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Is Percutaneous Endoscopic Gastrostomy Really a Safe Procedure for High Aged Patients?

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Percutaneous endoscopic gastrostomy (PEG), which was first performed in 12 children and 19 adults by Gauderer,[1] is nowadays widely used for providing enteral nutrition to patients who cannot take meals orally. The procedure is believed to be particularly useful in high risk patients because general anesthesia is not usually required. PEG is mainly performed on high-aged patients rather than on children. Complications are rare (6.6% major, 6.6% minor); PEG-related mortality and morbidity are 1–2% and 3–12%,[2,3] respectively, and are not influenced by patients' age.[4] However, little has been known about the incidence of complications and the outcomes of long-term PEG in Japan.

In this issue, Suzuki et al. report surveillance data on PEG in Japan they collected by asking 760 hospitals nationwide to complete questionnaires. Their results indicate that major complications such as death and peritonitis occurred in 24.7% of hospitals. Minor complications including wound infections (25.5%) and diarrhea (20.6%) occurred more frequently than pneumonia (12.3%), vomiting (9.9%), dermatitis (9.0%), granulation (8.8%), accidental self-exertion (7.0%), or constipation (4.5%). Approximately 25% of hospitals where more than one erroneous insertion occurred had higher 30-day mortality rates. The rate of negative outcomes seems to be higher than anticipated, with an unexpectedly low 14.3% of PEG patients unable to be discharged from hospital. In Japan, people aged 65 years or older comprised 20% of the population in 2005 and their number is rapidly increasing. This age group is predicted to comprise 25% of Japan's population in 2015, which indicates that a super-senile era is coming soon and with it a rapid increase in the number of high-aged patients requiring PEG.

Finally, as the number of lawsuits associated with medical trouble is increasing in Japan, doctors should take care when performing PEG to receive informed consent, ensuring that patients are aware of the possible negative outcomes.

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A Survey of Percutaneous Endoscopic Gastrostomy in 202 Japanese Medical Institutions

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Abstract

Background Percutaneous endoscopic gastrostomy (PEG) is widely used for enteral nutrition of patients unable to take food by mouth. In this study, we surveyed usefulness of PEG and determined the approximate rates of complications associated with PEG replacement in Japan.

Methods Questionnaires were sent to 760 hospitals; 202 hospitals returned their questionnaires (27% response rate).

Results 5,291 patients underwent PEG in 2004 among these Japanese hospitals. PEG was mainly performed in general hospitals by physicians and surgeons. Most patients were elderly (mean age: 79.8 ± 33.4 SD years old) with cerebral infarction/hemorrhage and dementia and required nutritional support. Major complications such as death and peritonitis were experienced by 24.7% of hospitals. Approximately 25% of hospitals experienced more than one erroneous insertion of the tube into the extra-gastrointestinal tract. Hospitals that experienced erroneous insertions had higher 30-day mortality rates, whether or not mortality was associated with PEG placement. On the other hand, the erroneous insertion rates as well as 30-day mortality were inversely associated with number of PEG procedures performed during year 2004 at each hospital.

Conclusion These surveillance data imply that a lower patient volume treated with PEG at an institute may be associated with negative outcomes, although a longitudinal study is necessary to confirm this conclusion.

Kew words Quality of life, Enteral nutrition, Patient care, Morbidity and mortality, Home care

Introduction

For patients with a functioning gastrointestinal tract but the inability to take food by mouth, early enteral nutrition reduces morbidity and mortality of several conditions compared with total parenteral nutrition.[1–5] Nasogastric tubes are simple enough to insert but are often intolerable for the patients. Moreover, these tubes are difficult to maintain in position and are associated with a significant risk of aspiration.[6] Nasojejunal tubes are more tolerable to patients, but they are easily blocked and also difficult keep in position.[7] Therefore, gastrostomy or occasionally jejunostomy may be used for patients who cannot take food orally. Although gastrostomy or jejunostomy may be easily performed with open surgery under general anesthesia, the risks of surgery may outweigh the benefits, because most patients with indications for gastrostomy are older, malnourished, and have other morbidities.[8]

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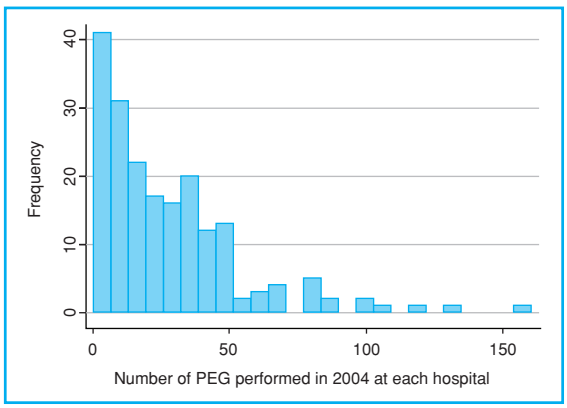

Fig. 1A Number of patients who underwent PEG at each medical facility in 2004

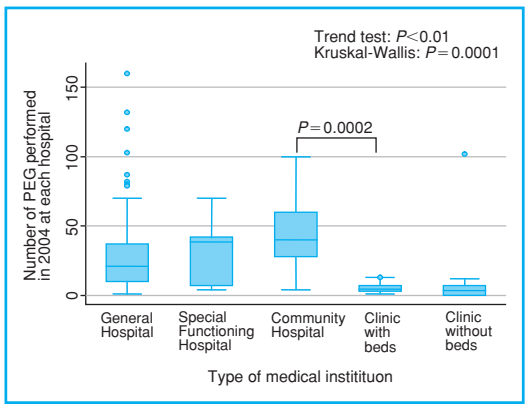

Fig. 1B Association between types of medical institutions and the number of PEG performed in 2004 at each institution

Percutaneous endoscopic gastrostomy (PEG) as well as percutaneous endoscopic jejunostomy/percutaneous endoscopic duodenostomy are fast, safe, and effective methods for long-term enteral tube feeding as long as no contraindications to enteral feeding exist.[9–13] Moreover, there may be less reflux and food aspiration with these methods.[14] Therefore, PEG is now the preferred treatment for patients with dysphagia, and its use has been growing in the United States and the United Kingdom.[15]

Although the primary indication for PEG is the inability to take food by mouth, indications vary widely depending on the physician's policy. Although PEG insertion and tube exchanges are not complicated, they can lead to serious and potentially lethal complications. However, such negative findings seem to be outweighed by the positive results[16–20] at least in Japan. We surveyed PEG usage in Japan by sending questionnaires to 760 medical institutions and received answers from 202 (27% response rate). The results are summarized in this paper.

Methods

Surveillance

We selected the 760 hospitals where one or more doctors are involved in performing PEG for patients and participate in the PEG doctor's network in Japan (http://www.peg.ne.jp/news/index.html). We sent questionnaires to these 760 hospitals and received answers to the questionnaires from 202 (27% response rate). A copy of the 83 questions on the questionnaire appears in Appendix I.

Statistical analysis

Factors associated with erroneous insertion of the tube into the extra-gastrointestinal tract were evaluated using either Chi-square test or Student's t-test. Kruskal-Wallis equality of populations rank tests adjusted for trend tests, as described by Cuzick,[21] were used to determine associations among three and more groups. All statistical analyses were performed using STATA 8.0 (STATA Corporation, College Station, TX).

Results

Characteristics of responding medical institutions

A total of 194 medical facilities performed PEG procedures on 5,291 patients in 2004. A mean of 27.3 ± 26.2 SD PEG procedures (range, 0 to 160) were performed at each of these medical institutions: 10th percentile = 4 patients, 25th percentile = 8 patients, 50th percentile = 20 patients, 75th percentile = 38 patients, and 90th percentile = 58 patients (Fig. 1A). The types of institutions that responded to the questionnaires were general hospitals (73.7%) followed by community hospitals (8.6%), clinic without beds (7.1%), special functioning hospitals (5.6%) and clinic with beds (5.1%). The total number of PEG procedures performed in 2004 was equivalent among general hospitals, special functioning hospitals, and community hospitals, but the number in community

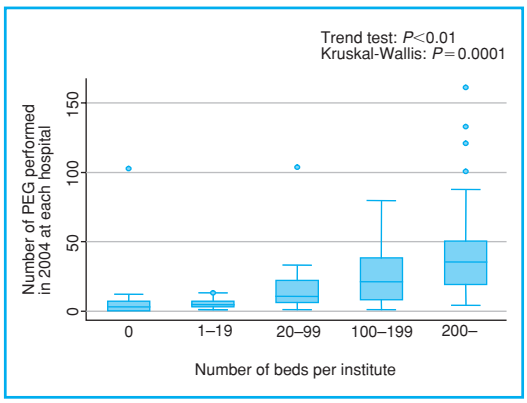

Fig. 1C Association between the number of beds per institute and the number of PEG performed in 2004 at each institution

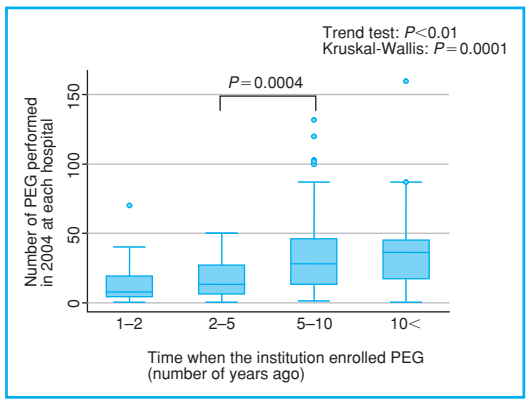

Fig. 1D Association between the timing when the institution enrolled PEG and the number of PEG performed in 2004 at each institution

hospitals was greater than in clinic with beds (Fig. 1B). Hospitals with more than 100 beds were most common in this survey: more than 200 beds: 40.7%; 100–200 beds: 25.6%; 20–99 beds: 22.1%; less than 19 beds: 5.0%; no beds: 6.5%. The number of PEG procedures per institution increased depending on the number of beds (Fig. 1C). The number of hospitals adopting PEG has grown steadily: PEG started more than 10 years ago: 19.8%; 5–10 years ago: 41.7%; 2–5 years ago: 22.9%; 1–2 years ago: 15.6%. In particular, medical institutes that began performing PEG procedures more than 5 years ago treated more patients than hospitals that began performing these procedures less than 5 years ago (Fig. 1D). PEG was mainly performed by physicians (44.7%) or surgeons (39.3%); few endoscopists (9.1%) reported performing this surgery. Fewer than three physicians at each institution performed PEG procedures among 73.1% of surveyed hospitals. As the number of physicians who performed PEG at each institute increased, the number of procedures per institution increased as well (data not shown).

Characteristics of patients who underwent PEG

As stated, 5,291 patients underwent PEG in 2004. The ratio between men and women was 13:14. The mean age was 79.8 ± 33.4 SD years, and most patients (95.1%) were aged 60 to 100 years. Enteral nutrition was the primary reason (98%) for undergoing PEG. Most of the underlying diseases were neurological dysfunction as follows: cerebral infarction: 46.2%; hemorrhage: 18.0%; dementia: 12.3%; Alzheimer disease: 4.0%; trauma: 2.4%; cancer: 3.8%. The underlying clinical condition of patients who underwent PEG was dysphagia in about 50% of patients; repeated aspiration pneumonia (19.9%) and reduced oral intake (18.9%) were the next most common conditions.

Methods of performing PEG and status of team support

PEG was typically performed in the endoscopy room (71.9%) and also in the operation room (12.4%) as well as in clinical wards (3.8%), either with conscious sedation (55.8%) or local anesthesia of the pharynx (21.6%), with (52.4%) or without (47.6%) the use of an anticholinergic agent, and using the pull method (69.7%). However, in some medical institutions, the procedure varied.

Approximately 25% of medical institutions performed a throat culture before the procedure. However, most institutions (91.9%) ignored the possible existence of pathogenic microorganisms in patients' throats and inserted the tube via the oral route. Bumper (75.1%) and balloon (17.6%) procedures were most common during the initial tube insertion, although neither way was fixed in other hospitals. Of the type of catheter to fix to the skin at initial construction, the tube type was preferred (66.8%) followed by the button type (18.7%). Whether or not the gastric wall was fixed to the abdominal wall varied by institution. Most institutions did not use fluoroscopy to

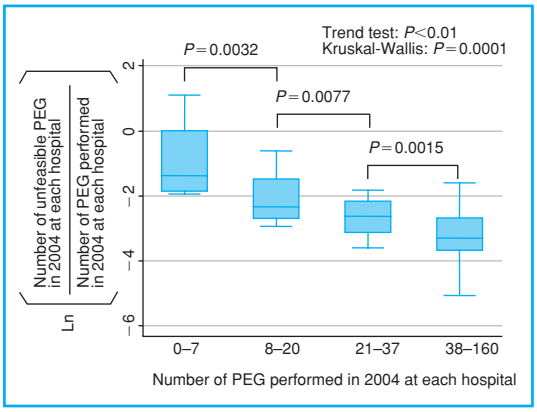

Fig. 2A Association between the feasibility of PEG and the number of PEG performed in 2004 at each hospital

The difference and trend among quantile of number of PEG performed in 2004 at each hospital were evaluated with Kruskal-Wallis test and trend test, respectively. Difference between two groups was calculated by Student's *t* test. Cutoff of *P*-value for statistical difference was set at 0.0167.

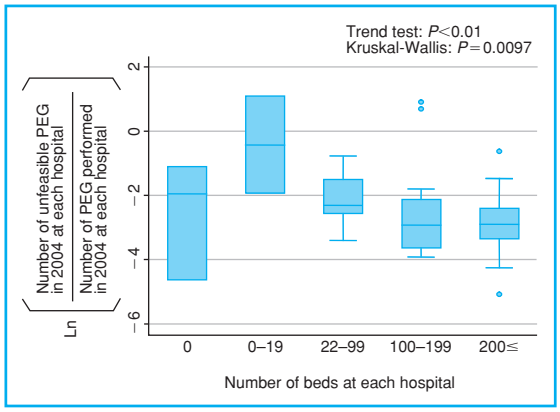

Fig. 2B Association between feasibility of PEG and number of beds at each hospital

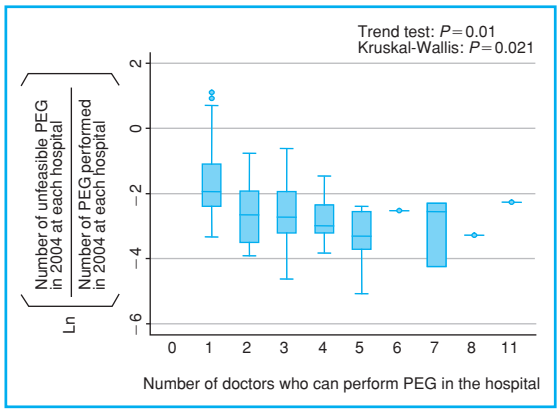

Fig. 2C Association between feasibility of PEG and number of doctors who can construct PEG in the hospital

confirm the status of the PEG tube (80.3%). During the exchange of the catheter, bumper (49.8%) and tube methods (26.3%) were most common. The duration between the initial tube insertion and the first exchange of the tube was significantly shorter with the balloon procedure (mean 2.22 ± 1.84 SD months) than with the bumper procedure (mean 5.23 ± 2.22 SD months) (Student's t-test: $P<0.0001$). Approximately 25% of institutions performed the first tube exchange under endoscopy, whereas more than 50% performed it manually. Institutes varied in the method in which they confirmed the status of the PEG tube at the first exchange, although an endoscopic procedure was used most frequently: endoscope: 32.5%; fluoroscopy: 19.5%; injecting air through PEG: 6.5%; checking influx of gastric acid: 20.0%. However, at the second exchange, fluoroscopy was used by most institutions (73.2%) to confirm the status of the PEG tube, whereas injecting air through PEG was the next (14.9%) and endoscopy was applied least (11.9%). Most second exchanges took place a mean of 5.23 ± 2.22 SD months after the first exchange. Approximately one-third of patients exchanged the PEG tube at home.

A preoperative conference for all patients who needed PEG was held by 16.5% of medical facilities. More than half (67.8%) the hospitals had no nutrition support team, whereas more than half (53.1%) had a clinical path designed for patients who were undergoing PEG.

Feasibility of performing PEG and frequency of erroneous insertion of the tube into the extra-gastrointestinal tract

Nearly half of the medical institutes (47%) had some patients in whom it was not feasible to insert the PEG tube. When the analysis was restricted to hospitals that had at least one patient in whom PEG tube insertion was not feasible, the natural logarithm of unfeasible PEG patients divided by the number of PEG procedures performed at each hospital in 2004 decreased by an increment of the number of

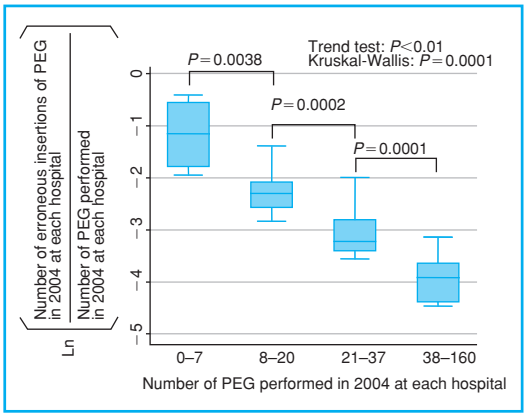

Fig. 3A Association between feasibility of PEG and number of PEG performed in 2004 at each hospital

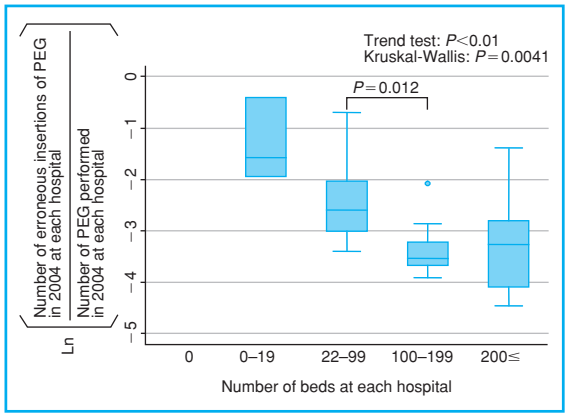

Fig. 3B Association between feasibility of PEG and number of beds at each hospital

PEG procedures performed at each hospital in 2004 (Kruskal-Wallis: $P<0.0001$: trend test: $P<0.01$) (Fig. 2A). Similarly, when the number of beds or the number of doctors at each institute increased, the ratio of unfeasible PEG procedures tended to decrease (Fig. 2B and Fig. 2C).

During tube exchange, 23.8% of hospitals experienced erroneous insertion of the tube into the extra-gastrointestinal tract. The number of erroneous insertions ranged from one to five. When the analysis was restricted to hospitals that experienced at least one erroneous insertion, the natural logarithm of the number of erroneous insertions of PEG tubes divided by the number of PEG procedures performed at each hospital in 2004 decreased by an increment of the number of PEG procedures performed at each hospital in 2004 (Kruskal-Wallis: $P<0.0001$: trend test: $P<0.01$) (Fig. 3A). Similarly, when the number of beds or number of doctors at each institute increased, the ratio of erroneous PEG insertions tended to decrease (Fig. 3B and Fig. 3C).

Factors associated with erroneous insertion of tubes into the extra-gastrointestinal tract are shown in Table 1. Institutes with no experience with erroneous insertions tended to use balloon and button procedures rather than bumper and tube procedures at exchange. When the PEG was exchanged under endoscopy, the risk of erroneous insertion decreased. Changing the tube at home did not significantly increase the risk of an erroneous insertion.

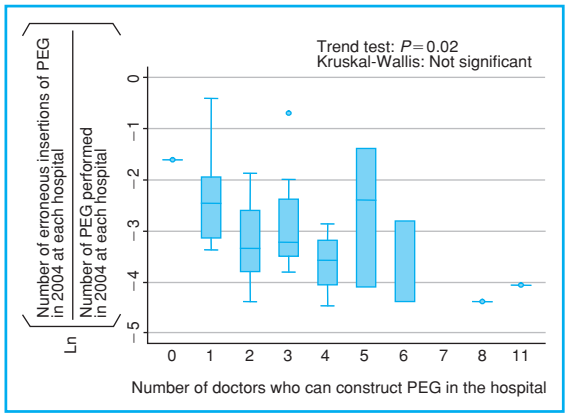

Fig. 3C Association between feasibility of PEG and number of doctors who can construct PEG in the hospital

Incidence of major and minor complications

Death as an adverse event was experienced by 40.7% of the institutes after adopting PEG; the number of deaths ranged from 0 to 19 with a mean of 0.94 ± 1.78 SD per hospital. Two institutes indicated that death was caused by the PEG procedure in 3 patients. The percentage of patients who died within 1 month and 6 months was 5.0% and 12.6%, respectively, although survival data for 20.1% of patients were not disclosed. Institutes that experienced erroneously inserted tubes into the extra-gastrointestinal tract also tended to have significantly higher risks of death within 1 month, whether or not it was due to a complication that occurred during the

Table 1 Factors associated with erroneous insertion of the tube into the extra-gastrointestinal tract

Questionnaire	No experience of error n = 47 (%)	More than one experience of error n = 155 (%)	*P* value*
Which method do you use for stomach internal fixation at exchange?			
Balloon	43 (28)	10 (15)	0.037
Bumper	78 (51)	12 (47)	
Balloon or bumper	33 (21)	24 (38)	
Which method do you use for outside the body shape at exchange?			
Button	78 (51)	14 (30)	0.006
Tube	35 (23)	9 (19)	
Button or tube	41 (27)	24 (51)	
Please select the method used at the first exchange			
Exchange under endoscopic observation	44 (29)	7 (15)	0.045
Manual exchange	89 (58)	28 (60)	
Either way	20 (13)	12 (26)	
What kind of confirmation method did you use at the first exchange?			
Endoscope	52 (34)	13 (28)	NS
Fluoroscopy	28 (18)	11 (23)	
Injecting air through PEG	11 (7)	2 (4)	
Check influx of gastric acid	30 (20)	10 (21)	
Varied by situation	32 (21)	11 (23)	
Were patients allowed to change the PEG tube at home?			
Yes	49 (32)	21 (46)	NS
No	106 (68)	25 (54)	

*: Calculated by chi-square test. When the *P*-value was less than 0.05, the difference was considered statistical significant.

Table 2 Outcomes associated with erroneous insertion of the tube into the extra-gastrointestinal tract

Questionnaire	Total n = 202 (%)	No experience of error n = 155 (%)	More than one experience of error n = 47 (%)	*P* value
Did you experience any deaths within 1 month after PEG insertion?				
Yes	77 (38)	50 (34)	27 (63)	
No	125 (62)	96 (66)	16 (37)	0.001*1
How many in 2004? (Mean ± SD)	0.94 ± 1.78	0.83 ± 1.86	1.33 ± 1.43	NS*2
Did you experience any deaths during tube exchange?				
Yes	2 (1)	1 (1)	1 (2)	
No	202 (99)	154 (99)	46 (98)	NS*1
How many in 2004? (Mean ± SD)	0.015 ± 0.157	0.01 ± 0.16	0.02 ± 0.15	NS*2
Did you experience major complications after PEG insertion?				
Yes	46 (25)	32 (23)	14 (32)	
No	140 (75)	110 (77)	30 (68)	NS*1
Did you experience any deaths related to a major complication within 1 month after PEG insertion?				
Yes	17 (9)	8 (6)	9 (20)	0.003*1
No	173 (91)	137 (94)	36 (80)	0.0111*2
How many in 2004? (Mean ± SD)	0.13 ± 0.45	0.08 ± 0.36	0.28 ± 0.63	

*1: Calculated by chi-square test; *2: Calculated by Student's *t* test

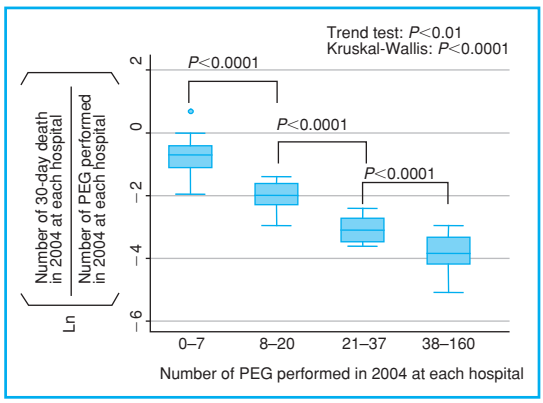

Fig. 4 Association between 30-day mortality after PEG and number of PEG performed in 2004 at each hospital

PEG procedure (Table 2). The 30-day mortality rate in each institute was inversely associated with the number of PEG procedures performed at each hospital in 2004 (Fig. 4).

Major complications such as death and peritonitis associated with the procedures of PEG insertion or replacement were experienced by 24.7% of hospitals during 2004. Minor complications, including wound infection (25.5%) and diarrhea (20.6%), occurred more frequently than pneumonia (12.3%), vomiting (9.9%), dermatitis (9.0%), granulation (8.8%), accidental self-exertion (7.0%), constipation (4.5%), and others among all patients treated with PEG in year 2004. The infection rate (number of infections/number of PEG procedures) was not associated with the usage patterns of antibiotics or the type of device used (data not shown).

After discharge from the medical institution where PEG was performed.

After discharge from the medical institute where PEG was performed, only 14.3% of patients went home. Most patients were transferred to other hospitals.

Issue of insurance

When asked "In your institute, are costs for gastric catheter exchange covered under special insurance medical care material costs?" 12.6% answered "yes". When asked "In medical facilities using diagnosis related grouping and institutions using insurance for the elderly, the costs associated with gastric catheter exchange cannot be separately claimed under insurance as a special healthcare material cost. Do you think that it should be paid separately as a special healthcare material cost?" most hospitals (96.9%) answered "yes". To the question "Do you file an insurance claim when you use enteral nutrition via PEG?" 82.5% answered "yes" and 3.2% answered "yes, but we are limited in the maximum charge for the claim". To the question "Excluding 'Elental', 'Elental P', 'Enterude', 'Twinline' and other medical nutrients of half digested state, do you think set dietary food for enteral nutrition should be a fee-for-service?" 79.1% of hospitals answered "yes".

Opinions of doctors who perform PEG

When asked "Do you think that PEG is the best way to provide nutritional support?" 33.3% answered "yes, it is the best way", 57.6% answered "yes, it is a good way", and the remainder answered "No, it is not the best way". When asked "PEG enables patients to be themselves, that is experience a 'recovery of everydayness', and allows care to be provided at home. Do you agree with this opinion?" 95% of doctors agreed.

Discussion

We selected 760 hospitals where one or more doctors are involved in performing PEG for patients and participate in the PEG doctor's network in Japan. We sent questionnaires to these 760 hospitals and received answers to the questionnaires from 202 (27% response rate). In these 202 institutions, totally 5,291 patients underwent PEG in 2004. Data indicate that PEG was mainly performed in general hospitals by physicians and surgeons on older patients with cerebral infarction/hemorrhage and dementia. Procedures were performed primarily in the endoscopy room under conscious sedation or anesthesia of the pharynx. These trends were similar to those in other countries.[22,23]

The pull and push method were preferred in 70% and 9% of surveyed institutions, respectively, which may reflect the evidence that percutaneous placement of a pull-type gastrostomy tube was performed with a minimum risk of tract disruption and peritonitis.[24–27] In contrast, one study showed that serious complications leading to laparotomy, wound infection, or intraperitoneal abscess developed in 17 patients (13%), in all of whom the introducer (ie, push) technique

had been used.[28] Bumper and tube methods were preferred for the initial PEG tube insertion. In contrast, bumper and button methods were preferred for the first manual exchange of the PEG tube. Endoscopy and fluoroscopy were used most frequently at the first and second tube exchange, respectively, to confirm the status of the tube placement. However, one study showed that repeated endoscopy might not be routinely required to assess the proper positioning of the internal bumper.[29]

Nearly half of medical institutes had patients who were not good candidates for PEG. Similarly, approximately 25% of institutes reported experiencing erroneous insertion of the tube into the extra-gastrointestinal tract, which can trigger lethal peritonitis. These ratios of unfeasible cases and erroneous insertions as well as 30-day mortality decreased as the annual number of PEG procedures, the number of beds, and the number of physicians who performed the surgery per institution increased, which is a novel and interesting finding. Similarly, neonatal mortality and outcomes of coronary angioplasty are affected by patient volume.[30,31] In addition, institutes with no experience of erroneous insertions tended to use balloon and button methods rather than bumper and tube methods during tube exchange. When the PEG was exchanged under endoscopy, the risk of erroneous insertion decreased. However, of interest, changing devices at home did not significantly increase the risk of erroneous insertions. One-third of patients performed PEG tube exchanges at home.

PEG procedure-related mortality and morbidity are reported to be 1%–2% and 3%–12%, respectively.[32,33] In this survey, two institutions reported three deaths related to the PEG procedure; however, this number may be biased by under-reporting and cannot be directly compared with previous reports. In this survey, 5% of patients died within 1 month; however, survival status was unknown for 20.1% of patients. Thus, the 30-day mortality in this study cannot be compared with that in other reports. Researchers in England reported that 30-day mortality for PEG was 22% during 2002 as opposed 10% 10 years earlier.[34–36] They speculate that this increase in mortality may be due to a trend towards less strict patient selection in the later years.

Major complications were experienced by 24.7% of hospitals. Minor complications, including wound infection, diarrhea, pneumonia, and others, were experienced in more than half of institutions. Infection rates were not associated with antibiotics usage patterns or type of devices used (data not shown), although antibiotic prophylaxis has been demonstrated to reduce the risk of peristomal wound infection associated with PEG insertion.[37]

In conclusion, PEG procedures are widely used in Japan. Lower rates of unfeasible cases and erroneous insertion as well as 30-day mortality were associated with a higher number of PEG procedures performed at each hospital. These results suggest that a lower patient volume treated with PEG at an institute may be associated with negative outcomes, although a longitudinal study is necessary to confirm these findings.

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Appendix I

The questionnaire

Q1 Which clinical department performs PEG in your hospital? (Select as many responses as apply)
1. Surgery, 2. Department of Internal Medicine, 3. Department of Endoscopy, 4. Other

Q2 How many years has your institute been performing PEG?
1. 1–2 years, 2. 2–5 years, 3. 5–10 years, 4. more than 10 years

Q3 Which department performs PEG most frequently in your institute?
1. Department of Gastroenterology, 2. Department of Endoscopy, 3. Department of Internal Medicine, 4. Other

Q4 How many times did you perform PEG between January and December in 2004?

Q5 Please divide the number that you provided in Q4 into men and women?

Q6 How many patients underwent PEG in your institute in 2004 by each age group?
1. <10 years, 2. 10–20 years, 3. 20–30 years, 4. 30–40 years, 5. 40–50 years, 6. 50–60 years, 7. 60–70 years,
8. 70–80 years, 9. 80–90 years, 10. 90–100 years, 11. 100–years

Q7 Why did you perform PEG?
1. Nutritional support, 2. Decompression, 3. Other

Q8 Please indicate the primary disease of the patient who underwent PEG.
1. Cerebral infarction, 2. Cerebral hemorrhage, 3. Dementia, 4. Alzheimer's disease, 5. Traumatic injury, 6. Carcinoma,
7. Decompression treatment, 8. Other

Q9 What kind of disabilities did the patient have? (Select all responses that apply)
1. Dysphagia due to cerebrovascular or other neural disease, 2. Repeated aspiration pneumonia, 3. Reduced oral intake,
4. Crohn's disease in which perioral intake of food could worsen inflammation in the gastrointestinal tract,
5. Disease or injury that oral intake impossible, 6. Inability to keep nasogastric tuve in place (patient pulled it out),
7. Discomfort due to insertion of a nasogastric tube for long periods, 8. Other

Q10 Was there a case in which it was not feasible to perform PEG? If yes, in how many cases did this occur?

Q11 Did you perform PEG after gastrectomy? If yes, how many?

Q12 Do you perform percutaneous transesophageal gastrotubing (PTEG)?

Q13 When did you perform PTEG?
1. When PEG could not be performed, 2. We perform PTEG even if PEG is available, 3. We do not perform PTEG

Q14 Do you have a preoperative meeting for risk evaluation/nutritional status evaluation/review of future condition of the patient who will undergo PEG?
1. For all cases, 2. On a case-by-case basis, 3. No

Q15 Does the NST (Nutrition Support Team) coordinate with doctors who perform PEG insertion?

Q16 Do you use a clinical pass?

Q17 Who is responsible for obtaining informed consent? (Select as many responses as apply)
1. Chief physician, 2. PEG performer, 3. Other (please specify)

Q18 What do you tell the patient and a family during informed consent? (Select as many responses as apply)
1. Importance of nutrition support therapy, 2. Benefit compared with peroral intake, 3. Reduction in nursing care,
4. Improve QOL of the patient, 5. Method of PEG construction, 6. Kind of a catheter and timing of exchange,
7. Kit/nutrient preparation, 8. Ways of managing the patient, 9. Medical insurance or cost, 10. Other

Q19 In addition to Q18, what else to you go over when you obtain informed consent?

Q20 Where do you perform PEG?
1. Operating room, 2. Endoscopy room, 3. Ward, 4. Other

Q21 What kind of anesthesia do you usually use while performing PEG?
1. General anesthesia, 2. Conscious sedation, 3. Anesthesia of the pharynx alone, 4. Determined on a case-by-case basis

Q22 Do you use an anti-cholinergic agent as pre-medication before PEG?

Q23 Which methods do you use during the first PEG construction?
1. Pull method, 2. Push method, 3. Introducer method, 4. Pull method or Introducer method,
5. Push method or Introducer method

Q24 Do you perform a preoperative throat culture?

Q25 When pathogenic microorganisms such as methicillin-resistant *Staphylococcus aureus* or *Pseudomonas* spp. are detected on preoperative throat culture, do you eradicate the organism from the throat?
1. We perform PEG after confirming that the pathogenic microorganism was eradicated,
2. We perform PEG combined with eradication treatment without confirming that the pathogenic microorganism was eradicated,
3. We perform PEG without eradication treatment as a general rule

Q26 When pathogenic microorganisms such as methicillin-resistant *Staphylococcus aureus* or *Pseudomonas* spp. are detected on preoperative throat culture, which method or kit do you use?
1. Introducer method, 2. Special device to prevent wound infection, 3. Ordinal method

Q27 When pathogenic microorganisms such as methicillin-resistant *Staphylococcus aureus* or *Pseudomonas* spp. are detected on preoperative throat culture, do you use postoperative prophylactic antibiotics?
1. Yes, we use antibiotics to which the microorganism is sensitive,
2. Yes, we use antibiotics independent of the sensitivity of the microorganism,
3. No, we do not use antibiotics

Q28 Which type do you use for stomach internal fixation at the first PEG construction?
1. Balloon type, 2. Bumper type, 3. Combination of Balloon type and Bumper type

Q29 Which type do you use outside the body at the first PEG construction?
1. Button type, 2. Tube type, 3. Combination of Button type and Tube type

Q30 At the first PEG construction, do you fix the gastric wall?
1. Yes, for all cases, 2. Determined on a case-by-case basis, 3. No

Q31 At the first PEG construction, do you perform radioscopy?

Q32 Which type do you use for stomach internal fixation at exchange?
1. Balloon type, 2. Bumper type, 3. Balloon type or Bumper type

Q33 Which type do you use outside the body at exchange?
1. Button type, 2. Tube type, 3. Combination of Button type and Tube type

Q34 How long is the period from PEG construction to first tube exchange using either balloon type or bumper type?
1. Balloon type (months), 2. Bumper type (months)

Q35 Please select the method used at the time of first tube exchange.
1. Exchange under endoscopic observation, 2. Manual exchange, 3. Combination of both

Q36 At the time of the first tube exchange, what method do you use to confirm tube placement?
1. Endoscopy, 2. Radioscopy, 3. Inject air through the PEG, 4. Check influx of gastric acid, 5. Varies by situation

Q37 When do you exchange the tube the third time? After ( ) months

Q38 Please select the method used at the second exchange to confirm tube placement.
1. Endoscopy, 2. Radioscopy, 3. Inject air through the PEG, 4. Check influx of gastric acid, 5. Varies by situation

Q39 After the second exchange, what method do you use to confirm tube placement?
1. Endoscopy, 2. Radioscopy, 3. Inject air through PEG, 4. Check influx of gastric acid, 5. Varies by situation

Q40 Do you allow tube exchange to be done at home?
1. Yes, 2. No

Q41 Have you experienced an intra-abdominal false insertion?
1. Yes, 2. No
If yes, how many times did you experience this?

Q42 Were any deaths triggered by an exchange error?
1. Yes, 2. No
If yes, how many times did this occur?

Q43 Do you give the patient's family a PEG diary?

Q44 Do you usually perform a pre-operative blood examination?

Q45 Do you usually order chest X-rays as part of the preoperative examination?

Q46 Do you usually order abdominal X-rays as part of the preoperative examination?

Q47 Do you usually order an abdominal CT as part of the preoperative examination?

Q48 Do you usually perform a throat culture as part of the preoperative examination?

Q49 Do you usually perform a nasal cavity culture test as part of the preoperative examination?

Q50 Do you usually perform mouth care as part of the preoperative treatment? If yes, how many times do you go on 1st?

Q51 Do you usually use an antacid agent as part of the preoperative treatment? If yes, please indicate the name of the medicine.

Q52 Do you usually use antibiotics before and during surgery?

Q53 Do you usually use antibiotics after surgery?
If yes, for how many days do you use antibiotics?

Q54 How many days after insertion of the PEG do you begin enteral feeding?

Q55 Please indicate whether or not you use each of the following nutrients (yes or no).
1. High-density liquid diet food, 2. Half-digested diet food, 3. Half-digested medical diet, 4. Full-digested medical diet,
5. Nutrient components medical diet

Q56 Do you use an antacid agent after surgery?
1. Yes, 2. No

Q57 How many days after PEG placement must the patient wait to take a shower?

Q58 Has any patient died within 1 month postoperatively of PEG placement? If yes, how many?
1. Yes (number), 2. No

Q59 Has any patient died within 1 month postoperatively due to PEG insertion? If yes, how many?
1. Yes (number), 2. No

Q60 Did you experience major complications with PEG placement?
1. Yes, 2. No, 3. Unavailable
If yes, what kind of complications?

Q61 Did you experience minor complications less than 2 weeks postoperatively after PEG placement? If yes, please indicate which complications occurred.
1. Yes, 2. No, 3. Accident (by oneself) withdrawal, 4. Pneumonia, 5. Vomiting, 6. Diarrhea, 7. Constipation,
8. Dermatitis by a leak of nutrient preparation, 9. A bad granulation tissue, 10. Other

Q63 How long did patients survive after PEG placement?
1. Less than 1 month, 2. Less than 6 months, 3. More than 7 months

Q64 After surgery, how many patients did your discharge from your hospital? Where were patients discharged?
1. Home, 2. Hale and hearty institution, 3. A medical treatment type sick bed institution, 4. Another hospital

Q65 In your institute, are costs for gastric catheter exchange covered under special insurance medical care material costs?
1. Yes, 2. No

Q66 In medical facilities using diagnosis related grouping and institutions using insurance for the elderly, the costs associated with gastric catheter exchange cannot be separately claimed under insurance as a special healthcare material cost. Do you think that it should be paid separately as a special healthcare material cost?

Q67 Do you file an insurance claim when you use enteral nutrition via PEG?
1. Yes, 2. No, 3. Yes, but we are limited in the maximum amount of the claim.

Q68 Excluding 'Elental', 'Elental P', 'Enterude' 'Twinline' and other medical nutrients of half-digested state, do you think set dietary food for enteral nutrition should be a fee-for-service?
1. Yes, 2. No

Q69 Do you have any specific opinions about health insurance for enteral nutrition? If yes, please indicate.

F1 How old is the person filling out this questionnaire?
1. 20's, 2. 30's, 3. 40's, 4. 50's, 5. 60's, 6. More than 70

F2 At the hospital you belong to, how many doctors perform PEG including you?

F3 At the hospital you belong to, how often is PEG performed annually?

F4 Which clinical department performs PEG in your hospital? (Select as many responses as apply)
1. Digestive organ surgery, 2. Digestive organ internal medicine, 3. Neurosurgery, 4. Nervous system internal medicine,
5. Respiratory division, 6. Otolaryngology, 7. Endoscopic division, 8. Rehabilitation department, 9. Other

F5 Which clinical department manages PEG in your hospital? (Select as many responses as apply)
1. Digestive organ surgery, 2. Digestive organ internal medicine, 3. Neurosurgery, 4. Nervous system internal medicine,
5. Respiratory division, 6. Otolaryngology, 7. Endoscopic division, 8. Rehabilitation department, 9. Other

F6 At your hospital, do you try rehabilitation after PEG and do you keep an early discharge of the patient in mind?

F7 At your hospital, do you have learning group such as "the gastrostomy committee?" What types of professionals participate as members? (Select as many responses as apply)
1. Doctors, 2. Nurses, 3. Dieticians, 4. Pharmacists, 5. Physical therapists, 6. Language hearing persons,
7. Clinical psychologists, 8. Health visitors, 9. Others, 10. There is no committee

F8 At your hospital, do you unify the manuals according to a type of the catheter used and the type of problems that can occur?
1. Yes, 2. No, but we will try to unify in the future, 3. No plan to unify for now

F9 Do you think that PEG is the best way to provide nutritional support?
1. Yes, it is the best way, 2. No, but it is a good way, 3. No, I do not think it is the best way to provide nutritional support

F10 PEG enables patients to be themselves, that is experience a 'recovery of everydayness', and allows care to be provided at home. Do you agree with this opinion?
1. Yes, very much, 2. Yes, somewhat, 3. No

F11 Do you know an HEQ studying group?
1. Yes, 2. No
We are involved in HEQ studying group already.
1. Yes, 2. No

F12 Please describe your hospital?
1. General hospital, 2. Special functioning hospital, 3. Community hospital, 4. Clinic with beds, 5. Clinic without beds

F13 How many beds do you have?
1. No beds, 2. Less than 20 beds, 3. 20–99 beds, 4. 100–199 beds, 5. More than 200 beds

F14 Where is your hospital located?
1. Hokkaido, 2. Tohoku, 3. Kanto/Keihin, 4. Shizuoka/Koshinetsu, 5. Hokuriku, 6. Tokai, 7. Kinki/Hanshin,
8. Chuugoku, 9. Shikoku, 10. Kyushu/Okinawa

How Elderly People Die of Nonmalignant Pulmonary Disease at Home

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Abstract

Background Elderly patients with nonmalignant pulmonary disease experience different symptoms and care from those of elderly patients with lung cancer in the last days of life; nevertheless, the literature on this issue is remarkably sparse. We studied the characteristics of the symptoms and care of elderly patients with nonmalignant pulmonary disease dying at home.

Methods The present analysis included 28 decedents who died of lung cancer and 29 who died of nonmalignant pulmonary disease selected from a database of 240 elderly Japanese subjects aged 65 or older dying at home. We assessed their symptom experience and end-of-life care receipt during the last two days of their lives and evaluated the differences between decedents dying of lung cancer and those dying of nonmalignant pulmonary disease.

Results Decedents from the non-malignancy group were more likely to experience cough or sputum and less likely to show controlled or uncontrolled pain, or coma. This group was also more likely to receive a lower volume of intravenous drip injection compared to the malignancy group in the 24–48 hours preceding death (800 ml vs 475 ml, respectively); they were also more likely to be given antibiotics and less likely to receive opioids.

Conclusions Adequate control of cough and sputum is important for elderly patients dying at home of nonmalignant pulmonary disease. Further studies on pain control and dehydration are needed to develop appropriate responses to the end-of-life needs of this group of patients.

Key words Opioids, Lung cancer, Aspiration pneumonia, Infusion, Sedation

Introduction

Due to the aging of the population, the preferences of elderly patients, and rising health care costs, a gradual shift from hospital to home is expected in the place where elderly people spend their last years.[1–4] Because this shift is expected to occur in the near future, end-of-life care for the elderly at home has become a major national concern in Japan.[5]

The focus of end-of-life care is quality of life,[6,7] which is maintained by controlling pain and other symptoms. Because it seems reasonable to assume that end-of-life care options at home are different from those offered at hospitals,[8,9] we should use information on how elderly patients die at home to assist general practitioners (GPs) in designing quality end-of-life care planning.

Furthermore, the elderly are more vulnerable to chronic medical problems such as dementia and stroke and are less able to perform activities of daily living (ADLs) than younger patients. Therefore, the aged often die of nonspecific illnesses that arise as a result of old age.[5,10] Pulmonary disease such as aspiration pneumonia is a

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common cause of death among elderly patients dying of old age.[10] Because we suppose that the symptoms experienced by elderly patients with advanced cancer differ from those of non-cancer patients,[10] we assume that the symptoms and care of elderly patients with a nonmalignant pulmonary disease differ from those of elderly patients with lung cancer in the last days of life. Nevertheless, the literature on this issue is remarkably sparse.

We assessed the frequency of symptoms and end-of-life care during the last two days of the lives of elderly patients dying at home of lung cancer or nonmalignant pulmonary disease and clarified the characteristics of elderly patients dying of nonmalignant pulmonary disease.

Methods

Study population

The Dying Elderly At Home (DEATH) Project is a prospective study of 240 elderly patients with end-stage illnesses dying at home conducted in collaboration with the Japanese Society of Hospice and Home Care, a non-profit organization consisting of GPs and other medical and social professionals interested in hospice and home-care. To recruit physicians for the study, we sent a prospectus on our research to clinical physicians who were principle members of society and who were experienced in providing end-of-life home care. Sixteen clinic physicians agreed to participate, representing 16 clinics in Western Japan. The subjects of the study were 240 consecutive decedents aged 65 or older who had used one of the study clinics while diagnosed with any illness, including advanced cancer, and who had died at home between October 2002 and September 2004. Decedents were excluded if they were transferred to a hospital at death. The following information was collected: sociodemographics, activities of daily living (ADLs) (classified according to the ranking for the disabled elderly described by the Japanese Ministry of Welfare[11]: Rank J independent in ADLs Rank A housebound Rank B chair-bound and Rank C bedridden), cognitive impairment, observed symptoms and end-of-life care provided during the last 48 hours of life. With the approval of the Japanese Society of Hospice and Home Care, we used a questionnaire that included a list of common symptoms and treatments at end-of-life:

Symptoms: dyspnea, uncontrolled pain, controlled pain, coma, acute confusion, anxiety, dizziness, nausea and vomiting, anorexia, diarrhea, constipation, fever, urinary and/or fecal incontinence, hematemesis, hemoptysis, bottom blood, other types of hemorrhage, cough, sputum, others.
End-of-life care: heart massage, intubation, mechanical ventilation, oxygen inhalation, airway placement, sputum suction, hyperalimentation, intravenous drip injection (except hyperalimentation), antibiotics, vasopressor, blood transfusion, opioids, urinary catheter placement, mental support, religious healing, others.

Data collection

Immediately after the death of each study patient, the patient's GP was asked to fill out a questionnaire based on the patient's medical charts and his or her recollection of the clinical course followed. Family members or visiting nurses who witnessed the last 48 hours of the patient's life were asked to provide additional information. The GPs and other information providers were blinded to the study hypothesis and to anticipated study results. For ethical reasons, all data on eligible participants obtained from the Japanese Society of Hospice and Home Care remained anonymous. The present research protocol was reviewed and approved by the Nagoya University Research Ethics Board.

Statistical analysis

The survey data was divided into two groups for analysis in order to confirm differences in the characteristics and clinical course between elderly decedents who died of primary or metastatic lung cancer and those who died of nonmalignant pulmonary disease. The cause of death was determined based on the report of the attending GP. If the decedents had lung or other cancer but died of nonmalignant pulmonary disease, we included them in the nonmalignant pulmonary disease group.

The data was analyzed using Statview-J5.0. Group differences were compared using the unpaired-*t* test and the chi-square test. *P* values of <0.05 were considered to be significant.

Results

Of the 240 decedents enrolled in the DEATH project, 28 (11.7%) who died of primary or meta-

Table 1 Characteristics of decedents with malignant and nonmalignant pulmonary disease

Variables		malignancy (n=28) n/average	%/SD	nonmalignancy (n=29) n/average	%/SD	*P*
Gender	Female	14	50.00	15	51.72	0.90
Age		75.21	1.42	84.72	1.86	<0.01
ADL	J=independent	1	3.57	1	3.45	0.15
	A=house-bound	5	17.86	2	6.90	
	B=chair-bound	7	25.00	3	10.34	
	C=bed-bound	12	42.86	22	75.86	
	unknown	3	10.71	1	3.45	
Cognitive impairment	Present	6	21.43	25	86.21	<0.01
Complication	Liver	2	7.14	0	0.00	—
	Cardiovascular	2	7.14	6	20.69	
	Cerebrovascular	1	3.57	5	17.24	
	Pulmonary	6	21.43	—	—	
	Gastrointestinal	0	0.00	0	0.00	
	Cancer	—	—	10*	34.48	
	Kidney	0	0.00	2	6.90	
	Others	3	10.71	12	41.38	
	Unknown	0	0.00	0	0.00	

*: 4 lung cancer included
ADL: activity of daily living

static lung cancer (malignancy group) and 29 (12.1%) who died of nonmalignant pulmonary disease (non-malignancy group) aged 65 and older were included in the present analysis. The distribution of the decedents' characteristics is shown in Table 1. Significantly more decedents from the non-malignancy group were older and showed lower cognitive function. One third of the group had cancer (lung cancer: 4/10) but died of nonmalignant pulmonary disease.

Table 2 shows the symptom experience of decedents of both groups during the last two days of their lives. Decedents from the non-malignancy group were more likely to experience cough or sputum and less likely to show controlled or uncontrolled pain, or coma. There were no significant differences in dyspnea between the two groups.

Table 3 shows the end-of-life care receipt of decedents of both groups during the last two days of their lives. Decedents from the non-malignancy group were more likely to receive antibiotics and a higher volume of intravenous drip injection as compared to the malignancy group during the last 24–48 hours before death (800 ml vs 475 ml, respectively). They were also less likely to receive opioids.

Discussion

According to the vital statistics surveyed by the Japanese Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai03/index.html), of the 1,015,034 individuals who died in Japan in 2003, 94,900 (9.3%) died of pneumonia and 56,701 (5.6%) died of lung cancer. Additionally, these statistics show that the percentage of pneumonia increased with advancing age, and that the percentage of all cancer decreased with advancing age. Thus, our study population included more decedents with lung cancer than the general population; our results are therefore not necessarily representative of all individuals aged 65 and older who died in Japan during the study period.

Little is known regarding the patterns of symptom experience and care receipt among elderly patients dying at home of nonmalignant pulmonary disease. The present study provides new insights into this issue. We found a high rate

Table 2 Symptom experience of decedents with malignant and nonmalignant pulmonary disease in last two days of life

Symptom	malignancy (n=28)		nonmalignancy (n=29)		*P*
	n	%	n	%	
Dyspnea	25	89.29	22	75.86	0.18
Pain (uncontrolled)	7	25.00	0	0.00	<0.01
Pain (controlled)	15	53.57	6	20.69	0.01
Coma	15	53.57	4	13.79	<0.01
Acute confusion	3	10.71	3	10.34	0.96
Anxiety	6	21.43	4	13.79	0.45
Dizziness	1	3.57	1	3.45	0.98
Nausea and Vomiting	3	10.71	1	3.45	0.28
Anorexia	16	57.14	16	55.17	0.88
Diarrhea	1	3.57	1	3.45	0.98
Constipation	1	3.57	3	10.34	0.32
Fever	11	39.29	17	58.62	0.14
Incontinence	2	7.14	4	13.79	0.41
Hematemesis	0	0.00	0	0.00	—
Hemoptysis	1	3.57	1	3.45	0.98
Bottom blood	0	0.00	2	6.90	0.16
Other hemorrhage	1	3.57	1	3.45	0.98
Cough	7	25.00	20	68.97	<0.01
Sputum	15	53.57	23	79.31	0.01
Other symptom	6	21.43	5	17.24	0.69

Table 3 Care receipt of decedents with malignant and nonmalignant pulmonary disease in last two days of life

Care	malignancy (n=28)		nonmalignancy (n=29)		*P*
	n/average	%/SD	n/average	%/SD	
Heart massage	0	0.00	3	10.34	0.08
Intubation	0	0.00	0	0.00	—
Mechanical ventilation	0	0.00	0	0.00	—
Oxygen inhalation	19	67.86	15	51.72	0.21
Airway placement	3	10.71	0	0.00	0.07
Sputum suction	12	42.86	18	62.07	0.15
Hyperalimentation	5	17.86	1	3.45	0.08
Antibiotics	5	17.86	15	51.72	<0.01
Vasopressor	0	0.00	0	0.00	—
Blood transfusion	0	0.00	0	0.00	—
Intravenous drip injection volume (average±SD)	9	32.14	10	34.48	0.85
24–48 hours before death	475.00	61.24	800.00	81.65	<0.01
0–24 hours before death	418.75	105.71	750.00	94.49	0.08
Opioids	17	60.71	4	13.79	<0.01
Urinary catheter placement	8	28.57	5	17.24	0.31
Mental support	0	0.00	0	0.00	—
Religious healing	0	0.00	0	0.00	—
Others	1	3.57	1	3.45	0.98

of prevalence of cough or sputum among elderly patients dying at home of nonmalignant pulmonary disease but a low rate of prevalence of pain or coma suggesting that patients with nonmalignant pulmonary disease need different types of treatment and interventions from lung cancer patients. For example, in the present study, the use of antibiotics was more prevalent in the non-malignancy group than in the malignancy group. One good explanation for this is that GPs use antibiotics to treat cough and sputum caused by respiratory infection.[12] These common end-of-life symptoms often distress patients physically and psychologically,[12] and therefore require appropriate intervention. Our results suggest that these symptoms are being treated appropriately.

However, our results also indicate that sputum suction was not provided frequently enough in the non-malignancy group, and may have been insufficient. In addition, our database did not always capture the full extent of the treatment and intervention for sputum and cough, especially the use of anticholinergic measures to reduce saliva, bronchodilators or corticosteroids.[12] Therefore, it is not clear whether the intervention and treatment for sputum and cough among decedents dying of nonmalignant pulmonary disease were appropriate in these cases. Further research is needed to evaluate differences in the prevalence of sputum and cough as well as in the referral patterns for symptom intervention between the malignancy and non-malignancy groups.

Coma was not prevalent among the non-malignancy group. Although coma is widely recognized to be a predictor of early mortality,[13] this may not apply to elderly patients dying of non-malignant pulmonary disease. Terminal sedation is important if distress symptoms are uncontrollable.[14,15] The present results stress the need for further discussion on how elderly patients dying of nonmalignant pulmonary disease should be sedated, as compared to elderly lung cancer patients.

Although the use of opioids was less common in the nonmalignant disease group, our results suggest that pain control was not a major problem for patients dying of nonmalignant disease at home, as compared to lung cancer decedents. One possible explanation for this finding is that decedents from the non-malignancy group were both more cognitively impaired and older than those of the malignancy group, because cognitively impaired and older patients tend to be more tolerant of pain.[2,16] It is also possible that the patients in the non-malignancy group may have failed to inform nurses and physicians about their pain since age and cognitive impairment are factors that cause serious communication difficulties.[2,16,17] Thus, we should interpret these results with caution.

As in a previous study in Japan,[18] the volume of drip infusion given to the malignancy group was approximately 500 ml/day, which was significantly less than that given to the non-malignancy group. Andrews et al[19] and Morita et al[20] suggest that dehydration in advanced cancer patients reduces sputum production and improves quality of life. The GPs may have deliberately dehydrated decedents from the lung cancer group based on this opinion resulting in reduced sputum among cancer decedents. There is currently little information available on appropriate strategies for giving drip infusions to non-cancer elderly patients in the last days of their lives. Additional studies are needed to examine the effect of dehydration on end-of-life symptoms in elderly patients dying of nonmalignant disease.

There are several important limitations to this study. First, we relied in part on family reports of patient symptoms because of the community setting of the study. This may have biased the assessors' evaluations and the results must therefore be interpreted with caution. Second, because of the large quantity of settings, we enlisted many different clinics to perform the evaluations. This may limit the validity of the results because the diagnosis procedures of cause of death may vary depending on the GPs in charge of data collection. Finally, the small number of patients and limited number of assisting clinics also limits generalization. The results of this secondary analytic study should be confirmed by further research focusing on the symptoms and end-of-life care of elderly patients dying at home of nonmalignant disease.

Conclusions

The purpose of this secondary analytic study was to evaluate differences in the symptoms and end-of-life care experienced in the last two days of life by elderly patients dying at home of lung cancer or nonmalignant pulmonary disease. We found a high rate of prevalence of cough

or sputum and a low rate of prevalence of pain or coma among decedents with nonmalignant pulmonary disease. These subjects were more likely to receive a lesser volume of intravenous drip injection during the last 24–48 hours before death. They were also more likely to be given antibiotics and less likely to receive opioids. Controlling cough and sputum is important for elderly patients dying at home of nonmalignant pulmonary disease. Further discussion is needed on pain control and dehydration during end-of-life care for this group of patients.

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Review Article

The History and the Present of Minamata Disease
—Entering the second half a century—

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Abstract

Minamata disease is a methylmercury poisoning with neurological symptoms and caused by the daily consumption of large quantities of fish and shellfish that were heavily contaminated with the toxic chemical generated in chemical factories and then discharged into the sea. The first epidemic occurred in the southern costal area of the Yatsushiro Sea including Minamata mainly through the 1950s to the 1960s and a second in the basin of the Agano River, in the 1960s. Minamata disease is one of the most significant negative consequences associated with environmental pollution caused by industrial activity in the world. These epidemics appeared during an era in which productivity took the highest priority and little consideration was given to the environment. Minamata disease not only took many lives among residents but also caused conflicts in the local community and has left a large variety of social and political issues. There are many lessons left to learn from the experience, and persisting issues are far from abating even half a century after the first identification of the disease.

Key words Methylmercury poisoning, Environmental pollution, Causative agent, Compensation of victims, Public health policy

Occurrence of Minamata Disease

Minamata is a small town facing the Yatsushiro Sea, also called Shiranui Sea, in Kumamoto Prefecture on Kyushu Island in southern Japan (Fig. 1) and abundant in fishing resources. On a spring day in 1956, a girl of five years old in the town was found to have unusual neurological symptoms. She had convulsions and difficulties in walking and speaking. She was the first well-documented case of Minamata disease, and was officially reported with other three cases including her sister on May 1, 1956.[1]

Minamata disease is a methylmercury poisoning associated with the daily consumption of large quantities of fish and shellfish heavily contaminated with the toxic chemical. The disease shows a variety of clinical symptoms depending on the exposure level to the chemical.[2] Severe cases are characterized by Hunter-Russell syndrome that includes sensory disturbance with predominance in distal portions of the extremities, cerebellar ataxia, and bilateral concentric constriction of the visual field.[3] Among other neurological signs and symptoms are dysarthria, hearing impairment, disturbance of ocular movement, equilibrium disturbance, tremors, etc. Relatively mild cases may be associated also with some subjective complaints including paresthesia, arthralgia and myalgia of the extremities, disability using the fingers, easy stumbling and unsteadiness, ageusia, anosmia, cramp, headaches, failure of memory, insomnia, etc.

Investigation of Causative Agent and Spread of the Pollution

The company responsible for the Minamata epidemic was the chemical company Chisso. Chisso

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Fig. 1 A view of central Minamata City, the Yatsushiro Sea and flow of the Minamata River on the right side

was a predominant company with advanced technologies in Japan at the time. In the Minamata disease episode, methylmercury was generated as a byproduct in reaction chambers for manufacturing acetaldehyde that was synthesized by a hydrolysis of acetylene using mercury as a catalyst. Methylmercury, after discharging into the sea, accumulated in fish and shellfish by the absorption through the gills or digestive tracts.

Following the official identification of the first patient in 1956, research teams were organized in Kumamoto University School of Medicine and later in the Ministry of Health and Welfare (MHW). The University research group identified the causative agent within the first three years. However, the epidemiological findings were not effectively exploited to prevent the spread of the disease.

Early epidemiological studies in 1956 found 55 cases of the disease, which included 17 deaths. These studies indicated that the disease was closely associated with the consumption of fish and shellfish and suggested that it might be a kind of heavy metal poisoning. The factory waste was suspected as the source of the causative agent but it seemed difficult to prove it. Since the ingestion of marine products caught in Minamata Bay apparently caused the disease, the Kumamoto Prefecture government recommended not eating fish and shellfish of the bay in 1957, but did not actually prohibit the fishing or eating of them.

As new patients continued to be found during the summer of 1958, the Minamata fishermen's cooperative claimed compensation for damages of fishing operation in the hazardous sea area and demanded immediate elucidation of the cause of the disease. In this period Chisso intended to increase the production of acetaldehyde, for which there was much demand as a raw material of octanol, a chemical used in polyvinyl chloride manufacturing. Engineers of the company assumed that if there were any toxicity contained in the waste, it could be eliminated by dilution with a large excess amount of seawater. Chisso changed the acetaldehyde drainage channel from the waste outfall of Minamata Bay, where water tends to stay, to the mouth of Minamata River in September 1958. However, the results differed from their expectations and strengthened suspicions about the association between the factory waste and the cause of the disease. In March of the following year, patients began to appear around the Minamata River mouth area in addition to the Minamata Bay and neighboring areas. The areas in which patients appeared expanded further around every costal region of the southern Yatsushiro Sea.

The research group of Kumamoto University presented, in July 1959, the organic mercury hypothesis for the etiology of Minamata disease based on pathological and clinical findings and on the fact that mercury was detected at extremely high concentrations in the sludge of Minamata Bay with a maximum of 2,000 ppm at the waste outfall. Chisso officially argued that 1) the factory had been using inorganic, but not organic, mercury as a catalyst since the 1930s without appearance of the disease, 2) Minamata disease had never been reported elsewhere in neighboring chemical plants using mercury, a common chemical, 3) although alkylmercury compounds are soluble in organic solvents, animal experiments using cats indicated that toxic agent could not be extracted from poisonous fish or shellfish with the solvents and were found to remain in insoluble fraction, and 4) the research group was unreliable, because it had been presenting other hypotheses of manganese, selenium, and thallium to that point without any success. However, the company had not mentioned at all several important facts, such as 1) the possible formation of methylmercury during the course of the chemical reaction in the synthesizing chamber containing inorganic mercury had been postulated, 2) the production of acetaldehyde had increased substantially in

the Minamata factory during the 1950s, 3) an oxidizer of the synthesizing process, manganese dioxide, was replaced by ferric sulfide in 1951, and 4) neurological signs resembling Minamata disease had been induced in the cats at the Chisso laboratory after the ingestion of not only fish and shellfish caught in the Minamata Bay but a diet mixed with the waste liquid obtained from the acetaldehyde process of the factory. The oxidizer change is now considered to affect the yield of methylmercury in the reaction chamber. Concerning the paradoxical findings on the extraction of methylmercury from biological samples, it has since been found that methylmercury covalently binds to cysteine residue of polypeptides in organisms (as mentioned below) and it cannot be extracted by organic solvents without the hydrolysis of protein.

Becoming a Social Issue

After the announcement of the methylmercury hypothesis by the research group, Minamata disease became a social problem. Fishermen's associations pushed Chisso to compensate the fishing industry, to establish a waste liquid processing facility, and to cease waste liquid drainage. The Ministry of International Trade and Industry (MITI) admonished Chisso in October 1959 to restore the drainage channel to the waste outfall of Minamata Bay and to complete the construction of a waste processing facility by the end of the year. In November 1959, more than two thousands members of fishing cooperatives gathered in Minamata from the coastal area of the Yatsushiro Sea to appeal to the Diet Investigation Team that visited Minamata. A thousand of the members then invaded the factory and at least a hundred were injured.

In December 1959, Chisso signed an agreement with fishermen's associations on fishery compensation and held a ceremony cerebrating the completion of the waste liquid processing facility "*Cyclator*". Kiichi Yoshioka, the President of Chisso, reported in the ceremony that the completion of the "*Cyclator*" had perfected the company's waste liquid management. He showed drinking a glass of the so-called "treated" water as the waste passed through the facility in front of the assembled guests including Prefecture's Governor. It was revealed many years later, however, that the main function of "*Cyclator*" was to precipitate insoluble suspended materials in water and dissolved chemicals in the waste could not be removed by the facility.

Chisso also made an agreement in December 1959 with the patients' association consisting of 78 patients and some of their families to pay an annuity of 100,000 yen as consolation money to each of adult patients. The contract, however, specified that the payments would cease if Chisso was found not to be involved in the cause of the disease, and that patients would make no further demand for compensation even if the cause of the disease was proven to be the Chisso factory waste. Chisso emphasized that the payments were made as a token of the company's sympathy for the patients, not as compensation for any damage.

The sub-committee of the Food and Sanitation Investigation Committee of MHW, including Kumamoto University research group, had carried out an investigation to elucidate the cause of Minamata disease. In November 1959, the Committee presented its official conclusion, based on the report of the sub-committee, that Minamata disease was a kind of organic mercury poisoning induced by the intake of polluted fish and shellfish caught in Minamata Bay. The Chairperson of the Committee said "although the factory waste was suspected as the cause, the further investigation of the Committee is impracticable and the matter should be entrusted to the ministries concerned". At the Cabinet meeting of November 13 in which the minister of MHW presented the report of the Committee, Hayato Ikeda, the minister of MITI (who promoted the rapid economic growth policy from 1960 to 1964 as prime minister) argued that it would be hasty to conclude that organic mercury had been discharged from the factory.

During the Silence

It was apparent that the organic mercury hypothesis had a significant influence not only on the chemical industries but also on government policy for industrial promotion. Further investigation on the cause was left to the new council established in February 1960 and comprised of the Economic Planning Agency, MITI, MHW, and the Fisheries Agency. The Japan Chemical Industry Association, a business community, also organized the so-called "Tamiya Committee"

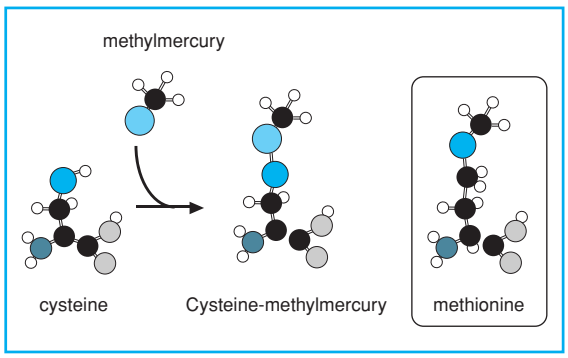

Fig. 2 Formation of cysteine-methlymercury, an analogue of methionine (after A Yasutake)

after the name of Chairperson Dr. Takeo Tamiya, the President of the Japanese Association of Medical Sciences. These committees, however, had drawn no conclusion on the cause of the disease. They gave the impression that methylmercury was only one among several different hypotheses including the degenerated amine hypothesis and that the cause of the disease had yet to be elucidated.

By the beginning of 1960s, it seemed as if the Minamata disease problem had terminated without having clarified the cause of the epidemic, after the contracts on the consolation money and the fishery compensations had been agreed, after the waste processing facility had been completed, and after the official comments of the government committee were issued. Meanwhile, Chisso increased the production of acetaldehyde in 1960 and 1961, and methylmercury pollution of the sea continued, resulting in the increase of potential patients, who were also discriminated and oppressed in the local community.

Since the mid 1950s the incidence of cerebral palsy had been extremely high among neonates in the area Minamata disease occurred. Incidences of abortion and stillbirth were also high, and the birth sex ratio indicated a significant decline of male birth during the 1950s in the district. Two girl patients who died in 1961 and 1962 were found to be fetal cases of Minamata disease after autopsy,[4] and 15 patients of cerebral palsy were certified as the cases in 1962. The occurrence of serious congenital effects by the exposure to toxic chemical in utero was unexpected, because the placental barrier had been considered to be effective in excluding most toxic chemicals from entering the fetus. It is now known that methylmercury covalently binds to cysteine, as mentioned above, to form cysteine-methylmercury, a structural analogue of an essential amino acid methionine (Fig. 2), which can effectively pass through not only the placenta but the blood-brain barrier via an amino acid transporter.[5]

A Chisso engineer successively isolated methylmercury in the waste from the acetaldehyde synthesizing process of the factory in 1961. However the company did not release the findings. In the following year, the isolation of methylmercury was published by members of Kumamoto University Research group, independently from the Chisso engineer's findings, from not only shellfish in the Minamata Bay but also the sediment of the bay. It was 1967 that the by-production of methylmercury was demonstrated in the synthesizing process.

Second Minamata Disease

In the history of public health, diseases can sometimes be eradicated before their causes are properly understood.[6] However, this was not the case with Minamata disease. The interruption of the exposure to causative agent is effective to prevent disease. From an epidemiological standpoint, it is not a necessary requirement to demonstrate strictly the causal relationship between specific agent and onset of the disease before removing the possibility of exposure. It should be argued that the delay in taking precautions to eliminate the suspected causative agent was a failure in political decision making.[7] While the causative agent of Minamata disease had not been officially accepted in spite of the research achievements and no comprehensive measure was taken to prevent the pollution from enlarging, another tragedy happened when patients of methylmercury poisoning were found along the basin of the Agano River in Niigata Prefecture in January 1965. It was the second Minamata disease epidemic. The experience in Minamata was enough for the government to take prompt measures including a medical examination involving a hair mercury survey of the inhabitants of the lower basin of the Agano River. Contraception was recommended for women who had hair mercury levels of 50 ppm

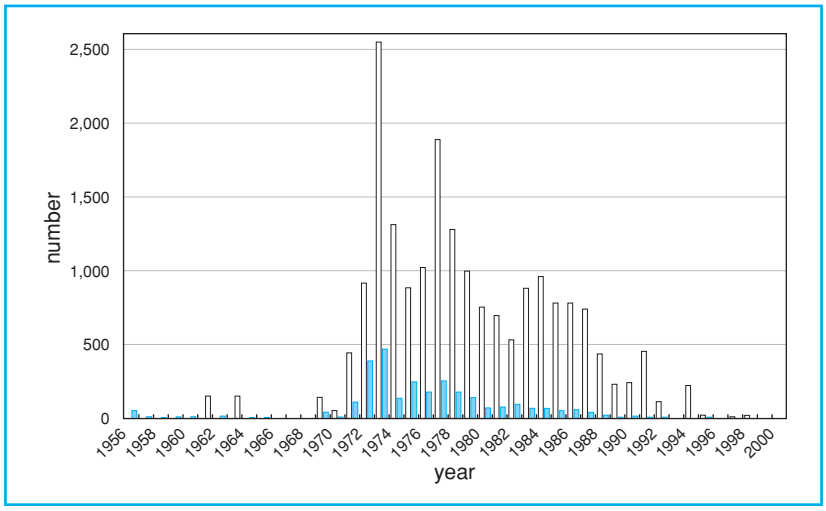

Fig. 3 Number of application (white bar) for the official certification and of certified patient (blue bar) of Minamata disease (up to 2000)

or higher to prevent fetal cases. Showa Denko's Kanose factory located on the upper Agano River, which had been synthesizing acetaldehyde until January 1965, was suspected as the most plausible source of methylmercury in the basin.[8]

By the mid 1960s in Japan, air and water pollution, known as *kogai* (public hazard), had become a serious problem as the negative consequences of the rapid growth of the heavy and chemical industries.[9] The Basic Law for Environmental Pollution Control was established in 1967. The central government had recognized that identifying a cause, instead of leaving it ambiguous, might help to settle the problems. The government had to determine whether Minamata disease was associated with environmental pollution that was under the jurisdiction of the law. In September 1968, the government presented a collective view on the two epidemics of Minamata disease and stated that the causative agent in Kumamoto was methylmercury discharged from Chisso Minamata factory and that the waste of Showa Denko's Kanose factory had substantially caused the methylmercury pollution in Niigata. Twelve years had already passed since the first recognition of the patient in 1956.

Compensation and Relief

Officially certified patients are eligible to receive compensation from the companies responsible. The total number of certified patients was 111 in Yatsushiro Sea area and 32 in Niigata by 1968, year of the government's announcement. After four years struggles in lawsuits, the Niigata and Kumamoto District Courts in 1971 and 1973 respectively, ruled that full responsibility for Minamata disease lay with the companies. The Kumamoto District Court also voided, because of a violation of public order, the consolation money agreement that specified for patients to renounce making claim for further compensation. It had become apparent that damages should not be tolerated even among a small number of residents as an acceptable cost for achievements in economic development as a whole. Company compensation was legally justified. Applications for certification of Minamata disease then increased since the 1970s (Fig. 3). It should be noted that the apparent increase in the number of patients and applications during the period does not indicate an actual increase in the onset of the disease but acceleration of making applications by pre-existing patients. The total number of certified cases was 2,955 by 2005 in the Yatsushiro Sea costal areas and the basin of the Agano River as shown in Table 1. Fig. 4 indicates the change in the number of living patients who receive compensation from Chisso, with the decrease in the number over

Table 1 Number of Minamata disease patients, recipients of official relief services and applicants for the certification as of 2005 (including deceased cases)

Total number of officially certified patients	2,955
Kumamoto Prefecture*	1,775
Kagoshima Prefecture*	490
Niigata Prefecture*	690
Recipients of the Medical Task of the Comprehensive Measure of Minamata disease (since 1992)	c.a.12,700
Patients manifesting health effects of methylmercury that were recognized by the ruling of the Supreme Court in 2004	58
Applicants for certification (before judgment)	>3,300

*: Patients of Kumamoto and Kagoshima Prefectures were residents of the costal area of the Yatsushiro Sea, and patients of Niigata Prefecture were in the basin of the Agano River.

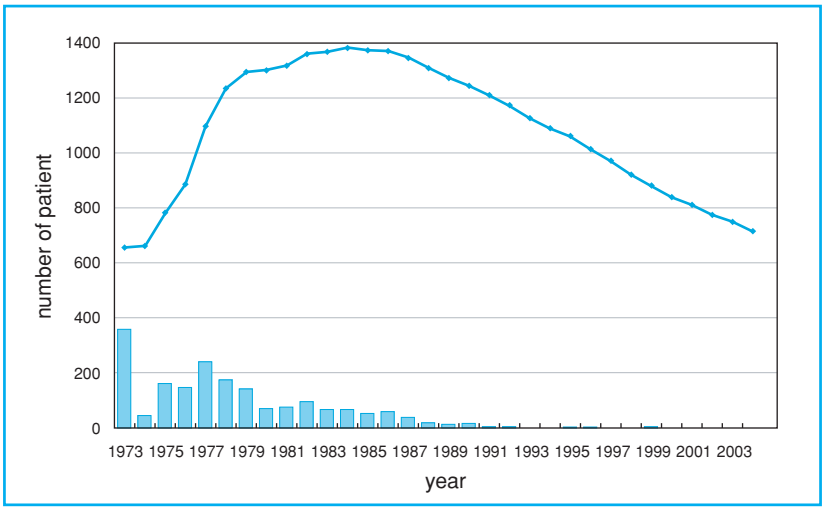

Fig. 4 Changes in the number of survived patients (solid line), who were officially certified as Minamata disease and receive compensation from Chisso
Solid bar indicates number of new certification. Data were taken by courtesy of Chisso Corp.

the decade indicating the aging of patients and about 700 still alive in 2004. The certification of Minamata disease has been conducted by the official Certification Boards on Minamata disease according to the medical criteria laid out by Ministry of the Environment. Only about 15% of applications have been certified as Minamata disease (c.a. 12% in Yatsushiro Sea costal areas, and c.a. 32% in the basin of the Agano River). Several lawsuits had been filed between 1973 and 1988 by plaintiffs including patients whose applications had been rejected, seeking to claim compensation from the companies responsible and from the governments.

There are two main difficulties concerning the evaluation of adverse health effects induced by methylmercury exposure at moderate or low doses. First, as methylmercury has a relatively short biological half life in the human body, 70–90 days on average,[10] it is difficult to assess the past exposure dose of the chemical using biological samples taken from residents. Second, most complaints of Minamata disease are subjective and may not be free from bias, especially given the possibility of linkage with compensation for the patients. Few large-scale epidemio-

logical surveys have therefore been conducted to investigate the association of methylmercury exposure and adverse health outcomes among residents in the polluted areas.

While the plaintiffs were becoming noticeably older, agreements were successively achieved for out of court settlements among almost all patient groups, companies responsible and governments in 1995. Inhabitants suffering from a part of the neurological signs specified in the criteria for Minamata disease certification, in which specific combinations of two or more symptoms are required for the certification, acquired official support including medical expenses and a lump sum payment. As many as 12,300 cases became recipients of aid in 1997 (the Medical Task of the Comprehensive Measure of Minamata disease in Table 1). In 2004, on the other hand, the Supreme Court gave a ruling on Kansai lawsuit, the only trial that had rejected the acceptance of the settlement in 1995, and identified the responsibility of governments for their failure to prevent the expanded spread of Minamata disease. More than 3,600 applications have been made for patient certification during about one year following the ruling, and some of the applicants (690 by the end of 2005) filed another case in 2005 aimed at securing compensation through the legal system.

The Present Issues

There are some discrepancies between the medical criteria for certification of Minamata disease of Ministry of the Environment and the borderline symptoms adopted by order of the Supreme Court,[11,14] and the significant controversy still exists concerning the diagnosis of Minamata disease. However, discussions are also necessary from the standpoint of how to construct the compensation system for a large variety of adverse health effects among residents including nonspecific symptoms associated with exposure to moderate or low doses of the chemical.

Memorial events are being prepared in Minamata and its neighboring areas by the governments, patient organizations, and citizens to commemorate 2006, which is fifty years since the first identification of the disease. On the other hand, there is increasing anxiety on physical conditions among aged patients particularly of fetal cases, who are mostly 40 years of age or older.[12] There is much to learn from the experience of Minamata disease, which has caused a variety of issues including social conflicts.[13] The negative consequences are far from abating even half a century after the first appearance of the problem.

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Review Article

Nonvalvular Atrial Fibrillation and Stroke

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Shinichi Takahashi*1

Abstract

Cardioembolism, responsible for approximately one-third of cerebral infarctions in Japan, causes serious cerebral infarction with poor prognosis. Nonvalvular atrial fibrillation (NVAF) is the most important cause of cardioembolism. Both the occurrence of NVAF and the frequency of its progression to cerebral infarction increase with age. Timely introduction of warfarin depending on the presence or absence of risk factors for cerebral infarction, including age, is essential for the prevention of cardioembolism. At present, monitoring based on PT-INR is indispensable for warfarin therapy. Oral direct thrombin inhibitors seem promising as a future therapy achieving a stable anticoagulation effect by the use of a fixed dose. Angiotensin II receptor blockers (ARBs) are expected to be effective in preventing new atrial fibrillation and maintaining sinus rhythm, offering a promise of clinical usefulness in reducing cerebral infarction, including the prevention of relapse.

Key words Cardioembolism, Aspirin, Warfarin, PT-INR, Ximelagatran, Angiotensin II receptor blocker (ARB)

Introduction

Japan is a country with an exceptionally long life expectancy. A leading cause of death in the Japanese population is cerebrovascular accident. The mortality rate from this condition has remained largely unchanged for several years, and it is still ranked third among the causes of death. More importantly, cerebrovascular accident is the commonest condition requiring nursing care and is the second-ranked disease in terms of health care cost. This means that the prevention of cerebrovascular accident is a key to the long and healthy life of the Japanese people. Among the types of cerebrovascular accidents, cerebral hemorrhage has been decreasing since its peak around 1960. Cerebral infarction, on the other hand, has been increasing gradually. Cardioembolism, a type of cerebral infarction resulting from atrial fibrillation and other cardiac disorders, often develops suddenly in a person who is leading an apparently healthy life, because atrial fibrillation rarely presents obvious subjective symptoms. This condition involves occlusion of the main trunk arteries of the brain, frequently resulting in massive cerebral infarction, and is apt to progress into hemorrhagic conversion. Both life prognosis and functional prognosis are poor because of these reasons.[1–3] An important fact is that appropriate prophylactic treatment may prevent this condition in a considerable percentage of potential patients. This report focuses on nonvalvular atrial fibrillation (NVAF), which is the most frequent cause of cardioembolism, and considers its relevance to the prevention of cerebral infarction.

Stroke and NVAF in the Japanese Population

According to the newest available statistical data on strokes in Japan published in the Acute-phase Stroke Patient Database (Stroke Data Bank 2005),[3] the 12,178 registered cases of cerebral infarction in Japan are comprised mostly of patient groups with the 3 major types of cerebral infarction: 32.0% with lacunar infarction, 33.1%

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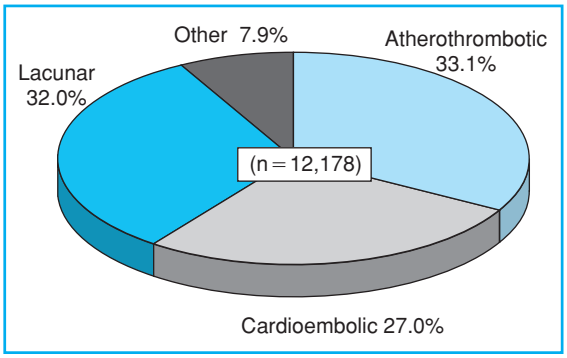

Fig. 1 Breakdown of cerebral infarction by clinical category in the Acute-phase Stroke Patient Data Base
(Drawn from Stroke Data Bank 2005[3])

Valvular heart disease:
Rheumatic valvular disease, Valve replacement, IE, Non-bacterial thromboendocarditis, Libman-Sacks endocarditis, Mitral valve prolapse, Aortic annular/mitral annular calcification, Mitral valve chord

Intracardiac thrombus:
Atrial fibrillation, SSS, Ventricular demand pacemaker, "Moyamoya" echo, AMI, Cardiomyopathy, LV aneurysm, CHF, Myxoma (tumor embolism), ASA

Paradoxical embolus:
ASD, VSD, Tetralogy of Fallot, PFO

Fig. 2 Causes of cardioembolism

with atherothrombotic infarction, and 27.0% with cardioembolic infarction, each representing approximately one-third of all patients (Fig. 1). Combined with the figures from the J-MUSIC study[4] in 2000 covering 16,922 patients in Japan, these data suggest that complete prevention of cardioembolism would result in the reduction of cerebral infarction to two-thirds of the present level.

Atrial fibrillation is the heart disorder causing cardioembolism in more than a half of cases. Diseases underlying the development of atrial fibrillation include valvular heart disease, hypertensive heart disease, cardiomyopathy, and hyperthyroidism (Fig. 2). In addition, there are cases of atrial fibrillation lacking an identifiable cause, called lone atrial fibrillation.[5] In the context of cerebral infarction, atrial fibrillation is usually categorized into valvular atrial fibrillation and the other types of atrial fibrillation, collectively NVAF.

There are two important points regarding the relation between atrial fibrillation and cerebral embolism. One is the age-related increase in the prevalence of atrial fibrillation, and the other is the age-related increase in the occurrence of cerebral infarction among the patients with atrial fibrillation.[1–3] This is a fact observed commonly in international studies. According to the statistical data from the Framingham study, the occurrence rate of NVAF is 0.5% at ages 50–59, 1.8% at ages 60–69, about 4.8% at ages 70–79, and 8.8% at ages 80–89.[6] The development of cerebral infarction from NVAF takes place at the rate of 1% at ages below 65 and 3.5% at the age of 75 or more. This rate is reported to be as high as 8.1% in patients with the risk factors discussed below.[7] Many aged persons may have NVAF without subjective symptoms, silently building up the risk for developing cerebral infarction.

While age is an important risk factor for developing cerebral infarction from NVAF, a past history of cerebrovascular accident such as cerebral infarction or transient ischemic attack (TIA) is associated with a dramatically elevated risk of recurrence. Other known risk factors include congestive heart failure, hypertension, diabetes mellitus, and coronary artery disease. Based on the weighted evaluation of these risk factors, the CHADS2 score[8] (C for congestive heart failure, H for hypertension, A for age, D for diabetes mellitus, and S for stroke and TIA) has been devised as a predictor of stroke in patients with atrial fibrillation.

Strategies for Drug Treatment of NVAF

The treatment strategy for a patient with NVAF depends on the presence or absence of each of these risk factors. Following the treatment guidelines in Western countries,[9] the Japanese Circulation Society also formulated the treatment guidelines for NVAF in 2001.[10] Firstly, these guidelines do not discriminate between persistent or permanent atrial fibrillation and paroxysmal atrial fibrillation in NVAF, because these do not differ from each other in the risk of cerebral infarction.[5,11] The annual risk of cerebral infarction in these patients on the whole is reported to be approximately 5%.[1–3] In contrast,

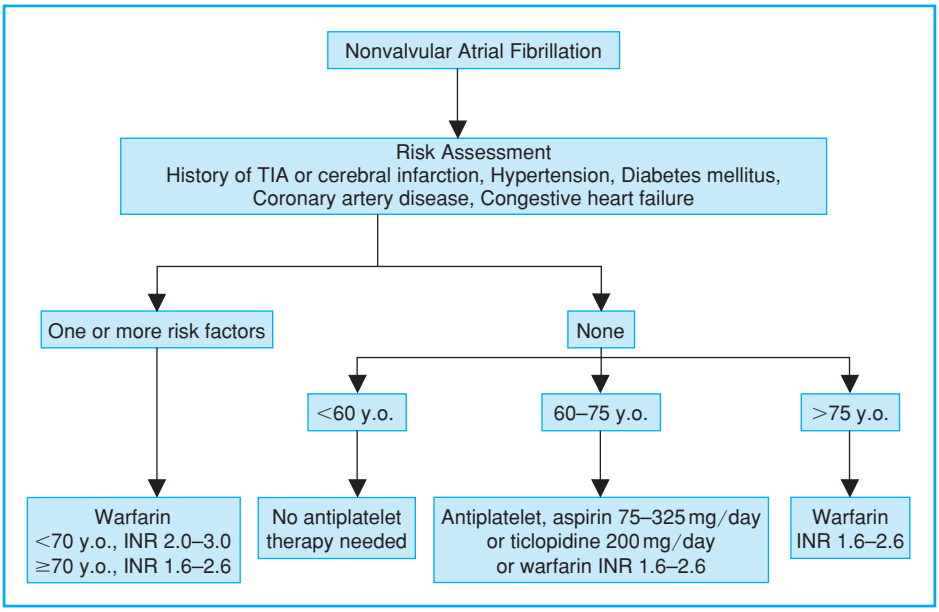

Fig. 3 Guidelines for the treatment of patients with NVAF by the Japanese Circulation Society
(Drawn from Guidelines for the Treatment of Atrial Fibrillation (Drug Therapy) in Guidelines for the Diagnosis and Treatment of Circulatory Diseases (Reports of Joint Study Team 1999–2000)[10])

a past history of cerebral infarction or TIA increases the annual risk to 12%.[12] Therefore, the past history of cerebral infarction or TIA by itself is considered a risk factor in patients with NVAF. In addition, patients with NVAF accompanied by any of the risk factors such as hypertension, diabetes mellitus, coronary artery disease, and congestive heart failure are also considered to be a high risk. Oral warfarin is indicated for these high-risk patients. The treatment strategy for patients with NVAF lacking these risk factors varies depending on age. According to the Japanese Circulation Society guidelines,[10] warfarin is indicated for patients at ages above 75, warfarin or an antiplatelet drug (aspirin or ticlopidine) for patients at ages from 60 to 75, and no treatment for patients younger than 60 years old. These treatment strategies are summarized in Fig. 3.

The results of a meta-analysis[13] of the 6 randomized clinical trials providing a basis for these guidelines indicate that aspirin reduces the risk of cardioembolism in patients with NVAF by 22% as compared with placebo, while warfarin reduces it by 62%. In a direct comparison, warfarin is 36% more effective in reducing the risk than aspirin.

In daily practice, clinicians tend to use aspirin more frequently than warfarin in aged patients, but this choice is not recommendable. Although the meta-analysis certainly showed that aspirin reduced the occurrence of cerebral infarction in patients with NVAF, it is likely that aspirin did not prevent cardioembolism but prevented other types of cerebral infarction (i.e. lacunar infarction) in patients with NVAF. In the Japan Atrial Fibrillation and Stroke Trial (JAST) study conducted by a study team of the Japanese Circulation Society, aspirin and placebo were administered to patients with NVAF and followup was continued for 770 days on average. The results indicated that aspirin did not prevent the development of cerebral, while it increased the occurrence of hemorrhagic complications.[14] At present, there is no evidence that positively supports the use of aspirin, except for the use in patients with contraindication to warfarin.

Practical Issues of Warfarin Dose Control

With respect to the practice of warfarin therapy, international guidelines specify that treatment

$$\text{PT-INR} = \left[\frac{\text{PT(sec) of the Patient}}{\text{PT(sec) of the Control}}\right]^{\text{ISI}}$$

ISI: international sensitivity index

Fig. 4 PT-INR (International Normalized Ratio)

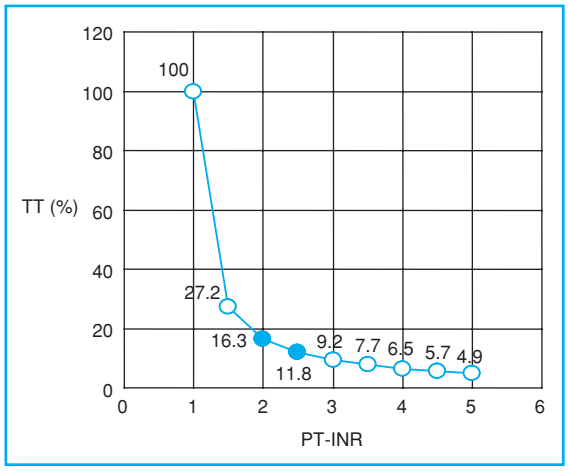

Fig. 5 Relation between PT-INR and thrombotest
(Drawn from Twelve years' experience with the St. Jude Medical Valve Prosthesis[16])

should be controlled based on the PT-INR value, which is determined as the prothrombin (PT) time of the patient divided by the PT time of the standard specimen and raised to the exponential power of the international sensitivity index (ISI) of the reagent used in the test (Fig. 4). A PT-INR value of 1.5 or less indicates that the effect of warfarin is almost absent, while a value of 2.6 or more indicates the excessive effect of warfarin. These two values are important, as the risk of cerebral infarction increases when PT-INR is lower than 1.5 and the risk of hemorrhagic complications increases when it is above 2.6. The dose of oral warfarin should be controlled between these levels.[15] Thrombotest was used widely in Japan and some facilities are still using it for the purpose of this control. Although the optimal dose range of warfarin corresponds to the 8–15% range in Thrombotest,[16] this method is not sufficiently accurate. The use of PT-INR is strongly recommended (Fig. 5).

The afore-mentioned guidelines of the Japanese Circulation Society[10] define the target range of warfarin control as PT-INR levels from 2.0 to 3.0 for ages less than 70 and from 1.6 to 2.6 for ages of 70 or more. This reflects the results of studies on the optimal dose of warfarin,[15,17] which proved that less stringent control is appropriate for patients aged 70 years or more. Oral warfarin may be indicated for patients older than 80 years and occasionally for patients older than 85 years, unless there is contraindication. In such cases, further less stringent control of PT-INR in the range from 1.8 to 1.9 may be a practical goal.

Because warfarin suppresses the production of vitamin K-dependent coagulation factor and exerts an anticoagulation effect, patients should be advised to limit the intake of food containing abundant vitamin K. Medication usually begins with the oral administration at the dose of 2–3 mg once daily, which is the normal maintenance dose. Initial loading (a high dose at the beginning) is avoided because of the risk for transient hypercoagulability called the "warfarin dilemma", which may result from the effect of warfarin suppressing the activities of protein C and protein S in addition to vitamin K-dependent coagulation factor. Warfarin interacts with various drugs, and therefore should be used with caution. While some patients with poor responsiveness to warfarin may require as much as 10 mg warfarin to achieve the therapeutic level of PT-INR, certain drug interactions may be utilized in such cases. A common method to reduce the dose of warfarin required for achieving a therapeutic effect is the combination of bucolome, an anti-hyperuricemic agent.

Appropriateness of the Combined Use of Warfarin and Aspirin

If controlled appropriately, oral warfarin can lower the occurrence of cerebral infarction by half in selected patients. However, this effect is limited to the prevention of cardioembolism, and warfarin may not be effective in preventing lacunar infarction and atherothrombotic infarction. Aspirin is the established first-choice drug for the prevention of these types of infarction, but the benefit of the combined use of warfarin and aspirin is controversial. The consensus from the mega-trials conducted so far has been that the addition of aspirin to low-dose warfarin does not improve the prevention of cerebral infarction but increases the risk of hemorrhagic complica-

tions.[18,19] However, the data from the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) in Spain, published in the Journal of the American College of Cardiology recently, showed that the combination of warfarin and triflusal, an antiplatelet agent, was better than warfarin alone in the prevention of cerebral infarction and reduced the occurrence of hemorrhagic complications.[20] This result may have an effect on the direction of future treatment. Whatever the case may be, it is essential to minimize the risk of hemorrhagic complications through maintenance of appropriate PT-INR and adequate control of blood pressure during warfarin therapy.

Tooth Extraction during Warfarin Therapy

We occasionally encounter a problematic situation where a patient on warfarin therapy requires tooth extraction and the dentist requests discontinuation of warfarin. Recent Western guidelines[21] generally recommend not discontinuing oral warfarin when the patient receives tooth extraction. A majority of the hemorrhagic complications from tooth extraction are considered to be the results of inadequate curettage of exuberant granulation or failure of the sutures after extraction. Because tooth extraction basically stimulates coagulation activity, discontinuation of warfarin may result in the elevated risk of cerebral infarction. It has been confirmed that the risk of hemorrhagic complications remains low if the condition is controlled within the range of 2.6 or less PT-INR. In view of these facts, physicians should cooperate with dentists and develop a system to ensure safe tooth extraction without discontinuing warfarin. Other surgical operations and invasive examinations would require discontinuation of warfarin. No consensus has been reached on whether or not we should switch to intravenous heparin. Decisions in this respect must be made on a case-by-case basis.

Development of Oral Direct Thrombin Inhibitors

At present, several oral anticoagulants to replace warfarin are in the process of development. A particularly promising class of these drugs includes oral antithrombins, which directly bind to thrombin and reduce its activity independently of vitamin K metabolism. A typical example is ximelagatran, which once was expected to be useful as an oral drug that, unlike warfarin, would not require frequent blood monitoring and would achieve a stable anticoagulation effect by the use of a fixed dose in all patients. In fact, the results of Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III[22] and those of SPORTIF V[23] published last year collectively demonstrated that the prophylactic effect of ximelagatran against systemic embolic events was equivalent to that of warfarin. However, because oral ximelagatran unfortunately induced liver dysfunction, the FDA in the U.S. did not approve this agent. There are no prospects for the approval in Japan, either.

Atrial Fibrillation and ARB

Finally, let us consider NVAF and cerebral infarction from a different perspective. While the prevalence of atrial fibrillation increases with age, the development of new atrial fibrillation from sinus rhythm involves various factors. Of the processes leading to fibrillation, electrical remodeling due to alteration of ion channels and anatomical remodeling such as myocardial fibrosis are recognized as particularly important. The involvement of angiotensin II type 1 receptors is well-known, and a growing body of recent evidence indicates that the occurrence of new atrial fibrillation is reduced by angiotensin II receptor blocker (ARB), which is also recognized as a hypotensor.[24] The Valsartan Heart Failure Trial (Val-HeFT) study and the Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity (CHARM) study, respectively, demonstrate that valsartan and candesartan lowered the occurrence of new atrial fibrillation, and the sub-analysis concerning atrial fibrillation in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study also derived similar results regarding the treatment with losartan. The use of these ARBs is considered to be a useful treatment strategy, as it is expected to achieve the prevention of cerebral infarction based on blood pressure management and also to inhibit the onset of NVAF leading to cardioembolism.

In summary, NVAF is extremely important as

a cause of cerebral embolism. Appropriate therapeutic agents should be selected considering stratification of various risk factors including age. When warfarin is used, dose monitoring based on PT-INR is essential.

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Short Communication

Professional Autonomy

JMAJ 49(3): 125–127, 2006

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Abstract

The term, "Professional Autonomy", has been ubiquitous since the World Medical Association Declaration of Madrid on Professional Autonomy and Self-Regulation. The word profession originally means swear to God, declare to the public, and fulfill one's duty in the occupation one chooses. Furthermore, the origin of the word "Autonomy" goes back to the philosophy of Immanuel Kant who stated that the human will, when working autonomically, transforms into conscience and good will.

Professional Autonomy means that physicians as professionals discipline themselves autonomically, and engage in medical care for their patients with the spirit of positive freedom. We now would like to reaffirm the significance of this philosophy.

Key words Professional Autonomy, Self-Regulation, Declaration of Madrid, Professional, Public mission, Moral law

Introduction

The term, "Professional Autonomy", came to be known when the WMA's Declaration of Madrid on Professional Autonomy and Self-Regulation adopted some basic principles during the 39th World Medical Assembly held in Madrid, Spain, in October 1987. Previously, more emphasis was placed on physicians' professional independence and discretion, and thus the term "professional freedom" was used in lieu of "professional autonomy". However, there was concern that the nuance of the word "freedom" might convey to society an egoistic impression, such as "refusal of interference" or "aspiration of escaping". Therefore, the term "Professional Autonomy", meaning free positive activities as physicians, is considered preferable.

Autonomy means "voluntary" or "self-disciplined". As such, the positive activities of the physician as a professional literally must be voluntary and self-disciplined.

At the time of the adoption of WMA's Declaration of Madrid, it was regrettable that Professional Autonomy was misinterpreted as professional freedom in Japan, and thus did not attract much attention. However, when we now look anew at the principle of Professional Autonomy, we realize that inherent in the principle are very profound concepts.

What is a Profession?

Profession means a professional career. The origin of the word "profession" is to profess, "to swear to the public", or "to declare to the public". In other words, "profession" means "to swear to God, declare to the public, and fulfill one's duty" in the occupation one chooses.

Through the ages, professions consisted of such careers as clergy, physicians, lawyers, and teachers. Historically speaking, it is widely believed that the first professional career was the clergy (pastors), followed by professors. They were followed in the 18th to 19th centuries by physicians and lawyers being referred to as professionals. Nowadays, these two professions

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typify the symbolic concept of modern professional careers.

The characteristics of professional careers are as follows:

1) A professional career is a profession with a public mission. It is a profession which serves society without concern for personal interest, gain, or loss.
2) A professional career requires advanced knowledge and technology beyond that of the general public. In this sense, it is the responsibility of professionals to ceaselessly study advancing medical knowledge and technologies.
   Additionally, liberal arts are essential in the education of professional careers, marking a difference from the vocational education for workers.
3) Those who have professional careers organize a group, draw up codes of behavior for the group, comply with the codes, educate the group members for mutual betterment, and operate the group voluntarily. This is to be autonomous, and this autonomy is the key to differentiate professions from non-professions. In this regard, Professional Autonomy means to dominate the decision making of activities to fulfill the responsibilities of one's profession.
4) A professional career has its own autonomous qualification system. A professional group creates standards, accredits the qualification as a professional, and gives assurance of quality to society, putting one's status as collateral. If anyone in the group is found to be underqualified as a professional, they will revoke the qualification themselves. This is also autonomy.
5) An important requirement of a professional career is to have a code of ethics. There must be self-regulation of the code of professional ethics. This is also autonomy.

What is Autonomy?

The origin of the word "Autonomy" goes back to the 18th century German philosopher Immanuel Kant. In his "Critique of Practical Reason" in 1788, Kant questioned: "What man should do?" and thought that "our inner voice is moral law and this is the voice of conscience given only to mankind".

It is said that there is no one who thought about "conscience" any deeper than Kant, and he said that human will can maintain its autonomy only when it works as "good will". Moral decision-making is human autonomy, and according to Kant, it is reason.

Kant said that good will and conscience are fundamental to mankind, and that they work autonomously and shine like a gem.

According to Kant's view of Professional Autonomy, "physicians as professionals discipline themselves on the basis of conscience, and engage in medical care to their patients with the spirit of positive freedom".

Professional Autonomy is autonomous in the sense that professions voluntarily create their own code of ethics on the basis of this active and positive freedom and comply with the code by themselves. This will describe the legitimacy of this positive freedom for professional careers as physicians' discretion.

When observing the Declaration of Madrid from this point of view, I have an acute feeling that this principle is indeed full of implications for current medical situations.

The Declaration of Madrid on Professional Autonomy and Self-Regulation

The World Medical Association adopted this declaration to recognize the importance of physicians' Professional Autonomy and professional Self-Regulation. This declaration consists of 10 articles. I will now summarize them simply as follows:

The central element of professional autonomy is the assurance that individual physicians have the freedom to exercise their professional judgment in the care and treatment of their patients.

Professional Autonomy is an essential principle of physicians' professional ethics. If this essential right is given to physicians, then physicians need to take on the responsibility of self-regulation.

The quality of care provided to patients and the competence of the physicians providing that care must always be a primary concern for physicians. Physicians should not apply unconvincing theories to patients.

Cost consciousness is an essential element of self-regulation. Cost containment activities must not be used to deny patients access to necessary medical care.

National medical associations are recom-

mended to create a system of self-regulation for physicians and actively work to maintain the system. By publicizing the system widely to the general public, people will come to have trust in medical care and to give it proper evaluation.

I would like to conclude with some background leading up to the adoption of this declaration. There have been significant advances in new technologies such as gene therapy and reproductive medicine, as well as the emergence of bioethical issues. I think these advancements are not completely unrelated to the adoption of the declaration. Furthermore, the years surrounding the adoption of the declaration was a time when we started to expect unlimited development of medical science and medical care with the identification of HIV (1983), the discovery of prion (1985), and the start of the human genome project (1988). On the other hand, the discussion of bioethics was active, with an increasing number of court cases taking up medical malpractice issues. With growing media coverage on medical errors or adverse effects from medication, public opinion critical of medical issues was becoming severe. With this background the World Medical Association outlined the principles of Professional Autonomy, and I think the significance is profound.

We, physicians whose mission is to serve the public, must pause to realize the meaning of the Professional Autonomy.

Hemosuccus Pancreaticus: Clearly identified by timely duodenoscopy, multiplanar volume reformation of CT image and celiac angiography

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Abstract

Although hemosuccus pancreaticus (HP) rarely causes gastrointestinal bleeding, it should be considered in cases of unexplained gastrointestinal bleeding. We report a case of hemosuccus pancreaticus in a 68-year-old man. The patient has a long-standing history of anemia with a causal relation to drinking alcohol. He consulted 3 medical institutions, but the source of bleeding could not be identified. The patient was admitted to our hospital. After an episode of melena, upper endoscopy was performed and fresh blood was observed to be oozing from the papilla of Vater. Computed tomography image processing using multiplanar volume reformation and angiography revealed pseudoaneurysm of the gastroduodenal artery. The pseudoaneurysm was embolized by transcatheter embolization using steel microcoils.

Key words Hemosuccus pancreaticus, Chronic pancreatitis, TAE, Pseudoaneurysm

Introduction

Endoscopy is a standard procedure in cases of gastrointestinal bleeding, and allows identification of the bleeding source in most cases. However, a definite origin of hemorrhage sometimes remains undetectable, despite repeated endoscopies. We present the case of a patient with asymptomatic chronic pancreatitis who experienced recurrent gastrointestinal bleeding caused by hemosuccus pancreaticus (HP).

Case Report

A 68-year-old man with a long-standing history of excessive alcohol consumption underwent a routine medical examination in May 2000, and asymptomatic anemia (hemoglobin (Hb), 10.5 g/dl) was identified. In May 2001, Hb was 8.3 g/dl, and he consulted a clinic due to deterioration of anemia. Upper and lower endoscopy were performed, but revealed no bleeding source. In August 2001, he consulted another clinic, and upper and lower endoscopy were again performed to no avail. On September 18, the patient noticed tarry stool and was admitted to hospital. Laboratory studies revealed iron-deficiency anemia (Hb, 5.0 g/dl), presumably caused by chronic gastrointestinal bleeding. However, upper and lower endoscopic examinations were again normal, and no definite origin of hemorrhage was detected. Blood transfusions were provided, symptoms improved, and the patient was discharged from the hospital.

He was admitted to our hospital 16 days later, due to tarry stool continuing for 3 days, weakness

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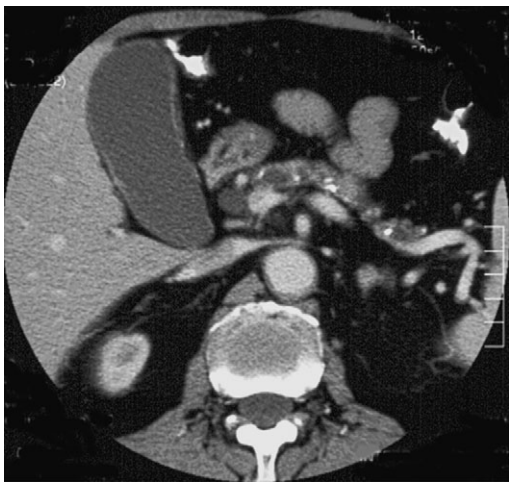

Fig. 1 Dynamic computed tomography with intravenous contrast injection showing diffuse calcifications with an irregularly dilated duct in the pancreas

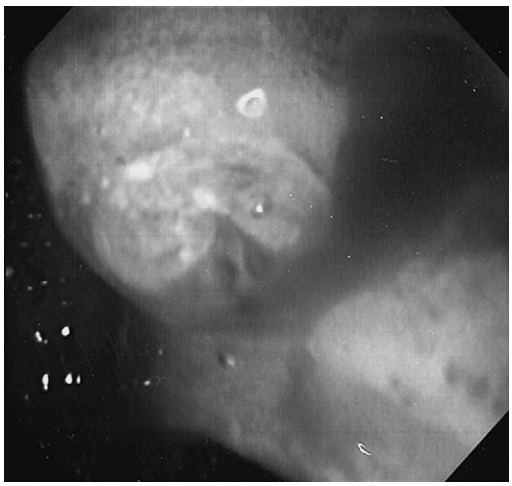

Fig. 2 Gastroduodenoscopy showing fresh blood oozing from the papilla

and dizziness. On admission, the patient appeared to be in relatively good general and nutritional condition (weight, 62 kg; height, 1.64 m). Blood pressure was stable (110/62 mmHg), but he was slightly tachycardic (heart rate, 98 beats/min). Significant findings on physical examination were pallor and melenic, guaiac-positive stools. No evidence of abdominal pain was apparent. Initial Hb was 6.6 g/dl, with a hematocrit of 20.0%. Blood urea nitrogen level was 23.0 mg/dl and total protein level was 5.5 g/dl. Serum creatinine, amylase and lipase levels were normal. Levels of tumor markers CA19-9 and CEA were also within normal ranges.

Initial endoscopy showed a small amount of fresh blood in the duodenum. However, no obvious bleeding source such as peptic ulcer, tumor or angiodysplasia was recognized. Enhanced computed tomography (CT) and abdominal ultrasonography (US) showed that the gallbladder and bile duct seemed normal, and no vessel abnormalities were apparent. Despite the absence of a history of chronic pancreatitis, CT showed diffuse calcifications with an irregularly dilated duct in the pancreas (Fig. 1). Scintigraphy with technetium-99-labeled erythrocytes did not show any origin of bleeding.

On hospital day 6, after an episode of painless melena, a second upper endoscopy was immediately performed, revealing fresh blood oozing from the papilla of Vater (Fig. 2). Hemobilia was thus suspected. Endoscopic ultrasonography (EUS) was performed, but did not demonstrate any findings of hemobilia such as blood or clotting in the gallbladder or bile duct.[1] Signs of chronic pancreatitis such as dilated pancreatic duct and pancreatic stones in the pancreatic head were demonstrated. We thus suspected that bleeding originated from the pancreatic orifice of the papilla Vater. Furthermore, CT image processing using multiplanar volume reformation (MPVR) was performed for vessels around the pancreas. MPVR of the gastroduodenal artery revealed a suspected pseudoaneurysm (Fig. 3). On the suspicion of HP with pseudoaneurysm rather than hemobilia, angiography of the celiac artery was performed. A small irregularity was seen along the gastroduodenal artery. Superselective angiography of the gastroduodenal artery was subsequently performed, revealing a small pseudoaneurysm of the artery similar to that seen on MPVR (Fig. 4).

Consideration of all these results led to a diagnosis of HP with chronic pancreatitis, due to pseudoaneurysm of the gastroduodenal artery. The pseudoaneurysm was successfully embolized using transcatheter embolization with steel microcoils. The postoperative course was uneventful. Clinical follow-up after 24 months revealed that the patient experienced no further episodes of bleeding.

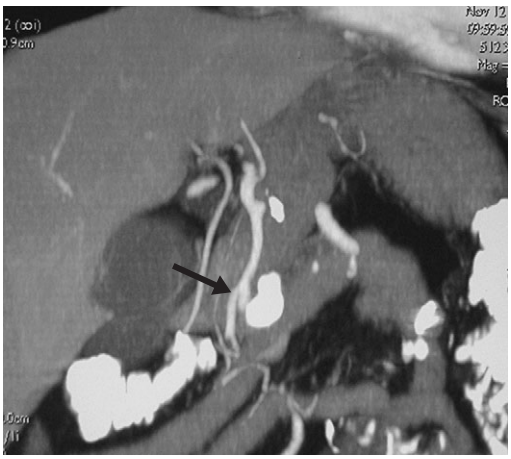

Fig. 3 Multiplanar volume reformation of CT image processing showing pseudoaneurysm of the gastroduodenal artery (arrow)

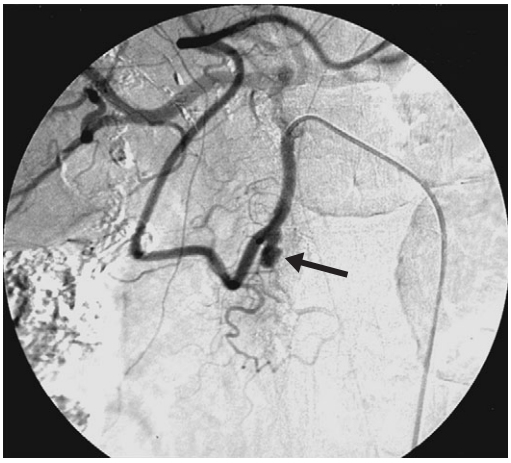

Fig. 4 Angiography of the gastroduodenal artery revealing a small pseudoaneurysm of the artery (arrow)

Discussion

Hemorrhage into the pancreatic duct causes blood flow through the duct and papilla into the duodenum, and is called "hemosuccus pancreaticus" (HP), as introduced by Sandblom in 1970.[2] In most cases, the underlying illness is chronic pancreatitis.[3] The cause of bleeding is usually rupture of an aneurysm in a visceral artery in the presence of chronic pancreatitis.[4,5] Other uncommon causes are pancreatolithiasis and pseudocysts of the pancreas.[6] HP represents a very rare cause of gastrointestinal bleeding, but should be considered in cases of unexplained gastrointestinal bleeding, particularly if the patient displays chronic pancreatitis. However, diagnosis is complicated by intermittent hemorrhaging from a source that is not readily accessible by endoscopy.[4,7]

In the present case, anemia with no definite bleeding was initially the only clinical sign. The patient underwent repeated endoscopies at several medical institutions, and diagnosis was difficult in the present patient. The pancreas was considered a potential source of bleeding only after numerous diagnostic procedures. Blood oozing from the papilla confirms a diagnosis of HP, but this situation is rare.[5] Assuming a diagnosis of HP is thus crucial. HP should be suspected if blood is seen in the second portion of the duodenum without evidence of a common source of bleeding, particularly in patients with chronic pancreatitis. Enhanced CT to estimate blood flow should be performed immediately as imaging for suspected HP. In the present case, enhanced CT did not reveal obvious pseudoaneurysm, but MPVR did. If HP is suspected, MPVR is useful. Hyperamylasemia may sometimes be detected,[2,8] and abdominal pain is often associated with bleeding.[2,4,5] These findings add to the suspicion of HP. The patient in the present case displayed neither hyperamylasemia nor marked abdominal pain, and these factors complicated identification of diagnosis.

Previous reports regarding HP in western countries remain mostly limited to case reports and short reviews.[9,10] We reviewed 41 cases of HP in Japan (Igaku Chuo Zassi: from 1974 to 2001). Mean age of patients is 50.9 years (range, 29–83 years), and patients are commonly male (37 males, 4 females). Long-term alcohol abuse is often present (70.7%), and most of these cases experience abdominal pain related to bleeding (73.2%). Because long-term alcohol abuse is related to chronic pancreatitis, the coincidence of alcohol abuse with HP is highly likely in this case. Hyperamylasemia has been identified in 20 cases (48.8%). However, normal amylase levels have been present in 13 cases (31.7%), including the present case. Bleeding artery is most frequently from the splenic artery (13 cases). Hemorrhage

from other abdominal vessels leading to HP is less common,[6,11] but the gastroduodenal artery was the source of bleeding in 6 cases. Similarly, other reports have described the splenic artery and its branches as the most common sources of bleeding (45%), followed by the gastroduodenal artery (17%) and pancreatoduodenal artery (16%).[4,12] Several arteries around the pancreas with pancreatitis may cause HP. In addition, HP has been attributed to ruptured pseudoaneurysm in 25 cases (62.5%). Therapy for HP involves surgical resection in most cases (26 cases), including distal pancreatectomy (15 cases), pancreatoduodenectomy (6 cases), ligation of aneurysm (3 cases), total pancreatectomy (1 case) and drainage of pseudocyst (1 case). As an alternative, successful selective arteriographic embolization has been reported in 10 cases. Transcatheter arterial embolization (TAE) can be performed safely and offers several advantages over surgery, such as precise localization of the aneurysm, assessment of collateral flow, low risk for patients who are not suitable candidates for surgery, and easier approach to aneurysms for which surgical exposure would be difficult.[13,14] TAE thus seems to offer the first choice therapy for HP.

In conclusion, HP rarely presents as gastrointestinal bleeding, but should be considered in cases of unexplained gastrointestinal bleeding, particularly if the patient displays chronic pancreatitis. In addition, diagnosis of HP can be incidental if the patient presents with no clinical signs or history of chronic pancreatitis.

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Measures Against Lifestyle Related Diseases

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Key words Lifestyle related disease, Diabetes, Potential diabetes patients, Family physician, Hospitals and clinics

Current Situation Concerning Diabetes

Due to changes in lifestyle habits and an increase in the elderly population, the number of patients with lifestyle related diseases as well as those with the potential of contracting such diseases is increasing. According to the figures issued by the Ministry of Health, Labour and Welfare, the number of diabetes patients including potential patients has reached 16.2 million, an increase of 2.5 million in the past 5 years.

Since diabetes has very few subjective symptoms, many people either do not see a doctor or stop seeing the doctor before the completion of treatment. Out of the lifestyle related diseases, however, diabetes is a particularly significant risk factor for cardiovascular and cerebrovascular diseases as well as for complications such as blindness and kidney failure. In other words, it is a disease that should not be underestimated. In addition, diabetic cases may range widely from mild to severe, with a variety of symptoms such as polyposia and polyuria as well as neurological, ophthalmologic, and dermatological symptoms. Diabetes also closely impacts the treatment of other diseases such as concomitant diseases or poor patient recovery. Consequently, all physicians in clinical practice need to be familiar with diabetes, regardless of their respective specialties.

Efforts by the Government

In May 2004, the government developed a ten-year strategy called the "Health Frontier Strategy" that targets the extension of the "healthy life expectancy" of citizens as its basic objective. This strategy has two basic components: "promotion of measures against lifestyle related diseases" and "promotion to prevent the need for nursing care." It sets numerical targets, and through the accomplishment of these targets, aims to extend healthy life expectancy by about 2 more years. The Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology have drawn up a list of measures that should be taken to promote this strategy. The measures to be taken against diabetes include decreasing the incidence by 20% and the government plans to call for more intensive measures.

In addition, a special research project conducted by the Ministry of Health, Labour and Welfare (Diabetes Outcome Intervention Trial: DOIT) recommends halving the transition rate from borderline diabetes to more advanced diabetes, halving the dropout rate of diabetic patients from treatment, and suppressing the progress of diabetes concomitant diseases by 30%.

Based on the results of this project, plans have been made for research covering three specific topics to be conducted as "strategic research for

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the prevention of diabetes" over the 5 years from fiscal year 2005.

Efforts by the Japan Medical Association (JMA)

The JMA has made continuous efforts to implement and improve measures against diabetes. It published the "Medical Care Manual for Diabetes" as a special issue of the Journal of the JMA in October 2003 as part of our CME series No. 63. In October 2002 it held a public forum on the "Prevention and Treatment of Diabetes" which was broadcast on TV. The videotapes of the forum were distributed to prefectural medical associations as well as city level medical associations in order to provide educational materials as part of the efforts to spread measures against diabetes.

To improve the health level and welfare of citizens by promoting measures against diabetes such as the prevention of onset of the disease and its complications, the JMA, Japan Diabetes Society and Japan Association for Diabetes Care and Education worked together to establish the "Japan Diabetes Prevention Committee" in February 2005. This committee has three objectives: 1) enhance the functions of family physicians and promote partnership in the roles of hospitals and clinics, 2) encourage patients to see a doctor and improve medical follow-up for the patient after the completion of his/her visit to the clinic, and 3) increase the achievement level in the treatment of diabetes.

In 2004, the committee produced two kinds of educational leaflets on diabetes for the general public and medical professionals and a book for the treatment guideline titled "The Essence of Diabetes Treatment."

• A guideline "The Essence of Diabetes Treatment" was created from the need for cooperative work between family doctors and medical specialists in the treatment of diabetes, which also requires consensus between them. The leaflet describes the treatment in five sections: 1) partnership in the roles between hospitals and clinics; 2) basics for initial consultations of diabetes patients; 3) treatment objectives, control indexes, dietetic therapy, and exercise therapy; 4) timing of drug therapy and prescription; and 5) diabetic complications. Some of the important topics to be cited are as follows: what is necessary to improve the treatment achievements is a daily practice which ensures smooth referral of the patient between the hospitals and clinics. Importance should be also emphasized on the team care which should include cooperative work not only between family physicians and specialists, but also co-medical personnel such as nurses and national registered dietitians, and physicians from other specialist fields such as ophthalmology. This guideline was distributed to about 160,000 JMA members in addition to 15,000 members of the Japan Diabetes Society and some 800 doctors in the Japan Association for Diabetes Care and Education. This leaflet has been in big demand even from non-association members and is distributed free-of-charge to anyone wishing to have a copy.

In September 2005, the JMA and Japan Diabetes Prevention Committee co-hosted a public forum with the theme of "Reduce diabetes!" We believe, however, it is more important along with these kinds of activities that we make utmost efforts focusing on how local communities can be engaged in specific measures such as strengthening of the partnership between hospitals and clinics in future.

In these environments, we plan to prepare basic materials to be used in the preventive and clinical settings such as "Basics for the treatment of diabetes" (draft), a check sheet for check-ups, a result table given to patients at the examination, an assessment sheet for patients in need of medical care in the diabetes screening, an assessment sheet following dietary guidance, a check sheet for diabetes treatment, and a model form of treatment information for the referral of diabetes patients.

The key to success of diabetes control lies in the efforts at the community level. As of November 2005, 23 prefectures have already established a diabetes prevention committee or similar body, 5 prefectures are planning to establish a diabetes prevention committee or similar body, and 14 prefectures have not established a committee but are in the process of or planning to implement some types of programs. Further efforts to challenge this problem are expected.

Future Perspectives

One serious problem in treating some 7.4 million diabetes patients in the future is reflected in the fact that only half of the diabetes patients

see a doctor. There is a need to prepare a program for all the patients to be covered. For the treatment options, dietary therapy or exercise therapy are more important than drug treatment. Cooperation between health nurses and dietitians as well as sports doctors may be necessary to support the patient's efforts to change their life-style.

Potential diabetes patients estimated to account for about 8,800,000 are not listed in the target areas for medical care, but they should be provided with prevention benefits.

As discussed above, measures against diabetes cover a number of issues concerning its prevention, early detection and treatment and prevention of complications. Enhancement of the functions of family physicians should be one of the top priorities, but encouraging patients to see doctors, improvement in the medical guidance, and partnership between hospitals and clinics are also important. The quality of medical care may be another top priority that is also required. It is also necessary to promote teamwork between doctors, nurses, nutritionists, and other health professionals. Finally, we must say that opportunities such as public forums should be provided for the general public to obtain correct knowledge about diabetes. This will surely lead to enhanced awareness of this disease by Japanese citizens.

Recent Topics in Myasthenia Gravis

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Tetsuro Konishi*1

Key words Myasthenia gravis, Epidemiology, Thymectomy, Muscle specific tyrodine kinase (MuSK), Tacrolimus

Introduction

Myasthenia gravis (MG), a T-cell-dependent chronic autoimmune disorder, is induced by the sustained production of antibodies that interact with nicotinic acetylcholine receptors (AChR) at the neuromuscular junction.[1] MG is characterized by the weakness and the fatigability of skeletal, bulbar and extraocular muscles presenting clinical features in various degrees, such as ptosis, diplopia, dysarthria, dysphagia, dyspnea and muscle weakness of the neck and extremities. This review describes four recent topics in MG: epidemiology, thymectomy, a new subtype of seronegative MG and tacrolimus.

Epidemiology of MG

In Japan, the prevalence of MG increased from 14 per million in 1973 to 89 per million in 1990. Female patients predominate over male patients 2.2 to 1.0. Although MG can develop at any age, the incidence of ocular MG peaks under the age of ten, and two further peaks have been recognized in generalized MG: The peak incidence in females occurs during their thirties and forties and in male patients at middle-age. Recent studies have shown an increased prevalence of MG especially among middle-aged and older patients.[2] One study in Nagano Prefecture, Japan revealed that the incidence of MG has increased particularly over the last 20 years, and in the case of elderly-onset MG patients over the age of 65.[3] A nation-wide survey of MG patients would serve to clarify the extent of the increased incidence of MG in the elderly population in Japan. The apparent increase in the prevalence of MG both globally and in Japan may be partly due to: 1) the increased accuracy of diagnostic procedures and detection of antibodies that interact with AChR, 2) improved prognosis as a result of managing myasthenic crisis using artificial respirators, which has dramatically decreased mortality, and 3) the advance of the aging society with associated increased life expectancy.

Thymectomy

In 1939, Blalock et al.[4] reported the remission of generalized MG after the removal of a cystic thymic tumor. Thymectomy, regardless of the presence of thymoma, has gained widespread acceptance as an early treatment for MG. A recent systematic review of studies describing outcomes in MG patients could not establish the benefit of thymectomy in nonthymomatous autoimmune MG.[5] This review concluded that thymectomy is recommended as an option to increase the probability of remission or improvement for patients with nonthymomatous MG. Double-blind studies of thymectomy of MG patients are now being conducted outside Japan and the results are expected within a few years.

Recent advances in endoscopic operations include video-assisted thoracoscopic extended

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thymectomy (VATET), which employs extensive removal of the mediastinal thymus and perithymic fat tissue with small operation scars. Outcomes in MG patients undergoing VATET are as favorable as those achieved previously following transsternal extended thymectomy.

Anti-MuSK Antibodies: A New Type of Antibody in Seronegative Patients

Antibodies that bind to acetylcholine receptors (AChR) are detected in 80 to 90% of MG patients,[1] and these patients have been defined as "seropositive" patients. However, about 15% of generalized MG patients do not have detectable AChR antibodies (seronegative MG).[6] Recently, another type of auto-antibodies against muscle-specific receptor tyrosine kinase (MuSK) was detected in these "seronegative" MG patients.[7] Then, the presence of anti-MuSK antibodies defines a subgroup of 40 to 50% of seronegative MG patients. The percentage of patients with anti-MuSK antibodies in AChR-ab seronegative MG cases is lower in Japan (around 30%) compared to the percentages reported elsewhere. Differences may be due to the race-specific patient profiles. Clinical features of anti-MuSK antibody positive patients are consistent across the countries including Japan. These include female predominance and oculo-bulbar and neck muscle weakness.[6] Wasting of bulbar muscles is evident in some patients with poor response to treatment of these muscles. Other indications include an absence of ocular MG and poor clinical improvement after thymectomy.

Although the pathophysiology of anti-MuSK antibody positive MG has not yet been clarified, morphological damage of motor endplates in these anti-MuSK antibody positive patients was less pronounced than in those with AChR antibodies.[8] The thymus is unlikely to be the main organ of autoimmune reaction in this disease due to the fewer thymic changes in anti-MuSK antibody positive patients than in anti-MuSK antibody negative patients.[9,10] A lack of improvement of MG symptoms after thymectomy in anti-MuSK antibody positive MG patients also supports the idea that the thymus gland is not implicated in its etiology. This feature of anti-MuSK antibody positive MG patients is quite different from the pathophysiology of seropositive MG, in which thymic abnormalities such as hyperplasia and/or the presence of thymoma are common. In addition, the presence of thymoma was reported in about 20% of seropositive MG patients, but only one patient with thymoma has been reported as an anti-MuSK antibody positive MG case. So far, the thymectomy is not recommended for anti-MuSK antibody positive MG patients without thymoma. For anti-MuSK antibody positive MG patients, treatment with steroids and/or other immunosuppressive drugs has resulted in clinical improvement.

Tacrolimus Treatment

The treatment of MG patients includes anticholinesterase agents, thymectomy, immunosuppressive therapy, plasma exchange (plasmapheresis) and intravenous immunoglobulin.[1] However, for these patients, steroids are the first choice of drugs along with various kinds of immunosuppressants, such as azathioprine, cyclophosphamide, cyclosporin and tacrolimus. Of these drugs, only tacrolimus can be prescribed to MG patients under the health insurance in Japan. Tacrolimus, a macrolide immunosuppressant derived from *Streptomyces tsukubaensis* discovered in Japan, possesses strong immunosuppressive effects and specifically inhibits the activation of T-cells. Tacrolimus inhibits the production of a number of cytokines interacting with helper T-cells, and consequently decreases the production of antibodies by B-cells. These immunosuppressive effects are similar to those of cyclosporin which a double-blind study has proved to be effective for the treatment of generalized MG.[11] Tacrolimus shows additional beneficial effects aside from those of cyclosporin. Firstly, tacrolimus increases the concentration of the intracellular calcium level enhancing the functioning of ryanodine receptors, which, in turn, increases the strength of muscle contraction. Secondly, tacrolimus also enhances the transition of steroids into the nucleus, which promotes the pharmacological effects of steroids.

These additional effects of tacrolimus are advantageous in the treatment of steroid-resistant MG in that lower dosages of steroids are required. Open-label studies of low-dose (3 mg/day) tacrolimus for steroid-dependent generalized MG show improvement in about 47% of patients within four months,[12] and a long-term study of more than one year's treatment

showed further improvement of MG symptoms.[13] No serious side effects were observed during these studies, but diabetogenic side effects are more likely than nephrotoxic side effects. There are many open-label studies of tacrolimus with progressive reduction of steroids achieving pharmacological remission. Yet, since tacrolimus lacks evidenced-based data, a double-blind study is planned for the near future in Japan.

Summary

At present, acquired autoimmune MG can be divided into at least three distinct subtypes according to the presence of auto-antibodies: 1) anti-AChR antibody positive (seropositive MG); 2) anti-MuSK antibody positive (in seronegative MG cases); 3) antibody undetermined. The increased incidence and prevalence, especially in aged populations, will be investigated in Japan in the near future. Evidence-based results will clarify the effects of thymectomy in nonthymomatous MG patients. Until then, experienced clinicians recommend thymectomy during the early stages of disease within one year from the onset of MG symptoms. The pathophysiology of the anti-MuSK antibody will become clear in the near future at which time the production of an autoimmune animal model will also be possible. Tacrolimus, one of the immunosuppressants, improves steroid-resistant MG symptoms with a reduction of steroid dosages.

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