.6)	0.0007
Blindness or other trouble seeing	143 (20.5)	64 (13.0)	0.0008
Chronic lung disease	75 (10.8)	16 (3.3)	<0.0001
Dermatitis or chronic skin rash	74 (10.6)	20 (4.1)	<0.0001
Deafness or trouble hearing	249 (35.8)	91 (18.5)	<0.0001
Limitation in the use of an arm or leg	122 (17.7)	44 (9.0)	<0.0001
Gastrointestinal diseases	no data	145 (29.5)	not available
Cerevrovascular diseases	no data	34 (6.9)	not available

Table 3 SF-36 scores of US and Japanese elderly

	US (n = 706)	Japan (n = 491)	P-value
Physical-functioning	63.4 ± 28.9	74.2 ± 22.6	<0.0001
Role-physical	57.4 ± 42.5	68.5 ± 39.2	<0.0001
Bodily pain	65.6 ± 26.6	68.5 ± 24.3	0.0492
General health perceptions	60.4 ± 22.1	57.9 ± 21.7	0.0573
Vitality	56.2 ± 23.2	64.1 ± 22.8	<0.0001
Social functioning	78.1 ± 26.9	82.6 ± 22.7	0.0159
Role-emotional	74.8 ± 38.8	72.6 ± 40.5	0.1687
Mental health	75.8 ± 18.9	73.4 ± 20.6	0.0289

were on the PF and RP scales. The Americans had higher scores on the MH scale. Scores on the GH and RE scales also tend to be lower in the Japanese than in the Americans but were not statistically significant.

Physical functioning and age

For the younger and middle-aged groups (54 years or younger), PF scores of the two populations were similar, but for the older groups (55 years or older), the PF scores of the Japanese were much higher than those of the Americans (Fig. 1).

Table 4 shows that elderly Japanese men reported higher PF scores than similarly aged Americans across all age groups. Elderly Japanese women aged 65 to 74 years also reported higher PF scores than Americans. PF scores

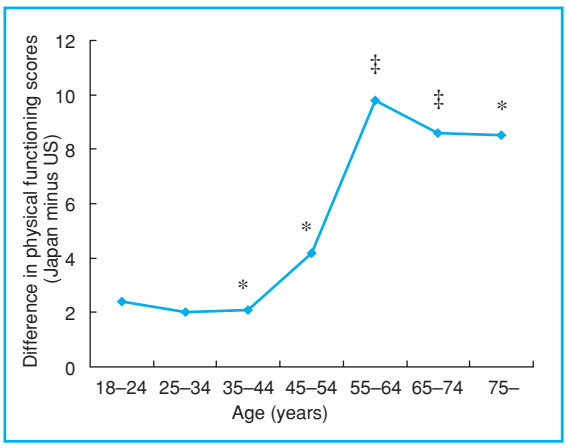

Fig. 1 Mean PF scores of elderly in the US and Japan
*: P<0.05, ‡: P<0.001

Table 4 Mean scores and sample size for Physical-functioning scale of SF-36 by gender and age

	Male			Female		
	US n=293	Japan n=266	P-value	US n=413	Japan n=225	P-value
Age groups (years)						
65–69	73.2±26.6 n=101	80.3±18.2 n=135	0.0223	71.1±26.7 n=136	79.1±17.9 n=110	0.0074
70–74	69.3±25.5 n=98	76.9±21.9 n=65	0.0574	63.8±25.8 n=107	73.0±18.5 n=70	0.0114
75–79	55.8±29.3 n=54	64.4±23.9 n=40	0.1353	56.6±27.2 n=82	61.5±28.1 n=24	0.4451
80–	51.0±30.7 n=40	67.1±31.5 n=26	0.0451	48.4±32.8 n=88	48.3±30.5 n=21	0.9963

Mean±SD

Table 5 Multivariate relationship of place (Japan or US) and other variables with PF score

Variable	Unit	Coefficient	Standard error	t-value	P-value	95% Conf. Interval	
Intercept	...	157.56027	8.47879	18.58	<0.0001	140.92414	174.19640
Place of living	1=Japan, 0=US	−2.70906	1.48256	−1.83	0.0679	−5.61798	0.19986
Age	Number of years	−1.06710	0.11279	−9.46	<0.0001	−1.28840	−0.84579
Gender	1=Male, 0=Female	1.70256	1.42494	1.19	0.2324	−1.09330	4.49843
Comorbid conditions	Number of medical conditions	−6.18324	0.37956	−16.29	<0.0001	−6.92797	−5.43851
Marital status	1=married, 0=else	3.50198	1.55250	2.26	0.0243	0.45585	6.54811
Educational status	1=more than 12 years 0=12 years or less	4.28179	1.40569	3.05	0.0024	1.52369	7.03988

Adjusted R^2 for model=0.3071

of elderly women aged 80 years or older were similar between Japan and US.

Factors associated with physical functioning scores

After adjustments for confounding factors, country of residence (i.e. Japan or the US) was not associated with PF scores (Table 5). The variable most strongly associated with PF scores was the number of medical conditions. For every 1 unit increase in the number of comorbid conditions, the PF score decreased by −6.18 points ($P<0.0001$).

Discussion

This study is the first to evaluate differences in self-reported HRQOL among community-dwelling elderly people in the general populations of the US and Japan. The strengths of this study are the sampling method and the use of the SF-36 to assess HRQOL multidimensionally.

The community-dwelling elderly Americans had much lower scores on the PF scale than did the community-dwelling elderly Japanese: that is, the elderly Americans reported being more limited physically in their daily life. This difference was apparent among those who were 55 years old and older. Differences in scores on the RP and VT scales, which are also interpreted as indicators of physical HRQOL, are consistent with the differences in PF scores. These findings are also consistent with previous data suggesting that active life expectancy among elderly people is longer in Japan than in the US,[12] and with the World Health Organization's data on healthy life expectancy, which takes into account both survival and disability.[13] In 1999, the estimated healthy life expectancy for babies born in Japan was 4.5 years longer than for those born in the US.[13] Sugisawa et al. found that elderly Japanese people had fewer medical conditions than did elderly Americans, and were more able to bathe, walk, and climb steps.[14]

Nonetheless, several limitations deserve note. Interpreting the difference in mean PF scores between the two highest groups of Japanese men is difficult, because the number of respondents aged 80 years or older was small.

The survey in Japan was conducted five years after that in the US. Medical technologies implemented during these five years could have had some effect on the health status of Japanese elderly people. Institutionalized people were excluded from the surveys in both countries, so the results apply only to those living in the community.

In the US, the questionnaire was distributed by mail or telephone, and in Japan, it was distributed and collected by trained personnel. McHorney et al. found that telephone responders had higher SF-36 scores than mail responders,[5] but it is not clear whether the scores of people whose responses are collected by telephone or by mail differ systematically from those of responders who are visited by trained data-collectors. All 13 of the medical conditions for which data were available were more common in the US than in Japan, but these data were self-reported and were not confirmed by healthcare providers or by review of medical records.

Healthcare systems differ between the US and Japan, and these differences may include the balance of institutional care and home care for elderly people, which might have affected the US-Japan differences in PF scores reported here.

Differences in survey time and method, the lower number of respondents aged 80 years or older, and differences resulting from translation of the questionnaire probably cannot explain the large disparity in PF scores between the US and the Japanese elderly subjects. With regard to daily activities, we conclude that the self-reported physical health status of elderly non-institutionalized people is significantly worse in the US than in Japan. Multivariate analyses suggest that this difference can be explained mainly by the number of medical conditions although the current study could not directly assess why the Americans reported worse physical functioning and more medical conditions than did the Japanese. Differences in genetic factors, diet, physical activity, social relations, and healthcare and social welfare systems, may all be important, but we hypothesize that obesity plays an important role in these differences.

Overweight and obesity are associated with chronic medical conditions[15] and with low PF scores on the SF-36.[16,17] Fewer than 20% of the elderly Japanese had a BMI of 25 or more. Although BMI data were not collected for the US sample in this study, Centers for Disease Control and Prevention reported that 76.2% of US men aged 65–74 had a BMI of 25 or more,

as did 67.4% of those aged 75 or older. It also reported that 70.9% of US women aged 65–74 had a BMI of 25 or more, as did 59.9% of those aged 75 or older.[18] While our results regarding BMI in the Japanese sample are based on data that were self-reported, they are generally consistent with the previous finding that, among people of all ages, BMI is much higher in the US than in Japan,[19] which may in part be due to cultural differences in diet. Diets differ greatly between the two countries.[20] Japanese-Americans eat more simple carbohydrates than do native Japanese.[20]

Overall physical fitness may contribute to differences found in PF and also differ greatly between the two countries. Japanese-Americans are less physically active in their daily lives than are Japanese people in Japan.[21] In their daily travels, many Japanese adults living in urban areas walk and use trains, and it is common for the walk between home and the nearest station to take 10 to 15 minutes. In contrast, many US adults use private cars, especially in rural and suburban areas and in cities where rapid transit is poor. It may be relatively uncommon for many Americans to walk for as much as 10 minutes continuously during a normal day. People living in urban "sprawl" areas have been found to be less physically active and to weigh more than those living in "compact" areas.[22] Because the US spends much more than Japan on health care, both per capita and as a percentage of gross domestic product (per capita (percentage of GDP): US $5,635 (15%); Japan $2,139 (7.9%)),[23] research on US-Japan differences in diet, physical activity, medical conditions, and physical health could be particularly useful in considering how to improve the physical health of Americans. As is well recognized, lifestyle changes are necessary for Americans to improve their physical HRQOL, particularly later in life.

Our results also clearly show why SF-36 scores obtained in all clinical studies comparing US and Japanese patients should be interpreted with caution. Investigators using the SF-36 might assume that its normative scores are similar between countries. However, the PF scores of elderly subjects differed significantly between the US and Japan, and the differences in health status between the elderly populations of countries can confound differences between patient populations because many patients are elderly. Moreover, in many clinical trials using the SF-36, the PF scale is important because it is easy to interpret as an index of physical health. A study of the SF-36 scores of American and Japanese dialysis patients also showed the need to take into account national-norm data in making international comparisons between patient populations.[24] Appropriate methods of accounting for differences in national-norm data are important in all international clinical research.

Elderly people in the US and Japan differed with regard to both physical functioning and mental health, but the differences were in the opposite directions. Scores on the mental health scale were significantly higher among the elderly subjects in the US than among those in Japan. Although the difference in mental health scores was not large, it was part of a clear dissociation between mental and physical health (a dissociation that would have remained hidden had we used a unidimensional measure of HRQOL): The Americans reported being more limited physically but having fewer problems with moods and feelings than did the Japanese. These international differences can focus attention on national needs. In the US, the lower level of physical functioning and the higher number of chronic medical conditions probably reflect a greater prevalence of overweight and obesity, physical inactivity, and unhealthy diet than in Japan. In Japan, considerable stigma accompanies the diagnosis of depression, and antidepressant therapy may be underused in primary care,[25] so the lower mental health scores in Japan might reflect a need to increase physicians' and elderly people's awareness of mental health problems.

We conclude that differences exist in health-related quality of life between community-dwelling elderly Americans and Japanese. Further study is necessary to determine causal mechanisms.

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Review Article

Helicobacter pylori Infection and Gastric Cancer

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Abstract

Twenty-three years have passed since the first isolation and cultivation of *H. pylori*. However, such spiral microorganisms had already been discovered in the 1890s. In Japan, 85 years ago, Rokuzo Kobayashi et al. discovered that a spirochete-like organism (*Helicobacter felis*) colonized the stomachs of dogs and cats. It was not until 70 years later that scientists again began attempting to treat *Helicobacter spp.*-associated gastroduodenal diseases. *H. pylori* is now believed to be one of the major pathogenetic factors in the development of gastroduodenal diseases. The inflammation associated with *H. pylori* damages the epithelial cells, which probably links this infection to preneoplastic lesions such as gastric atrophy or intestinal metaplasia. Recently, a large-scale randomized controlled study revealed the potent link between *H. pylori* infection and gastric cancer development. However, the molecular pathogenesis of *H. pylori*-associated carcinogenesis has been unknown. According to a recent investigation, sonic hedgehog (Shh), morphogen, is also expressed in normal adult gastric fundic mucosa, and this expression disappears in the fundic glandular cells of the *H. pylori*-colonized stomach, demonstrating for the first time that *H. pylori* infection leads to deregulation of the expression of a morphogen and that its infection could be linked to the misregulation of the gastric regenerative pathway. Research to seek the relation between *H. pylori* and gastric cancer development is consistent with the recent trend in molecular regenerative medicine.

Key words *Helicobacter pylori*, Gastric cancer, Preneoplastic lesion, Gastric fundic gland, Intestinal metaplasia, Gastric atrophy

Twenty-three years ago, Marshall and Warren demonstrated *Helicobacter pylori* infection in biopsy specimens from patients with gastritis and proved its pathogenicity. Later, chronic atrophic gastritis and certain types of gastric cancer came to be recognized as conditions caused by *H. pylori* infection. Important known factors involved in the pathogenicity of *H. pylori* include urease-dependent NH_3, bacterial cytotoxins such as CagA and VacA, and outer membrane proteins such as heat shock protein and OipA. In addition, the host's immune responses in the form of inflammatory reactions involving the production of cytokines, such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-12, and TNF-α, and the enhancement of proliferation of epithelial cells were also found to be involved in the processes of gastric mucosal atrophy and carcinogenesis. This article outlines the updated information concerning *H. pylori* infection and inflammation of the gastric mucosa, as well as the processes leading from atrophy to carcinogenesis.

History of *H. pylori* Research

Marshall and Warren, the discoverers of *H. pylori*, reported the association between chronic gastritis and *H. pylori* infection in 1984.[1,2] This year, they were awarded the 2005 Nobel Prize in physiology or medicine. In an infection experiment using oral administration of *H. pylori* suspension, Marshall et al. reported the development of a condition consistent with acute gastritis shortly after infection,[3] and Morris et al. proved that the

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Table 1 The history of *Helicobacter* research

- 1892: Bizzozero; Discovery of snake-line bodies in a dog stomach
- 1906: Krienitz; Discovery of spirochete-like bodies in human stomach
- 1919: Kasai & Kobayashi: Establishment of an animal model for *H. felis* infection and first *Helicobacter* eradication experiment
- 1938: Doenges; Isolation of spirochete-like organism from a human stomach
- 1954: Palmer; Denied the existence of microorganism in the stomach
- 1976: Lieber; Reduction of gastric NH_3 by ampicillin
- 1982: Warren & Marshall; Detection and isolation of *Campylobacter*-like organism from gastric biopsied specimen (*Campylobacter pyloridis*)
- 1994: NIH Consensus Development Conference; Recommendation of *H. pylori* eradication therapy for all patients with peptic ulcer disease
- 1994: WHO/IARC; Recognition as a fefinite carcinogen
- 1997: Tomb; Total genome analysis of *H. pylori*
- 2002: Marshall; Awarded the Keio Medical Prize
- 2005: Warren & Marshall; Awarded the 2005 Nobel Prize in physiology or medicine

persistence of *H. pylori* infection resulted in a condition consistent with chronic active gastritis.[4] Later animal experiments using various species confirmed the induction of acute gastric mucosal lesions and chronic gastritis by *H. pylori* infection. However, the presence of spirochete-like bacteria in the stomach has been known since the late 19th century.[5] Surprisingly, it was in the 1910s that a Japanese team at the Kitasato Institute led by Rokuzo Kobayashi (Professor Emeritus, Keio University) and Katsuya Kasai isolated spirochete-like bacteria conceivably belonging to *Helicobacter* species from animal stomachs. They proved that infection with these bacteria induced gastric mucosal lesions and used arsaminol in the world's first attempts to eradicate *Helicobacter* species.[6] However, the report of Palmer[7] in the 1950s completely disproved the presence of bacteria in the stomach, and the gastric lumen was believed to be aseptic for about 30 years thereafter.

As for the relationship between gastric cancer and *H. pylori* infection, the report of Parsonnet in 1991 and many other epidemiological studies demonstrated close association between these two conditions,[8–10] and the WHO/IARC recognized the infection as a definite carcinogen in 1994. An animal model of carcinogenesis using Mongolian gerbils was developed in Japan in 1998.[11,12]

A recent large-scale meta-analysis clearly showed that *H. pylori* infection is an important factor causing gastric cancer.[13] According to this study, the association is stronger for cancers occurring in the non-cardiac part of the stomach than those in the cardiac part, and the risk of carcinogenesis is similar between well-differentiated and poorly-differentiated gastric cancers. Although comparison among various cancer stages indicates stronger association for early-stage gastric cancer than at the later stages, this result seems to reflect the fact that the presence of *H. pylori* was evaluated solely based on serum antibody titers in this study, because we can reasonably consider that the progression of gastric cancer is accompanied by the progression of gastric mucosal atrophy, resulting in a decrease in the antibody titer as an index of *H. pylori* infection. Recent prospective clinical studies also support the causal relationship between *H. pylori* and carcinogenesis.[14–16]

One of these studies is a 9-year prospective cohort study conducted by Yamagata et al. as a part of the Kyushu University Hisayama Town Study.[17] While *H. pylori*-positive males showed a significant excess in the occurrence of gastric cancer, females showed no significant difference in gastric cancer depending on the status of *H. pylori* infection. Although this result suggests the involvement of female hormones in the

development of well-differentiated adenocarcinoma from atrophic gastritis, this does not explain the mechanism for the development of poorly-differentiated adenocarcinoma.

On the other hand, Uemura et al.[14] used more precise diagnosis of *H. pylori* infection combining microscopic examination of multiple gastric biopsy specimens, rapid urease test, and serum antibody titer measurement. In this study, *H. pylori*-positive subjects developed gastric cancer at a rate of 36 patients among 1,246 patients (2.9%) during the follow-up period of 8 years on average, while there were no cases of gastric cancer among the 280 subjects without *H. pylori* infection. This report is very important in that *H. pylori* infection was diagnosed precisely using multiple methods, and strict exclusion of false negative cases enabled the accurate evaluation of gastric cancer risk associated with *H. pylori* infection. In addition, this study analyzed the pattern of gastritis among *H. pylori*-positive subjects, revealing frequent development of well-differentiated adenocarcinoma among *H. pylori*-positive subjects with corpus-predominant gastritis.

However, the results of a large-scale randomized comparative study in China published last year reported that 1,630 *H. pylori*-positive subjects (817 patients receiving and 813 patients not receiving *H. pylori* eradication therapy) were followed for 7 years, and no significant difference in gastric cancer occurrence was found between treatment arms ($P = 0.33$). A subanalysis of the subjects showing no atrophic gastritis or other preneoplastic lesions demonstrated a significant prophylactic effect of *H. pylori* eradication against gastric cancer ($P = 0.02$), detecting 6 cases of gastric cancer in the subjects receiving eradication and none in the subjects not receiving eradication.[15] Although this study was conducted as an RCT, the study population was limited to a part of China. Another problem with this study was the fact that the definition of preneoplastic lesions included so-called "early gastric cancer" in the category of dysplasia, which meant that all cases of gastric cancer counted in this study were cases of advanced cancer. These problems prevent the direct comparison of data from this study and other studies. When only the subjects with no preneoplastic lesions such as intestinal metaplasia and dysplasia were compared in this study conducted by Wong et al., eradication treatment resulted in significant reduction in gastric cancer risk. This fact suggests that eradication alone might not be effective in avoiding the risk of carcinogenesis in *H. pylori*-positive subjects who have already had preneoplastic lesions.

In addition, Uemura et al. reported that eradication resulted in significantly less frequent recurrence of gastric cancer after endoscopic mucosal resection (EMR) for early gastric cancer.[18] Animal experiments also suggest that early eradication reduces cancer risk.[19] These observations, considered together, support the possibility that eradication treatment may lead to prevention of gastric cancer.

The Japan Interventional Trial of *H. pylori* (JITHP), conducted to clarify the causal relationship between *H. pylori* and gastric cancer, completed the follow-up period in 2004, and the results of analysis covering the subjects followed for 4 years or more were partly reported by Saito et al. of the Central Hospital, National Cancer Center.[20] In JITHP, *H. pylori*-positive subjects were randomly allocated to eradication and no-eradication groups, and the study was started using the endpoints of (i) emergence or progression of preneoplastic conditions including atrophic gastritis and intestinal metaplasia and (ii) frequency of gastric cancer development. However, the study plan was changed to use only endpoint (i), because the number of subjects turned out to be insufficient. At the time of closure of enrollment in December 2000, there were 751 subjects enrolled (379 in the eradication group and 372 in the no-eradication group). The number of subjects that were followed for 4 years or more and received histological evaluation was 186 in the eradication group and 206 in the no-eradication group. Among the subjects with baseline presence of atrophy, the percentage of subjects showing improvement of atrophy was higher in the eradication group than in the no-eradication group, irrespective of the location of the lesions: greater curvature of the gastric corpus, lesser curvature of the gastric corpus, or greater curvature of the pyloric antrum. No sexual difference was found in the improvement of atrophy. Eradication improved the condition in all age groups and even when atrophy had progressed to a certain degree. On the other hand, intestinal metaplasia improved at a higher rate in the eradication group than in the

no-eradication group, and this improvement was observed even in the subjects that had extensive intestinal metaplasia at baseline. These results suggest that eradication is effective even when the gastric mucosa had atrophy and intestinal metaplasia.

Recent studies in Japan have shown that gastric cancer may develop during the long-term follow-up of patients after successful eradication. At the 11th symposium of the Japanese Society for *Helicobacter* Research, Murakami et al. reported that gastric cancer develops in 0.8% of cases after eradication and suggested that the development of gastric cancer after eradication may depend on the presence of upper gastrointestinal disorders other than duodenal ulcer, the patient's age at the time of eradication, and the extent of endoscopic atrophy. In this study, gastric cancer developed in 12 subjects out of the 1,554 subjects that were observed for 26 months on average. An analysis using Kaplan-Meier curves revealed that development of gastric cancer from duodenal ulcer was significantly ($P = 0.0276$) less frequent than that from gastric ulcer, and the development from duodenal ulcer was significantly ($P = 0.0002$) lower than that after EMR. Furthermore, the patient's age at the time of eradication tended to be higher among the patients developing cancer than that in the patients developing no cancer. The age at the time of eradication was suggested to be an important factor determining the later development of gastric cancer (personal communication).

Nodular gastritis characterized by a goose flesh-like endoscopic appearance is a condition with uniform distribution of nodular protrusions in the area from the antrum to the gastric angle. This condition is frequently observed in young people, particularly young women. Recent observation that nodular gastritis is often found in *H. pylori*-positive young adults has aroused attention to the relationship between this condition and gastric cancer. At the same symposium, Kamada et al. reported the study of 25 subjects with gastric cancer accompanying nodular gastritis, and examined the relationship with age, sex, site of gastric cancer, macroscopic typing, histological typing, and *H. pylori* infection. The 25 subjects had a mean age of 33.3 years and included 23 females. Macroscopic typing was 0-IIc in 17 subjects. Histological typing was undifferentiated in 24 subjects and differentiated in 1 case (personal communication). *H. pylori* infection was positive in all 22 subjects that were studied for this parameter. These results suggest that gastric cancer accompanying nodular gastritis is typically undifferentiated cancer in the gastric corpus of young women associated with *H. pylori* infection.

Factors Involved in the Pathogenicity of *H. pylori*

Various factors involved in the pathogenicity of *H. pylori* have been reported. First, neutrophils infiltrating into the foci of *H. pylori* infection produce reactive oxygen species and myeloperoxidase-dependently produce hypochlorous acid, which reacts with the ammonia resulting from the action of urease produced by *H. pylori*. This reaction results in the generation of monochloramine, which exerts strong cytotoxicity.[21] This monochloramine further induces apoptosis of the gastric epithelial cells, significantly affecting the cellular turnover of the gastric mucosa.[22–26] Attention has also been paid to the damage to the host cells inflicted by nitric oxide (NO) produced by the action of inducible nitric oxide synthetase (iNOS) expressed in the macrophages and other inflammatory cells, as well as peroxynitrite ($ONOO^-$) resulting from the reaction between NO and superoxide (O_2^-).

In addition, heat shock protein 60 (HSP60) localized in the outer membrane contributes to the adhesion of *H. pylori* to the gastric epithelial cells and induces the production of IL-8. Autoimmune reaction has been reported to occur via IL-8-mediated immunoreactivity to self-antigens. Outer membrane protein OipA also promotes the infiltration of inflammatory cells and the production of inflammatory mediators.[27]

Other typical pathogenic factors include CagA, which is injected directly from the bacterial cell to the host cell via Type IV secretion apparatus, and Vac A, a vacuolating cytotoxin secreted to the extracellular space. *H. pylori* strains possessing CagA are known to be particularly virulent, and nearly 100% of strains detected in Japan have the *cag* pathogenicity island (cagPAI). Once injected into gastric epithelial cells, CagA is considered to undergo tyrosine phosphorylation, bind to Src homology 2-containing protein tyrosine phosphatase

(SHP-2), and enhance its activity, to the effect of promoting cellular proliferation and carcinogenesis. The part of the CagA molecule that undergoes tyrosine phosphorylation and binds to SHP-2 is characterized by the Glu-Pro-Ile-Tyr-Ala sequence (EPIYA motif), and the Tyr residue in this sequence is phosphorylated. The number of instances of this EPIYA motif, as well as the amino acid sequence around them, differs in different strains isolated from clinical specimens. In particular, the difference in amino acid sequence between a strain in East Asia (EPIYATIDF) and a strain in Western countries (EPIYATIDD) is reflected in the difference in the biological activity of CagA. The CagA of the East Asian strain shows stronger biological activity compared with that of the Western strain, suggesting the closer involvement of the former in the development of gastric mucosal atrophy and gastric cancer.[28]

H. pylori and the Cytokine Network

The gastric mucosal tissues with *H. pylori* infection have been reported to show enhanced production of cytokines, including IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-12, and TNF-α. These cytokines and chemokines not only act as mediators in the inflammation caused by *H. pylori* infection, but also affect gastric acid secretion and other gastric functions and inflict damage on the gastric mucosa. Many of the components of bacterial cells act on gastric mucosal cells and macrophages, promoting the secretion of IL-8, IL-1β, IL-6, TNF-α, etc. This results in the activation, differentiation, and proliferation of immune cells responding to these chemical mediators, and the excessive generation of reactive oxygen species and cytokines inflicts mucosal damage. IL-1 is produced by monocytes and macrophages; acts on endothelial cells; promotes the adhesion of lymphocytes, monocytes, and neutrophils to the endothelium; and promotes neutrophil migration. It is particularly important that IL-1β induces apoptosis of the gastric epithelial cells.[29] IL-1β is involved in the progression of atrophic gastritis via its strong action to inhibit gastric acid secretion, and El-Omar et al. reported the association between IL-1β polymorphism and gastric cancer.[30] The intron 2 of *IL-1RN* gene involved in the activity of IL-1β has 5 different patterns of 86-bp tandem repeats. Their study showed that people possessing *IL-1RN**2 (2 repeats) are at higher risk of developing gastric cancer and more frequently have hypoacidity. Hsu et al. reported that *IL-1RN**2 is a risk factor for gastric and duodenal ulcer.[31] However, IL-1β polymorphism involves considerable ethnic difference, and the results in Japanese populations do not always agree with those in other countries.

H. pylori Infection and Gastric Preneoplastic Lesions

In 1975, Correa et al. proposed a theory that gastric cancer develops from atrophic gastritis via intestinal metaplasia.[32] Although this theory preceded the advent of *H. pylori* in 1982,[1] it accurately described the natural history of gastric lesions resulting from *H. pylori* infection. In 1994, Gilvarry et al. reported that persistence of *H. pylori* infection lead to the progression from chronic gastritis to chronic atrophic gastritis.[33] Sakaki et al. studied the relationship between *H. pylori* infection and atrophic gastritis through endoscopic follow-up of 43 subjects for 10 years. According to their study, the subjects that remained *H. pylori* negative during follow-up had histologically normal gastric mucosa and no atrophic changes were observed throughout the observation. On the other hand, the 35 subjects that were *H. pylori* positive showed gastric glandular atrophy in 45.7%, progression of intestinal metaplasia in 48.6%, and the shift of the endoscopic atrophic border toward the oral side in 42.9%.[34]

Progress in research on the molecular mechanism for atrophy has also been remarkable. Recently, we reported that the expression of sonic hedgehog (shh), a morphogen involved in the differentiation and control of fundic glands, is down-regulated in the presence of *H. pylori* gastritis.[35] Shh is a morphogen belonging to the hedgehog family, and is crucially involved in the determination of the craniocaudal axis during embryogenesis, as well as in controlling the morphogenesis of the central nervous system and various other organs. It has been demonstrated that Shh is also expressed in the fundic glandular mucosa of adults, and this expression disappears in intestinal metaplasia.[36] In the *H. pylori* gastritis induced in Mongolian gerbils, the expression of Shh dwindled synchro-

nously with the expansion of gastritis from the antrum to the corpus, corresponding to the disappearance of parietal cells and the abnormality of the axis of differentiation from mucous neck cells to chief cells. This observation supports the possible involvement of Shh inhibition in the mechanism for atrophy.[35] The regions showing this disappearance of parietal cells show not only a change in the distribution of Muc 6 (class III mucin)-positive cells but also the presence of glands that are positive for trefoil factor 2 (TFF-2). TFF-2-positive atrophic glands are recently called SPEM (spasmolytic polypeptide-expressing metaplasia), and are attracting much attention as preneoplastic lesions. In fundic glandular mucosa, Shh has been suggested to play an important role in the differentiation from mucous neck cells to chief cells or the differentiation from immature parietal cells to parietal cells.[37] Disruption of these processes is considered to result in preneoplastic changes such as atrophy, SPEM, and intestinal metaplasia. On the other hand, runt domain transcription factor (RUNX) 3 is a transcription factor situated downstream of the TGF-β/BMP signal cascade. In the gastric mucosa of adults, this gene is strongly expressed in cells with well differentiated, such as gastric surface mucous cells and chief cells, and is working as a tumor suppressor gene.[38] It has been reported that the expression of RUNX3 is frequently suppressed in intestinal metaplasia and gastric cancer, suggesting that mutation of the *RUNX3* gene can trigger tumor generation and growth.

On the other hand, ghrelin is a peptide produced by endocrine cells called A-like cells, which are located in the mucosa of the gastric corpus, and has activity to promote appetite, acid secretion, and movement of the digestive tract. It is a physiologically active peptide consisting of 28 amino acids, which was purified by Kangawa et al. from rat and human stomachs as an endogenous ligand of growth hormone secretagogue receptor (GHS-R).[39] We studied the kinetics of ghrelin in *H. pylori*-positive Mongolian gerbils, and reported that *H. pylori* infection caused gradual decrease in ghrelin in the stomach.[40] We showed that the secretion of ghrelin decreased with the progression of atrophy, and the distribution of ghrelin-immunoreactive cells in the gastric corpus was also decreased by *H. pylori* infection. In addition, we conducted endoscopy in patients with chronic gastritis to evaluate the relationship between the extent of atrophy and plasma ghrelin level, and reported that plasma ghrelin could be used as a marker for gastric mucosal atrophy, as it was significantly lower in the subjects with severe atrophy.[41] A study using close observation before and after eradication demonstrated that ghrelin and pepsinogen reacted to treatment differently from each other. While no endoscopic improvement of atrophy was observed and serum pepsinogen II dropped with the increase in the pepsinogen I/II ratio shortly after eradication, plasma ghrelin did not change for a while and started to increase gradually 1.5 years after eradication in concordance with the endoscopic improvement of atrophy. This difference is considered to reflect different aspects of the process following eradication.[42] These findings support the prospect that plasma ghrelin can be used as a marker for individuals at high risk of atrophic gastritis or gastric cancer (Japanese Patent Application 2003-155212 by Hidekazu Suzuki, et al.).

H. pylori Infection and Malignant Transformation

H. pylori has been recognized by WHO/IARC as a definite carcinogen for gastric cancer.[43] The currently accepted mechanism leading from *H. pylori* infection to the development of gastric cancer can be summarized as follows: The persistence of *H. pylori* infection causes the persistence of histological gastritis, in which exfoliation and repair of the mucosa take place repeatedly. With additional involvement of genetic and environmental factors, this leads to the development and progression of gastric mucosal atrophy, followed by the changes from intestinal metaplasia to dysplasia. The cascade of these changes is considered to represent the preneoplastic condition leading to well-differentiated gastric cancer. In addition, reactive oxygen species released from inflammatory cells infiltrating the gastric mucosa with *H. pylori* infection cause DNA damage and enhancement of cellular turnover. As mentioned above, a pathogenic factor specific to *H. pylori* infection is monochloramine, which is an oxidant with high reactivity and strong cytotoxicity.[21,23,24] It is probable that the oxidative stress from these and other factors may impair the DNA repair mechanism, resulting

in the occurrence and accumulation of various gene abnormalities. In other words, the development of gastric cancer may be preceded by the mutation of cancer-related genes, which may trigger the development and growth of tumors. The reason that only some *H. pylori*-positive individuals develop gastric cancer is now being studied, considering the differences in other environmental factors, host-side factors, *H. pylori* strain diversity, and the timing of infection.

The mechanism for carcinogenesis due to *H. pylori* involves complicated interactions among factors inherent to *H. pylori* and a multitude of factors related to *H. pylori*. Future studies are expected to provide further insight into this problem.

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Review Article

Treatment and Recent Topics of Postherpetic Neuralgia

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Abstract

Postherpetic neuralgia (PHN), the most common sequela of herpes zoster (HZ), occurs in about 10% of patients with HZ. It is a condition with neuropathic pain arising from the degeneration of the relevant nerves as a result of neuritis caused by the reactivation of the varicella-zoster virus (VZV). The hypofunction of the descending inhibition system is considered to be the entity causing pain. Although several therapies have been attempted to treat PHN, none has been proved decisively effective. The most important strategy at present is the complete control of symptoms of HZ that trigger PHN. PHN tends to develop in elderly patients, resulting in significant deterioration of their quality of life (QOL). This disorder is an important issue in Japan in the face of the serious aging of the population. It should not be left unchecked merely because it is not life threatening. It is necessary to consider the use of varicella vaccine to prevent HZ within the national healthcare policy.

Key words Herpes zoster (HZ), Postherpetic neuralgia (PHN), Neuropathic pain, Varicella vaccine

Introduction

Herpes zoster (HZ) is a disorder characterized by the sudden onset of skin eruption and severe pain caused by the reactivation of the varicella-zoster virus (VZV) occurring latently in ganglia after initial infection.

Pain along the course of the nerves develops simultaneously with the onset of HZ or before the appearance of skin eruption. This is the acute-phase pain of HZ. Pain of a different nature from the acute-phase pain may develop gradually in some cases. This pain is generally referred to as postherpetic neuralgia (PHN).

Common complications of HZ include motor nerve paralysis and ocular complications. Rare complications include myelitis and encephalitis. Among these conditions, PHN is a neurological complication observed in an overwhelming majority of patients. This condition is extremely important in an aging society.

Clinical Features of PHN

The pain of PHN is characterized by the fact that the skin surface of the affected part always presents hyposensitivity such as hypesthesia or anesthesia including pain sensation, accompanied by single or combined complaints of burning pain, aching pain, shooting pain, lancinating pain, tight pain, etc. Allodynia may be remarkable in some cases or absent in others.

The International Association for the Study of Pain defines PHN as “chronic pain with skin changes in a dermatomal distribution subsequent to acute herpes zoster”,[1] without mentioning the timing of symptom onset.

With respect to the time from skin eruption due to HZ to the transition to PHN, different authors have used different definitions, requiring that the period after the onset of skin eruption be at least 1 month, 6 weeks, 2 months, 9 weeks, 3 months, or 6 months. Some others consider

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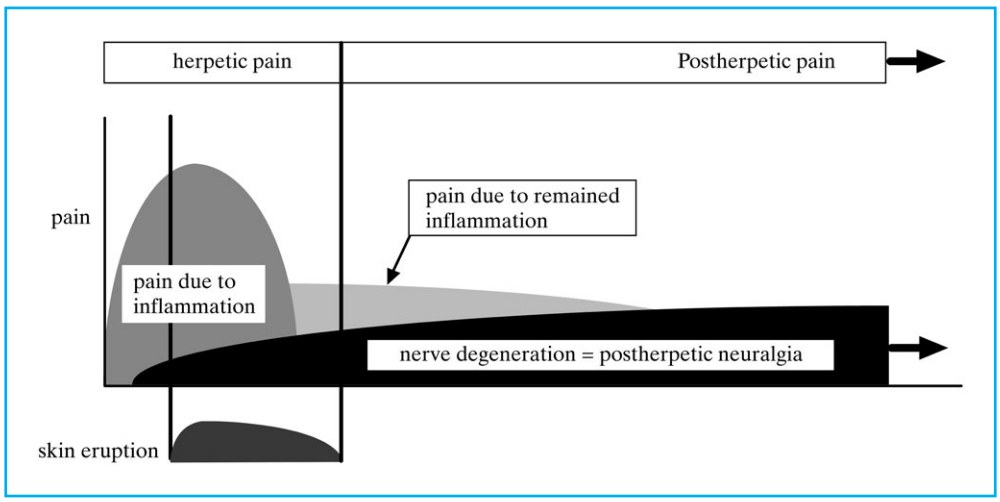

Fig. 1 Hypothesis about formation of postherpetic neuralgia

If postherpetic neuralgia arises from nerve degeneration as a result of inflammation caused by the reactivation of the varicella-zoster virus, postherpetic neuralgia can occur both before and after the appearance of skin eruption.

that PHN refers to the pain remaining after the healing of skin eruption. There is no established definition or consensus in this respect.[2–6]

When we observe the pain during the acute phase of HZ, we encounter many cases in which the nature of the pain changes irrespective of the presence or absence of skin eruption. It is also common that a patient who initially had skin eruption without pain later starts to complain of pain. These changes should be considered to mark the onset of PHN, and the length of time after the onset of skin eruption is not an important factor in defining PHN. This means that some patients that were conventionally considered to have the pain of acute-phase HZ might actually have PHN. On the other hand, some patients considered to have PHN might actually have continuation of acute-phase pain. The report showing the effectiveness of subarachnoidal injection of steroids for PHN[7] indicates that the study subjects, considered to have PHN based on time, included cases of protracted inflammation.

The sites most commonly affected by PHN are naturally the same as those affected by HZ, which include the areas served by the trigeminal and thoracic spinal nerves. PHN develops more frequently in persons aged 50 or more than in younger persons, and the incidence increases with age.[5,8,9]

The reported incidence of PHN ranges widely. While a study reported pain remaining in 3% of patients 6 months after the onset of skin eruption,[10] another reported the rate of more than 20% after 1 year.[5] On average, PHN seems to develop in about 10% of patients after 6 months.[11,12]

PHN is Surely Neuropathic Pain

Hypothesis on the formation of PHN (Fig. 1)

The features of PHN closely resemble those of so-called neuropathic pain, which is the symptom cluster of pain arising from neuropathy due to various causes.[13] In this respect, PHN deserves much attention as a form of pain derived from neuropathy caused by the disease.

When HZ has developed as a result of reactivation of VZV, the patient should be regarded as having undergone or being in the process of nerve degeneration triggering PHN. In extreme cases, nerve degeneration may be present when pain is observed several days or weeks before the appearance of skin eruption. The patient in this stage should be considered to be in the process of developing PHN.[14]

In fact, it has been reported that autopsy of a patient with myeloma who developed HZ in the first division of the trigeminal nerve and died while presenting acute-phase pain demonstrated

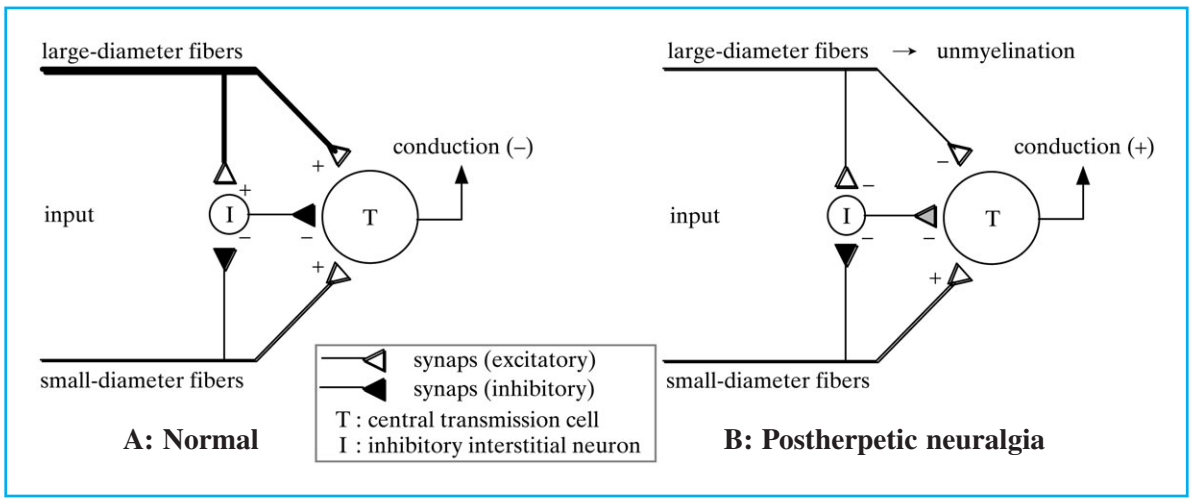

Fig. 2 Functional change in descending inhibition system

[**A: Normal**] The impulse (pain) carried by small-diameter fibers excites the central transmission cell (T) and is transmitted to the central system. Because this impulse also inhibits the inhibitory neuron (I), it causes secondary excitation of the T cell, resulting in the promotion of impulse transmission to the central system. On the other hand, while the impulse carried by large-diameter fibers also excites the T cell and is transmitted to the central system, it simultaneously excites the inhibitory interstitial neuron and this results in gradual suppression of the activity of the T cell. This suppresses the impulse transmission along small-diameter fibers.

[**B: Postherpetic neuralgia**] Demyelination of large-diameter (myelinated) fibers causes the inability to excite the inhibitory interstitial neuron, resulting in the inability to inhibit T cell activity. This results in the prompt transmission of impulse (pain) from small-diameter fibers to the central system.

uneven but strong nerve degeneration.[15]

Histopathological facts

Although there have been only a limited number of reports of the histopathological examination of patients with PHN, some remarkable facts have been reported. Inflammation of the sensory nerve ganglia, destruction of the nerve cells, and degeneration and fibrosis of the sensory nerve ganglia have been observed.[16,17] It has also been noted that peripheral nerve fibers in the affected parts of patients with PHN show a significant decrease in thick myelinated nerve fibers compared with thin unmyelinated nerve fibers.[18]

In addition, comparison between cases of HZ with pain and those without pain demonstrated no difference in terms of nerve degeneration, suggesting a lack of association between nerve degeneration and the development of PHN.[19] However, it is a well-known fact that neuropathic pain does not occur in all patients with nerve degeneration. Neuropathic pain is caused by some unknown mechanism in addition to nerve degeneration.

Mechanism for pain in PHN (Fig. 2)

We consider that PHN is clearly a form of neuropathic pain on the basis of the aforementioned histopathological changes in nerve fibers and ganglion cells, as well as clinical symptoms such as the loss of pain sensation and tactile sensation in the skin.

Pain of this type, whether it is caused by disease or injury, is a result of neuropathy, and is considered to arise from the dysfunction of either the ascending systems or the descending inhibition system involved in pain transmission from the peripheral to the central systems.

Since PHN is characterized by deafferentation pain, it is considered to arise from the hypofunction of the descending inhibition system. The normal body has a system called the descending inhibition system, which inhibits the transmission of noxious stimuli to the central system. When only myelinated nerve fibers are damaged and unmyelinated nerve fibers are not damaged among afferent fibers, the descending inhibition system does not work normally and pain is generated. The histopathological changes

observed in nerve fibers and ganglia in PHN support pain generation through this mechanism.

We sometimes encounter cases in which all symptoms of neuropathic pain are present without a clear sign of nerve impairment and the pain is eliminated by sympathetic nerve block. This condition, called sympathetically maintained pain, is assumed to involve the result of abnormal activity of sympathetic nerve functions and the continuous excitation of wide-dynamic-range neurons occurring in the spinal cord dorsal horn.[20] Some cases of PHN respond well to sympathetic nerve block, similarly to these cases of pain. The presence of meningitis and other complications also suggest the involvement of impairment of higher-level neurons. These observations illustrate the very complex nature of PHN.

Treatment of PHN

If PHN is a result of nerve degeneration, all methods attempted for the treatment of neuropathic pain may be indicated for PHN. Although many attempts have been made in this direction, none has been proved decisively effective.

Importance of treatment of acute-phase pain

The most important goals of treatment at present are pain reduction and the prevention of transition from HZ to PHN.

The pain during the acute phase of HZ is caused by inflammation. Therefore, the use of nonsteroidal anti-inflammatory drugs and the use of antiviral agents to remove the pathogens are essential.[21,22] However, the treatment of HZ normally begins when skin symptoms are confirmed, and there is a possibility that nerve degeneration has already occurred or is going to occur at this point.

Since this disease is nowadays considered to develop in parallel with the alteration of cellular immunity, it is reasonable to consider the use of various immunostimulation therapies, as well as immunosuppressive therapies and steroids. However, no definitive results have been obtained.

The use of opioid analgesics and similar agents against intense pain is an issue requiring future examination. If neuropathic pain is already going to develop in the acute phase of HZ, early administration of an antidepressant drug to high-risk patients may be an effective treatment.[23]

While persistence of pain is considered to establish a vicious cycle of pain, appropriate nerve block is greatly effective in stopping this cycle, and should be encouraged as a treatment for acute-phase pain. While blocking sensory nerves provides sufficient analgesia, blocking sympathetic nerves is considered to help prevention of nerve degeneration because it increases local blood flow.[24]

Frequent warm bathing and thermotherapy are recommended as methods of pain relief, although these are not suitable for patients with broken blisters and infection.

Treatment of PHN

The treatment of neuropathic pain is extremely difficult. Various therapies have been devised, attempted, and sought. The situation is similar to the treatment of PHN. No definitive method has been established, and all possible means of pain treatment are attempted at present.[25]

(1) Nerve block

While about 20 different methods of nerve block are used for the treatment of pain, those frequently used for PHN include sympathetic nerve block (such as stellate ganglion block), epidural block, trigeminal nerve block, and spinal nerve block.

Nerve block is usually performed under local anesthesia. The use of neurolytic agents or thermocoagulation techniques is selected in some cases.

(2) Pharmacotherapy

Antidepressants and anticonvulsants, such as amitriptyline and carbamazepine, are still frequently used.

With the progress of recent efforts to clarify the mechanisms leading to neuropathic pain, studies are conducted to evaluate the effectiveness of substances such as Na channel blocker, NMDA receptor antagonist, Ca channel blocker, GABA receptor activator, opioid analgesics, α2-adrenoceptors, serotonin antagonist, capsaicin, gabapentin, selective serotonin reuptake inhibitor, and selective noradorenaline reuptake inhibitor.

Nonsteroidal analgesic drugs, exerting an analgesic effect through the suppression of local inflammation, are still used widely for PHN. However, such use is not rational because the pathogenesis of PHN suggests that inflammation no longer exists in PHN.[26]

(3) Other therapies
Various methods are being attempted, including transcutaneous electrical nerve stimulation, spinal colon electrical stimulation, deep brain electrical stimulation, electrical convulsive therapy, laser beam therapy, dry ice therapy, iontophoresis, lidocaine ointment, and capsicin ointment.

Is HZ Prevention Possible?

A logical strategy for preventing the development of PHN is to prevent the development of HZ, which precedes PHN. In fact, varicella vaccine is expected to be effective in preventing the onset of HZ and to have a better chance of limiting the severity of HZ symptoms when vaccinated individuals develop HZ.[27]

It is an unquestionable fact that reactivation of latent VZV in the body causes the development of HZ, and some form of nerve degeneration resulting from this process triggers PHN.

The reactivation of latent VZV requires a change in the internal environment of the host. Crudely speaking, this change means weakening the immunocompetence of the host, as indicated by the fact that patients with factors such as malignant tumors, autoimmune disease, HIV infection, and immunosuppressive therapy are liable to contract HZ and its progression to severe conditions.[28,29]

A considerably high percentage of HZ patients in the general population are elderly patients, probably reflecting the decline in cellular immunity. A study examining patients within 7 days after the onset of HZ using tuberculin reaction as an index for general cellular immunity and intradermal reaction to varicella as an index for specific immunity demonstrated that these patients had decreased specific immunity against VZV rather than a decrease in cellular immunity in general.[30] Such a decrease in specific immunity has also been reported in patients with ocular herpes.[31]

A study using VZV-specific lymphoproliferation tests (SI) in middle-aged and elderly persons, normal adults, and pediatricians demonstrated that the SI in middle-aged and elderly persons was significantly lower than that in other groups, and that it decreased with age. In addition, the SI in normal adults was significantly lower than that in pediatricians.[32] This result suggests that specific immunity decreases in persons with fewer opportunities for re-infection of VZV. Therefore, it is considered possible to enhance VZV-specific immunity by using varicella vaccine to induce re-infection before the decline in specific immunity.

It has been reported that the use of varicella vaccine in elderly persons clearly enhanced the specific immunity against VZV, although a half of this booster effect disappeared within 6 years.[33] Symptoms remained very mild in the patients who developed HZ during this period.[34]

In addition, the use of varicella vaccine in elderly persons provided the same degree of VZV-specific immunity as in the elderly patients who developed HZ.[35]

These results support the effectiveness of HZ prevention using varicella vaccine. A number of practical questions remain to be examined in the future, including when vaccination should be performed, how many inoculations are required for the acquisition of sufficient specific immunity, and how long the acquired immunity persists.

Conclusion

HZ frequently develops in elderly persons, and the likelihood of permanent sequelae increases with age. Treatment of PHN, as well as the treatment of HZ to prevent the transition from HZ to PHN, is an important issue, considering the aging of the population in Japan. However, treatment of PHN, which is a form of neuropathic pain, is extremely difficult and no definitive method has been established. On the other hand, the use of varicella vaccine is expected to inhibit the development of HZ and prevent progression to PHN.

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Short Communication

The Mental Health of Doctors

—Reverence for persons living with illness—

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Key words Mental health, Mental care, Physicians, Patients, Physicianology

The Physician as a "Person Living with Illness"[1]

Physicians are generally regarded as persons who treat the diseases of patients. However, a frequently forgotten fact is that they are also persons who can suffer from diseases and disability themselves.

In daily medical training and clinical practice, physicians are accustomed to looking at diseases objectively and considering patients as the objects of their practice. For physicians, diseases are something belonging to patients, while they themselves are supposed to observe and treat diseases from the outside.

Confronted with a disease or disability, physicians suddenly become aware of and are shocked by the obvious fact that they also can be ill. The experiences as a physician help little, as they are limited to the diseases of other people. Being a specialist in diseases, the physician does not know how to respond to his or her own disease. At this moment, the disease is transformed from something passing by to something that he or she must bear.

Physicians can suffer from various mental and psychological problems in the current clinical setting. In particular, the burden imposed on physicians has been increased by the recent rapid advancement of medical technology, sophistication and diversification of medical care, and the use of information technology in clinical practice.

The number of physicians in Japan has exceeded 200 per 100,000 population. Although the total number is approaching a satisfactory level, the disparity between urban and rural areas is still serious, and there is an extreme shortage of physicians in some departments, such as pediatrics and obstetrics-gynecology. The concentration of the workload of particular physicians is a factor causing the emerging problem of death and suicide associated with overwork. While the recent criticism concerning physicians and medical practice is generally reasonable and requires an earnest response, little has been discussed from the perspective of the increasing workload of physicians within the current situation of medical care and the limitation of medical resources in Japan. The current circumstances in Japan demand the self-sacrificing efforts of individual physicians and medical institutions because of the lack of a systematic response to the changes in social structure.

Mental Care for Physicians

So, how should physicians cope with this situation?

The mental health of physicians may be protected by creating outpatient clinics or counseling/treating institutions specializing in

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the care of physicians, where psychiatric care would be given respecting the fact that the patients are physicians. Physicians tend to be more hesitant about visiting a psychiatric department than other people because of the concern about their social reputation and because of the deplorable fact that some physicians have a hidden prejudice against mental disorders. The creation of mental clinics for physicians is desirable in this respect. Physicians with mental disorders want to be treated as physicians rather than mentally disabled persons. An effective solution would be a care system operated by the universities to provide counseling and other care to graduates as a part of the continued lifelong education of physicians.

The introduction of a research-oriented perspective in daily clinical practice would also be effective in maintaining the good mental health of physicians. Although physicians tend to acquire particular "chronic" attitude in their long careers as clinicians, enthusiasm in their profession should be maintained through the pursuit of favorite study themes disregarding the acquisition of degrees or the career promotion. Researches not only provide the concrete goals in life, but also serve as a means for a temporary retreat from the repetition of clinical work. In particular, establishing one's own pace and style in research activities and having a world to immerse oneself in without worrying about evaluation from other people may contribute to the mental stability of physicians.

When a Physician Has Fallen Ill

In any case, physicians may fall ill for various reasons. Being ill, however, may have positive aspects for physicians. Particularly in the case of mental illness, it may be a warning against maintaining the same way of life as before. Illness can be a cue to reconsidering one's way of life.

Being ill also allows the physician to gain first-hand understanding of how illness is perceived by patients, and this improves his or her comprehension of the feelings of patients and their families. Even if a physician, surviving a competitive society, tended to look at things from a winner's standpoint and lacked sympathy for those who are socially weak, for the physician, being in the position of needing support from others may be an opportunity to acquire a tolerant, non-competitive sense of value.

Furthermore, the realization that physicians themselves can be ill attenuates the hierarchy between the physician and the patient, and an alliance may develop between them who have endured the same sufferings and overcome the same difficulties. In such a moment, the physician realizes that the patient is not simply a person with a disease or disability, but a person who strives to lead a better life, enduring the distress imposed by the disease. This realization may lead to "the reverence for persons living with illness".[2]

With increasing attention directed to mental care, the importance of the mental health of physicians will be recognized more and more seriously. This is an issue involving problems affecting the quality of medical services and the occurrence of medical accidents. The solution to this issue should be pursued not only by the efforts of individual physicians but also through a systematic approach including improvement of public awareness. To this end, we first need a study of the mental health of physicians and the education of "physicianology".[4]

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A Case of Pneumatosis Cytoides Intestinalis Successfully Treated by Inhalation of High Concentration Oxygen

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Abstract

A 44-year-old man was referred to our hospital because of a positive fecal occult blood test. A barium enema study revealed numerous oval-shaped, elevated lesions with smooth surfaces in the region including the ascending colon. He was admitted to our hospital for investigation and therapy. Based on colonoscopic examination, we diagnosed him as having pneumatosis cytoides intestinalis (PCI). He was treated with oxygen (5 L/min × 5 hours/day for 14 days) via a nasal cannula. Most of the multiple cysts diminished and some changed into white scars. The simplicity of oxygen therapy supports its use as a first-line treatment.

Key words Pneumatosis cystoides interstinalis, High-concentration oxygen inhalation

Introduction

Pneumatosis cystoides intestinalis (PCI) is a relatively rare condition in which numerous gas-filled cysts mainly containing nitrogen are formed within the intestinal wall. While idiopathic and secondary cases are known, the latter may result from exposure to trichloroethylene, chronic respiratory diseases such as pulmonary emphysema, and collagen disease. We report our experience with a case of PCI, which was detected by workup following a positive fecal occult blood test, including literature-based discussion of this disease.

Case

Patient: 44-year-old male.

Chief complaint: None.

Medical history: Not remarkable.

Family history: Not remarkable.

Past exposure: No past exposure to trichloroethylene.

Present illness: The patient was found to be positive for fecal occult blood on a health screening, and was referred to our hospital for detailed examination. An outpatient barium enema study revealed numerous oval-shaped, elevated lesions with smooth surfaces in the region from the hepatic flexure to the ascending colon. The patient was hospitalized for investigation and therapy.

Condition at the time of hospitalization: Height 165 cm, body weight 67 kg, blood pressure 136/74 mmHg, heart rate 72/min, regular pulse, no signs of anemia in palpebral conjunctiva, no jaundice in bulbar conjunctiva, no abnormal findings in cardiopulmonary auscultation, no palpable hepatosplenomegaly or masses in the abdomen.

Laboratory findings at the time of hospital-

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Table 1 Laboratory findings at the time of hospitalization

RBC	552 $\times 10^4$/mm^3	Na	138 mEq/L
Hb	17.0 g/dl	K	3.8 mEq/L
Ht	48.5%	Cl	100 mEq/L
Plt	18.9 $\times 10^4$/mm^3	BUN	13.9 mg/dl
WBC	5280/mm^3	Cr	0.91 mg/dl
TP	7.3 g/dL	CRP	0.02 mg/dl
Alb	4.3/dL	Antinuclear antibodies	(−)
T. Bil	2.24 mg/dL	Anti-RNP antibodies	(−)
AST	22 U/L	Anti-Scl-70 antibodies	(−)
ALT	31 U/L	Anti-Jo-1 antibodies	(−)
ALP	226 U/L		
LAP	127 mU/ml	PH	7.412
γ-GTP	17 U/L	PO_2	90.9 mmHg
CHE	333 U/L	PCO_2	40.0 mmHg
LDH	135 U/L	BE	0.9 mmol/l
CPK	90 U/L	SaO_2	98.2%

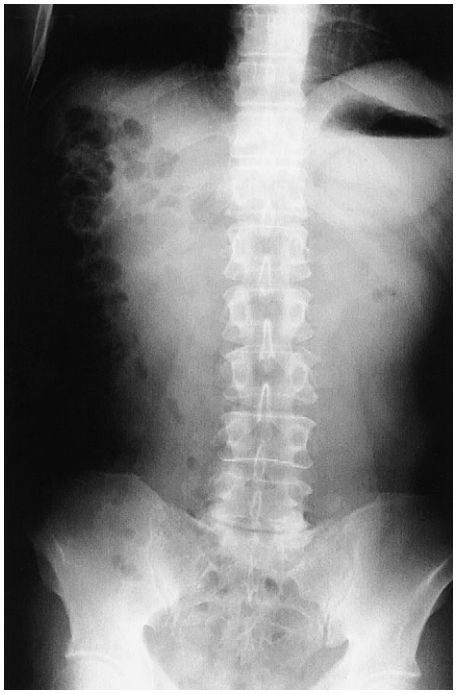

Fig. 1 Abdominal X-ray

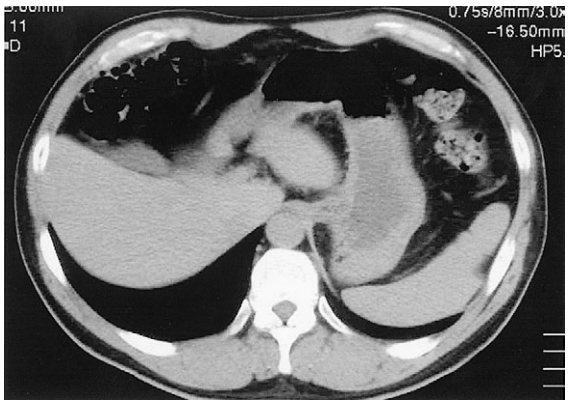

Fig. 2 Abdominal CT

ization (Table 1): No abnormalities were found in general hematology tests. Blood chemistry tests showed no abnormalities except for a slight increase in total bilirubin (2.24). Antinuclear antibodies, anti-RNP antibodies, anti-Scl-70 antibodies, and anti-Jo-1 antibodies were negative. Blood gas analyses were within normal ranges, including pH 7.412, PCO_2 40 mmHg, PO_2 90.9 mmHg, BE 0.9, and SaO_2 98.2%.

Abdominal X-ray at the time of hospitalization (Fig. 1): Aggregation of numerous round-shaped transparencies was seen in the region from the hepatic flexure to the ascending colon.

Abdominal CT at the time of hospitalization

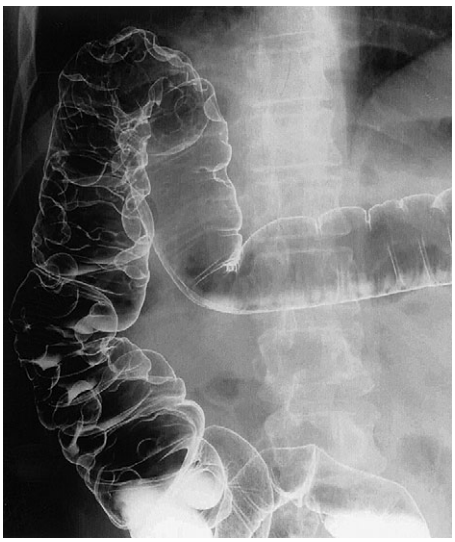

Fig. 3 Barium enema X-ray

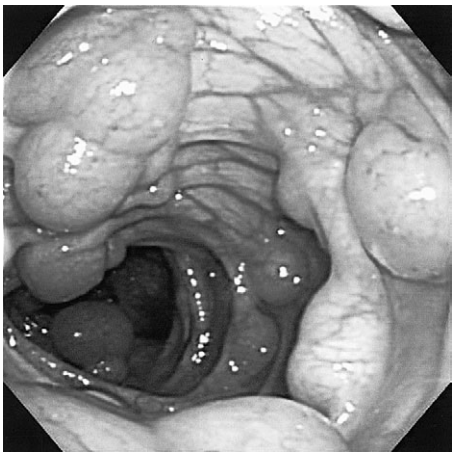

Fig. 4 Colon endoscopy (at the time of hospitalization)

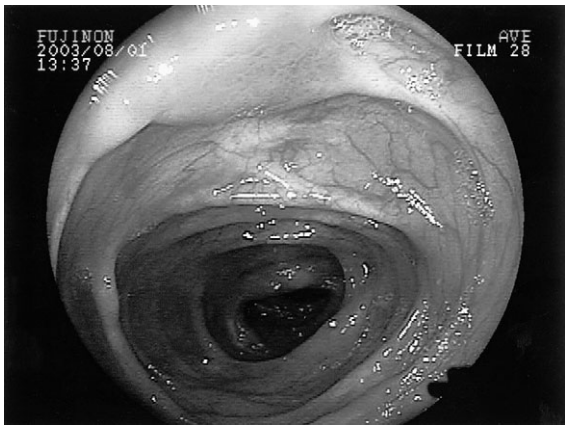

Fig. 5 Colon endoscopy (day 15)

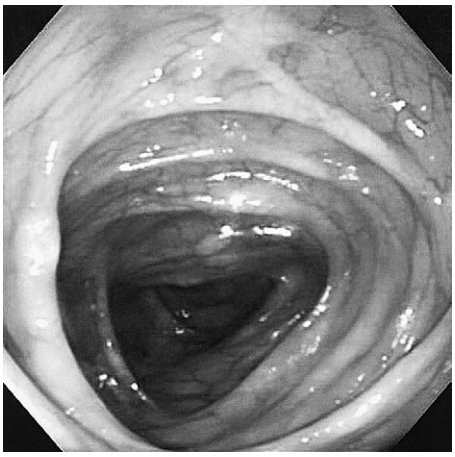

Fig. 6 Colon endoscopy (day 70)

(Fig. 2): Although air was depicted in the intestinal wall in the hepatic flexure, no wall thickening or other signs of inflammation were seen.

Barium enema X-ray at the time of hospitalization (Fig. 3): Diffusely distributed elevated lesions with smooth surfaces were seen in the region from the hepatic flexure to the ascending colon.

Colonoscopic findings (Fig. 4): Numerous multiple cysts were seen in the region from the ascending colon to the hepatic flexure.

Based on the above findings, we diagnosed the patient as having PCI and commenced intermittent high-concentration oxygen inhalation. Oxygen was administered via a nasal cannula at the rate of 5 L/min, 5 hours/day for 2 weeks.

Colonoscopy on the day after the end of oxygen therapy (Fig. 5): Most of the multiple cysts had diminished, although some small reddish elevated lesions remained.

Colonoscopy 8 weeks after the end of oxygen therapy (Fig. 6): Multiple cysts had largely disappeared and only white scars were observed.

Discussion

PCI was first described by Du Vernoi in 1730.[1] The first report of this disease in Japan was made by Miwa in 1901,[2] and according to Matsuoka et al.,[3] there were 509 cases reported by 1997. Although it was previously considered to occur preferentially in the ileum,[4] recent reports suggest a high occurrence in the large intestine, in particular the sigmoid colon.[5] While older reports indicated higher prevalence in males than females, recent cases include more females than males.[6] No symptoms specific to PCI are known. Cases involving the small intestine often show abdominal distention, abdominal pain, and flatulence, while those involving the large intestine usually present bloody mucous stool, melena, and diarrhea.[7]

The entity of PCI is the presence of gas-filled cysts in intestinal walls. An overwhelming majority of PCI cases have some underlying disease, as 15% of all cases are idiopathic and 85% are secondary to underlying disease.[4]

The etiology of PCI has not been well clarified. Bacterial, mechanical, and chemical mechanisms have been proposed. The bacterial theory depends on the fact that necrotizing enterocolitis in children is often complicated with PCI. It presumes that the gas-generating bacteria in the intestines invade into the intestinal wall and form cysts.[8] However, the bacterial theory seems to be disproved by the fact that gas-generating bacteria mainly produce hydrogen and methane, while the gas in PCI lesions consists of 90% nitrogen.[9] At present, the mechanical theory is considered plausible. There are 2 possible mechanical processes causing PCI. One is the mechanism depending on intestinal factors, where the elevation of pressure in the intestinal lumen due to intestinal obstruction, surgery, endoscopy, or trauma is considered to cause infiltration of intestinal gas through minute cracks in the mucosa.[10] The other possibility, assuming the causal involvement of the lungs, is that painless rupture of pulmonary alveolar walls may develop in such conditions as chronic obstructive pulmonary disease and the gas may enter the intestinal walls via the mediastinum, retroperitoneal tissues, and the tissues around mesenteric arteries.[11] With respect to the chemical theory, Yamaguchi et al.[12] reported a high occurrence of PCI among persons chronically exposed to trichloroethylene and the detection of trichloroethylene in the gas-filled cysts. In addition, there have been reports of PCI accompanying collagen disease such as systemic scleroderma.[13] Because our case had no history of surgery or trauma, showed no abnormality in chest X-ray and blood gas analyses, and lacked a history of exposure to trichloroethylene, we considered that this case was idiopathic.

It is difficult to diagnose PCI solely based on clinical symptoms, but a physician with the knowledge of this disease can relatively easily identify this disease based on the findings from abdominal X-ray, barium enema X-ray, and endoscopy. PCI most frequently develops in the subserous tissues of the intestines, followed by submucous tissues, and the development of PCI within the muscular layer is considered rare.[14] In cases where the gas-filled cysts are located predominantly in the submucous layer, abdominal X-ray depicts numerous oval-shaped bubbles of various sizes like bunches of grapes along the intestinal wall, and barium enema study reveals multiple filling defects resembling holly leaves.[15] If there are gas-filled cysts in the subserous layer, lesions are identified as froth-like clustering of small transparencies or linear transparencies along the outer perimeter of the intestines.[16]

PCI can be treated either with surgical removal or with a conservative method using oxygen inhalation. According to the compilation by Sakashita et al.,[17] surgery has been selected for the cases showing severe melena and other symptoms, cases with suspected digestive tract perforation due to pneumoperitoneum, cases developing ileus, cases in which malignancy could not be ruled out, and cases that actually developed digestive tract perforation. With respect to oxygen therapy, Forgacs[18] reported successful disappearance of pneumatosis after continuous inhalation of 75% high-concentration oxygen for 6 days in 1973. In Japan, Daitoku et al.[19] reported the effectiveness of this therapy in 1980, followed by reports of high-concentration oxygen therapy using a non-breathing face mask and nasal catheter, high-pressure oxygen therapy, and a number of other methods. The mechanism of this treatment has been explained as follows: Because the gas in the cysts mainly consists of nitrogen, the elevation of arterial oxygen partial pressure caused by high-concentration oxygen

inhalation may result in replacement of the nitrogen in the cysts with oxygen and the oxygen may gradually be absorbed in adjacent tissues, to the effect of the disappearance of gas-filled cysts. Many reports on oxygen inhalation therapy indicate that methods such as high-pressure oxygen therapy, oxygen mask, and oxygen cannula are appropriate, provided that a 200–300 mmHg elevation of PaO_2 can be achieved, and that the administration of oxygen for 5 or 6 hours per day over the period of 1 or 2 weeks provides largely satisfactory results.[20,21] In our case, nearly complete disappearance of multiple cysts was achieved by oxygen administration via a nasal cannula at the rate of 5 L/min, 5 hours/day for 2 weeks.

Conservative treatment such as oxygen inhalation is considered the first-line therapy for this disease. However, patients must be followed with careful observation, since some cases may develop melena or digestive tract perforation. According to Senoo et al.,[21] the disease recurred in 26% of the patients receiving oxygen inhalation therapy. This fact emphasizes the need for long-term follow-up after treatment.

Conclusion

We experienced a case of idiopathic PCI in the ascending colon. High-concentration oxygen therapy for 2 weeks was effective in this case.

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Activities of the Japan Medical Association's Center for Clinical Trials

JMAJ 48(10): 518–521, 2005

Hiroshi Mikami*1

Key words Clinical trial, Doctor-led clinical trial, GCP, Adverse drug reaction, Clinical research

Introduction

Clinical trials are the final stage in the process of development and application for approval of new drugs and medical devices. The environment in which clinical trials are conducted in Japan has been changing greatly during the past decade.

It has become difficult to carry out high-quality clinical trials in a timely manner and without undue expense, because of delays in developing a basis for their strict implementation under the Good Clinical Practice ordinance of the Ministry of Health, Labor and Welfare, an ordinance that must be followed when conducting clinical trials. As a result, clinical trials are increasingly being carried out overseas instead of in Japan, creating an outflow of clinical research and placing excessive restrictions on trials conducted in Japan.

As a result, the following problems have emerged:

1) Delays in the approval of new drugs, and therefore delays in the opportunity for patients to benefit from these drugs.
2) Difficulty in providing high-quality medical care because of delays in introducing new drugs that are already available outside Japan.
3) Adverse effects on the development of domestic industries.

Thus, the restrictions that have been placed on clinical trials are not at all favorable.

To stem this adverse trend and strengthen Japan's ability to compete internationally in drug research and development, the Ministry of Health, Labor and Welfare issued a report in 2002 that outlines its vision for the pharmaceutical industry.

In this context, and in cooperation with the Ministry of Education, Science and Technology, a nationwide clinical trial 3-year activation plan was developed to include the following:

1) Construction of a large-scale clinical trial network
2) Improvement of the system for clinical trial implementation in medical institutions
3) Support for patients' participation in clinical trials
4) Reduction of the burden of clinical trials imposed on companies
5) Promotion of clinical research as a whole.

As part of these governmental policies, the Japan Medical Association (JMA) set up the JMA Center for Clinical Trials (JMACCT) in 2003 to promote clinical trials in Japan. This project, supported by a grant-in-aid from the Ministry of Health, Labor and Welfare, is attempting to prepare a basis for the implementation of clinical trials in Japan by constructing a nationwide clinical trial network and providing support for so-called doctor-led clinical trials.

Organization of JMA's Center for Clinical Trials

Although JMACCT was set up by JMA, it is financially independent of JMA and is organized

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mainly by a steering committee comprised of members appointed by the president of JMA. The Center has two external committees to ensure fairness and transparency in carrying out projects.

One of the two external committees is the General Planning and Evaluation Committee, which is in charge of comprehensive planning and evaluation processes necessary for the proper implementation of projects and their smooth progress. The other is the Technology Planning and Evaluation Committee, which carries out discussions of specific technical issues.

Doctor-led Clinical Trials

Doctor-led clinical trials will be described briefly in this section, as they represent a new form of clinical trials.

Clinical trials so far have been carried out by companies. Clinical trials conducted by an individual doctor were not authorized to have agents manufactured on commission by an outside entity or to receive supplies of non-approved drugs or devices from the manufacturer. This made it necessary for doctors trying to conduct a clinical trial to purchase drug samples within their limited research budget, thereby restricting the scope of studies. In addition, the results of such studies generally were not admissible for application for approval because the study did not meet the standards prescribed in the Pharmaceutical Affairs Law.

However, the Pharmaceutical Affairs Law, as amended in 2002, took effect on July 30, 2003, and as a result the planning and implementation of clinical trials, which previously had been the exclusive province of companies, was permissible for doctors and dentists, marking the initiation of doctor-facilitated clinical trials.

Certain drugs that have been proved effective on the basis of clinical experience in other countries are not yet approved in Japan because of the lack of potential profit for manufacturers. Another case may be that in which drugs are approved in Japan for certain indications but commonly are used for non-approved or uninsurable indications. Doctor-led clinical trials are expected to improve the quality of medical care if doctors themselves are able to plan and conduct clinical trials of such drugs. Such clinical trials may solve problems such as the use of drugs that are not covered by Japanese health insurance but are available through parallel import or drugs used for non-approved indications even though both doctors and patients are aware of this.

Nevertheless, questions have been posed from various quarters as to whether doctors who are engaged in daily clinical practice are capable of planning and conducting clinical trials. Various other issues also require solutions. The task of JMACCT is to try to resolve such issues and to support doctor-led clinical trials.

Selection of Investigational Agents and Research Projects

Approval for doctor-led clinical trials supported by JMACCT requires that the investigating doctor submit an application, which then will be reviewed in external committees before being approved as a research project. The investigational agent is chosen from among drugs recommended by various member societies of the Japanese Association of Medical Sciences, on the basis of the need for the drug in clinical medical settings. The candidate drugs recommended by member societies are listed on the web-site of JMACCT (in Japanese).

If an investigator wishes to examine one of the candidate drugs, he or she may submit an application to JMACCT for support in planning the clinical trial. At this stage, the protocol of the intended clinical trial, case report forms, an informed consent form, and other documents are prepared. The expenses incurred in using the clinical trial consultation services of the Pharmaceuticals and Medical Devices Agency (PMDA) can be covered by the research funds.

Once a plan has been developed for the clinical trial, the investigator can apply for JMACCT's support in coordinating and managing the clinical trial. At this stage, the doctor, as the coordinating investigator, carries out coordination and management procedures prior to implementation of the clinical trial. If the application for the research project is approved at this stage, it is assured of being conducted.

Construction of the Clinical Trial Network

When the clinical trial of a particular agent is slated to take place, a site needs to be determined. The clinical trial network plays an

important role here. JMACCT constructs and maintains a large-scale, nationwide network for clinical trials.

Since its founding, JMACCT has invited medical institutions to register for inclusion in the network, under the following requirements: the institution is willing to participate in clinical trials, understands the meaning and structure of projects, and is able to cooperate in implementing clinical trials; the head of the institution agrees that the institution as a whole can apply for registration for including in the network and will respond to a brief questionnaire from JMACCT. This questionnaire is intended to ascertain the current situation of clinical trials in member institutions of the network as well as to inform the institution of what is required of medical institutions under the revised GCP. Medical institutions can apply to register at any time by going to the URL of JMACCT. About 800 institutions had registered with the network as of December 2004.

Medical institutions where doctor-led clinical trials supported by JMACCT are conducted are chosen from among member institutions registered with the clinical trial network. After it has been registered in the network, the member institution can receive information free of charge about clinical trials and notices of recruitment of institutions for company-supported clinical trials, in addition to being able to participate in doctor-led clinical trials for the adopted research projects.

Local Networks for Clinical Trials

JMACCT also supports local networks for clinical trials, which serve as branches of the large-scale clinical trial network, in the hope of enhancing the network. More specifically, 10 local networks were chosen in 2004 for research on the implementation of clinical trials. These networks include those of local medical associations, the National Hospital Organization, and universities.

Other Roles of JMACCT

JMACCT is taking various other actions to foster the smooth implementation of doctor-led clinical trials.

Development of model standard operating procedures

The first JMACCT activity is to develop model standard operating procedures. GCP prescribes that doctors who plan to perform a doctor-led clinical trial should prepare detailed, written operating procedures. It is not easy for doctors in daily clinical practice to prepare operating procedures by themselves, as operating procedures up to now have been prepared by companies that have sections specializing in this area. JMACCT supports doctors who wish to conduct clinical trials by preparing and publishing a template that can be used to describe operating procedures.

Compensation and liability insurance for doctor-led clinical trials

Another activity of JMACCT is that of developing compensation and liability insurance for clinical studies. GCP prescribes that in doctor-led clinical trials, doctors who carry out the clinical trial should provide some compensation for the study subjects. Compared with companies, it is more difficult for individual doctors to undertake compensation and liability measures. Therefore, JMACCT, in cooperation with an insurance company, has developed a new insurance service for doctor-led clinical trials. The insurance is available for doctors who carry out clinical trials of their own research projects, and the cost of insurance can be covered by the research funding.

Support for preparation of adverse drug reaction reports

If a serious adverse drug reaction occurs during a clinical trial, the investigator is obligated to report it to the national government. This is, however, not an easy procedure. For certain adverse reactions, the report needs to be submitted within 7 days of occurrence.

If an adverse drug reaction occurs in one of the participating institutions in a multicenter collaborative study, the investigator immediately must send information about the adverse reaction to other participating institutions, although appropriate treatment of the patient is certainly the first priority. Investigators of the various participating institutions also are obligated to file such reports. The reports should include detailed descriptions. To neglect this obligation may correspond to a violation of the Pharmaceutical

Affairs Law, and the clinical trial itself may be deemed as having been conducted unjustly.

JMACCT provides advice about the system used to report adverse drug reactions. This system provides smooth, safe transmission of information for each clinical trial. The Center is now developing software for adverse drug reaction reporting to facilitate the preparation of such reports.

Development and maintenance of a basis for implementing clinical trials

In addition to the above activities, JMACCT engages in various other projects to develop and maintain a firm basis for implementing clinical trials.

One of these activities was the "Industry-Government-Academia Joint Forum for the Promotion of Clinical Trials" held in November 2004 under JMACCT sponsorship. About 350 participants gathered in the JMA Hall to attend the forum.

Leading figures from various quarters participated as speakers or panelists. Panelists included Hatsuo Aoki, president of the Japan Pharmaceutical Manufacturers Association; Kazuhiko Adachi, head of the Research and Development Division, Ministry of Health, Labor and Welfare; Keiji Ueda, adviser of the Pharmaceuticals and Medical Devices Agency; Shigeyuki Nakano, chairman of the board of directors of the Japanese Society of Clinical Pharmacology and Therapeutics, as a representative of the academic sector; Yoshio Yazaki, chairman of the board of directors of the National Hospital Organization; and Mitsuko Ishii, an actress who has a nurse's license, as a representative of the general public.

Audience opinion indicated that 80% of the participants expected clinical trials to be carried out more actively in Japan. Many participants also indicated that JMA should promote the participation of private medical practitioners in clinical trials and should foster a better understanding of clinical trials among the general public.

A better understanding of clinical trials by medical practitioners and their active participation in them were considered extremely important, particularly in promoting the development of agents for the treatment of lifestyle-related diseases, because many of the patients who have lifestyle-related diseases attend small and medium-sized medical institutions. To further educate doctors working in such medical institutions, JMACCT plans to issue a clinical trial-related textbook tentatively called "The ABC's of Clinical Trials" by late 2005.

To educate the general public, promotional posters were sent to medical institutions throughout the country. In addition, by utilizing local networks for clinical trials, local citizens will come to have a better understanding of such trials.

Future schedule

JMACCT set up a new Data Management Section in February 2005 to manage data obtained not only from clinical trials of new drugs but also from clinical research on drugs available on the market. To play a role as a databank, in addition to supporting research, JMACCT is building a framework to foster the transmission of information from Japan to other countries.

Health Care Administration and Clinical Trials

Finally, changes in health care administration in relation to clinical trials need to be discussed.

In December 2004, the Ministry of Health, Labor and Welfare issued an agreement regarding the combined use of insurable and uninsurable health care services. In this context, the use of drugs not yet approved in Japan was taken up as an important issue, and major reform of the system was scheduled to take place within the current fiscal year, 2005. The following fundamental principles of this reform have been stated as follows:

1) Secure implementation of clinical trials
2) Development and maintenance of a support system for doctor-led clinical trials
3) Introduction of additional clinical trials
4) Combined use of health insurance treatment to avoid interruption in treatment

Thus, it is presumed that clinical trials will assume greater importance in improving the quality of medical care in Japan. JMACCT wishes to underline the importance of enhancing the support system for doctor-led clinical trials and to encourage the further development and maintenance of the basis for implementation of clinical trials, which are extremely important in Japan's health care system. JMA as a whole intends to address this issue in a more active and aggressive manner.

Safe Management of Blood Products for Transfusion in Japan

JMAJ 48(10): 522–526, 2005

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Key words Component transfusion, Transfusion adverse reactions, Type and screen, Informed consent, Hospital transfusion committee, Suitable blood usage

Problems in Transfusion Therapy

In recent years, the safety of blood products used for transfusion has increased considerably. The previous year has seen no reports of death from post-transfusion hepatitis or graft-versus-host disease (GVHD). However, the risk of ABO incompatible transfusion errors remains, and the adverse reaction of acute respiratory failure termed "transfusion-associated acute lung injury", which is attributable to leukocyte antibodies, has been attracting increased attention. As a result of these problems, the Law to Secure the Stable Supply of Safe Blood Products, the so-called "New Blood Law," was enacted in 2003, stipulating the obligations of doctors in implementing blood transfusion. Under the law, doctors are required to have knowledge of the complications of transfusion therapy and the measures to be taken against them.

Safe Blood Transfusion

To implement safe blood transfusions, proper blood transfusion practices are indispensable. Proper blood transfusion involves the minimum necessary transfusion. Because the function of the immune system is to recognize "self" and "non-self", and because viruses have been incorporated into human genes during the course of human evolution, it is theoretically impossible for exogenous blood to be completely innocuous. Since there is no possibility of securing zero risk, it is important to avoid blood transfusion unless the situation is critical and to supply only components necessary for life support. However, because patients undergoing blood transfusion are at high vital risk, doctors are likely to provide excessive transfusion for fear the patient might otherwise die. Although extensive clinical experience is necessary to overcome the strong fear of the patient's life being lost, not all doctors are able to acquire such experience. Therefore, education in transfusion medicine is of great importance.

Types of Blood Products Used for Transfusion

At present, Japanese Red Cross Society (JRCS) blood centers supply medical institutions with the following four types of blood products for transfusion: 1) banked whole blood, 2) red cell concentrates, 3) platelets, and 4) fresh frozen plasma. Among these, types 2–4 are the main ones used. Each type of blood product needs to be stored at a specific temperature. Red cell concentrate units, which are almost completely devoid of plasma components, contain mannitol-adenine-phosphate (MAP) solution as a preservative for the extended storage of red cells, and

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should be kept at 4 degrees Celsius. Such cells can be stored for up to 21 days. All platelet concentrates have been obtained by apheresis techniques since November 2004. Platelet concentrates are prepared by removing leukocytes, with the guarantee that the number of residual leukocytes does not exceed 1,000,000 per bag. Platelet concentrates are kept at 22 degrees Celsius while being shaken horizontally. They remain suitable for use only 72 hours after collection. Fresh frozen plasma is prepared by rapidly freezing the plasma component isolated from whole blood or obtained by component collection. Fresh frozen plasma units are kept at −20 degrees Celsius or colder and can be used for up to one year. In the event that the red cells isolated from the same whole blood unit are infected, the new quarantine system requires that delivery of the products be withheld for six months. The six-month quarantine period of the current fresh frozen plasma units terminated at the end of July. Because of the quarantine stipulation, the period of validity is, therefore, effectively 6 months.

Why is Component Transfusion Necessary?

Blood components targeted for transfusion show great variety in distribution and concentration in blood (Table 1). Therefore, it is important to use only the necessary component. Component transfusion is also important from the viewpoint of safety. Although the greatest problem involved in blood transfusion is incompatibility, platelets and fresh frozen plasma do not cause hemolysis as a result of incompatibility even if an improper blood type is used by mistake. If red cells in MAP solution are used, no adverse reaction due to anti-A and anti-B antibodies present in the plasma (minor incompatibility reaction) will occur.

Temperature Control of Blood Products

Because the red cells and platelets used for transfusion are living cells, the following storage conditions should be strictly observed to maintain cell function outside the body until just before use.

Red cells: 4 ± 2 degrees Celsius
Platelets: 22 ± 2 degrees Celsius

Although fresh frozen plasma units contain no cell components, the function of coagulation factors rapidly deteriorates, and therefore strict temperature control to −20 degrees Celsius is required.

Preparation Prior to Blood Transfusion

Informed consent

Informed consent should be obtained from the patient or his or her family before implementing blood transfusion. In case of emergency bleeding, written informed consent based on the provision of sufficient information may be obtained after transfusion. Information provided to the patient and family includes the need for blood transfusion, its possible adverse effects, and the blood component to be used. If the option of autologous blood transfusion is available, it should be included in the information given.

"Type and screen" and cross match

The patient's blood type must be tested before transfusion. ABO and RhD blood typing is routine. In order to detect ABO abnormality (ABO subtypes), two tests, i.e., cell grouping and reverse grouping, are carried out. Next, the patient is examined for the presence of irregular antibodies against red cell antigens other than ABO antigens. Irregular antibodies are known to exist in about 1% of patients. Whereas 99% of patients are negative for irregular antibodies, blood

Table 1 Body distribution of the blood components

	In blood vessel	In extra-cellular fluid	In spleen
Red cells	Almost 100%	—	—
Platelets	70%	—	30%
Albumin	40%	60%	—

product units that are associated with negative reactions should be chosen for positive patients from among the stock in JRCS blood centers. In rare cases, only several suitable units may be available in Japan, and thus sufficient time should be allowed before use. The above process is called "type and screen (T & S)". In addition, the cross match test, by which the patient's blood and the blood product to be transfused are mixed to check their compatibility, is carried out just before use. When all the test results are favorable, the blood transfusion can be performed safely. Platelet and fresh frozen plasma units, which contain no red cells, can be used after ABO typing without cross matching.

Practical Aspects of Blood Transfusion

To implement a blood transfusion, a blood product unit maintained under proper conditions should be taken from the shelf together with a cross match test voucher just prior to use, by two individuals (doctor or nurse). The patient's name and blood type (ABO, Rh), and the lot number of the blood product unit should be confirmed. One of the two individuals reads out every item, and the other confirms that the cross match test voucher agrees with the information on the blood bag. If the patient is conscious, it is also recommended that the patient give his or her own name and have the doctor or nurse confirm it with the patient name mentioned in the voucher. Most transfusion errors occur at the bedside, and thus due caution is necessary in this process.

Observation of Patients Just after Blood Transfusion

The doctor and nurse should not leave the patient immediately after the blood component unit is connected to the intravenous drip, but should stay at the bedside for at least 5 minutes and observe the patient. Thereafter, the patient should be observed at 15 and 30 minutes, at the end of transfusion, and 24 hours after transfusion. Since fever and urticaria occur in 5% of patients, antihistaminics and antipyretics should always be available. Steroids tend to be used frequently, but their overuse should be avoided.

Preservation of Transfusion Records

In cases of blood transfusion, the lot number of the blood product units used should be recorded and maintained for 21 years. The need for such a prolonged period of record keeping is due to the

Table 2 Services of hospital transfusion committee

1. Provision of guidance to other doctors regarding proper blood transfusion
Preparation of informed consent
Promotion of component transfusion
Development of a transfusion practice manual
Termination of the use of fresh blood and whole blood
Restriction of the excessive use of fresh frozen plasma
Management of transfusion records
Storage of patient specimens
2. Prevention of errors
Posting of the attending blood transfusion technician
Preparation of a 24-hour testing system by laboratory technicians
Incident report
Introduction of automated machinery
Introduction of computerized cross-matching
Introduction of a computerized on-site checking system
3. Reduction of deficits
Checking of insurance assessments
Ascertainment of abandoned blood products

risk of transfusion-mediated infection of variant Creutzfeldt-Jakob disease, a prion infection, which cannot be eliminated at present.

Confirmation of Transfusion-transmitted Infectious Diseases

Medical institutions in Japan currently are not obliged to keep patient sera. However, if the patient's blood is kept in the institution prior to transfusion, it can be determined whether the origin of post-transfusion infection such as post-transfusion hepatitis, if any, is a result of the transfusion or of other causes. Ideally, it is desirable to keep pre-transfusion patient sera in a frozen state for at least one year. On this issue, the Japanese Ministry of Health, Labor and Welfare gave notice to approve pre-transfusion hepatitis B and C virus marker tests under the name of the chief of the Pharmacy and Food Safety Bureau in September 2004. The approved tests include three types of hepatitis B test, i.e., HBs antigen, HBs antibody, and HBc antibody tests, and two types of hepatitis C test, i.e., HCV antibody and HCV core antigen tests. Administration of the nucleic acid amplification test 3 months after transfusion is approved for hepatitis B, and administration of the HCV core antigen test 1–3 months after transfusion is approved for hepatitis C.

Institutional Transfusion Therapy Committee

Each medical institution should have a transfusion therapy committee to improve the safety of transfusion. Each committee is required to nominate a doctor who assumes overall responsibility for transfusion. It is important that the doctor responsible be an executive of the hospital who is able to provide guidance to doctors from other fields. The tasks of this doctor are shown in Table 2.

The primary purpose of this committee is to facilitate the proper use of blood products; its second purpose is to provide measures against transfusion errors; and its third purpose is to restrain excessive transfusion expenditures by decreasing abandoned blood products through determining the actual situation of blood product use in hospitals. If each aspect of transfusion management were left to different sections, e.g., ordering of blood products to the attending doctor, blood testing to the laboratory, and irradiation to the radiology department, it would not be possible to control blood products in terms of the validity period. When these procedures are unified into a single well-organized transfusion department, abandoned blood products can be reduced dramatically. This kind of system is known as unification of transfusion management ("one refrigerator for one hospital").

Assessment of the Hospital Management System

An accrediting system to certify that a particular medical institution has developed such a management system is necessary. The US has had an inspection and accreditation (I & A) system for more than 20 years. This system seems to correspond to the medical inspection (on-the-spot inspection) system used in Japan.

Although the American Association of Blood Banks (AABB) initially took the lead in the I & A system, the Food and Drug Administration (FDA), the organization corresponding to the Ministry of Health, Labor and Welfare in Japan, began this type of inspection a decade ago.

Since no medical institution can practice blood transfusion without this accreditation, only about 3,000 institutions in the US are allowed to perform blood transfusions. According to a survey by the JRCS in 2004, Japan had approximately 15,000 medical institutions in which at least one unit of blood had been used for transfusion. Adjusting for the populations of the two countries, ten times more medical institutions in Japan provide blood transfusions than do in the US.

Under the national health insurance system of Japan, transfusion therapy has been handled as a general treatment, and, as a result, many institutions have been allowed to perform blood transfusions. However, if the strict I & A program of the US were applied to Japan, few Japanese medical institutions, including even some university hospitals, would obtain accreditation. Therefore, great confusion could occur if the same system were abruptly introduced to Japan.

I & A system of the Japan Society of Blood Transfusion

Taking its cue from the US AABB program, the

Japan Society of Blood Transfusion set up the I & A Committee, divided the country into 8 blocks, and proposed separate activities for each block. At present, several accredited doctors and technicians in charge of blood transfusion are volunteering in I & A activities in the Kanto and Kyushu areas. It is by no means easy for the limited number of executive transfusion staff to inspect other institutions, with some using their own paid vacation time. An inspection checklist is available at the URL of the Japan Society of Blood Transfusion (http://www.yuketsu.gr.jp).

Mutual Collaboration among Neighboring Institutions (Joint Conference of the Prefectural Transfusion Therapy Committees)

In 1998, the Fukuoka prefectural government took the lead in holding the first joint conference of prefectural blood transfusion therapy committees. This support by a local government was advantageous in encouraging a large number of medical institutions to participate. At that time, a questionnaire survey was carried out to determine the situation regarding the use of blood products in each institution. From the results, it became apparent that red cell concentrates were in use in a large number of institutions, whereas the use of platelets and fresh frozen plasma tended to be centered in large hospitals. In addition, the amount of blood products used in the 20 hospitals with the highest consumption accounted for about 80% of all blood product consumption. The most useful finding from the survey was a large variation in the consumption of blood products per bed among different medical institutions. Knowledge of such variation in blood product use makes it easier to set standards for blood transfusion as a therapeutic procedure. If a 3-fold difference in the consumption of fresh frozen plasma is noted between institutions A and B, the reason for the discrepancy needs to be clarified. A comparison among different institutions would highlight improper use of blood products that otherwise might remain unrecognized in individual institutions, and could help to curtail excessive use. Currently, it seems that some form of guidance in the proper use of blood products based on such data would be suitable for the situation existing in Japan.

Concluding Remarks

The safety of blood products used for transfusion was improved to a great extent by the development of the hepatitis C test in the late 1980s and the subsequent introduction of nucleic acid amplification into the test.

Current blood products are at least 1000-fold safer than they were around 1990. However, this does not constitute perfection, because there has been no change in the risk of morbid patients undergoing blood transfusion. The survival rate at 1 year after the first transfusion is 75%. In other words, as many as 25% of patients die within 1 year. Patient death is always a concern for the attending physician, and he or she may be prone to excessive blood transfusion in the hope of somehow saving the patient's life. This may create a situation in which emotions interfere with the scientific wisdom on blood transfusion.

Consequently, it may lead to improper blood transfusion, such as combined use of red cells and fresh frozen plasma at a ratio of 1:1, transfusion of fresh frozen plasma without pre-transfusion coagulation test, and the use of banked whole blood for the treatment of bleeding, thereby imposing excessive risk on the patient.

Safe blood transfusion can be achieved when the doctor directs proper transfusion and the nurse implements it accurately. Serious attention needs to be paid to the important role of institutional transfusion therapy committees in implementing a system of safe blood transfusion.