Current Status of Clinical Care for Familial Endocrine Tumor Syndromes in Japan

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Abstract. We performed nationwide questionnaire-based surveys to characterize the current status of medical services for endocrine tumor syndromes, such as multiple endocrine neoplasia (MEN) and von Hippel-Lindau disease (VHL), in Japan. About 30% of the respondents had seen patients with either MEN or VHL, but the number of patients most of respondents had encountered was 5 or fewer. On the other hand, a large number of patients had been seen in a few hospitals, which seemed to be the result of the availability of specialists, rather than of geographic location. Although nearly 90% of hospitals had performed genetic tests, less than half of the hospitals had a clinical genetics division that provided genetic counseling to patients and/or family members. Not all of the respondents were thoroughly familiar with the “Guidelines for genetic testing” proposed by the consortium of Japanese genetic-medicine-related societies in 2003. Only 27.8% of respondents have read the guidelines and understood their concepts.

Key words: Multiple endocrine neoplasia, von Hippel-Lindau disease, Genetic test, Genetic counseling

NEOPLASTIC diseases can occur in any endocrine organ. In addition to the clinical symptoms generally seen in various types of tumors, many endocrine tumors are associated with abnormal secretion of specific hormones, which increases patient morbidity. Many endocrine tumors are sporadic, but some show a familial predisposition. The occurrence of two or more endocrine tumors in one patient is usually attributable to a genetic disorder. Several familial endocrine tumor syndromes, such as multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), and Carney complex, are known, and they are all transmitted in an autosomal dominant manner with high penetrance. The causative genes of these syndromes have been identified during the last decade, and their discovery rapidly changed the standard procedure for screening for family members from conventional biochemical measurement and radioimaging to more reliable genetic tests that allow detection of gene carriers before clinical symptoms develop [1, 2]. The clinical utility of genetic tests for those syndromes has therefore come to be widely recognized.

Since neoplasms develop in different organs and at different times in familial endocrine tumor syndromes, patients need to undergo a variety of regular studies (i.e., biochemical tests and imaging studies) and usually require surgery more than once. Genetic testing of patients and family members can cause them significant psychological distress [3, 4]. We performed nationwide questionnaire-based surveys to characterize the current status of medical services in regard to endocrine tumor syndromes in Japan.
Methods

All surveys were performed in January, 2005, and questionnaires were sent by e-mail. The first questionnaire asked if they had experience with the medical care of patients with MEN1, MEN2, VHL, Carney complex, and Cowden disease during the past 5 years. It was sent to 892 clinicians/scientists who were members of either the Japan Society for Familial Tumors or the Japan Association of Endocrine Surgeons, or were selected members of the board of representatives of the Japan Endocrine Society. Among them, 384 (43.0%) were surgeons, 142 (15.9%) were urologists, and 125 (14.0%) were internists (Fig. 1A). When more than one reply was returned from the same institution, we counted only the first reply we received, and did not include any others in the analysis. Valid replies were returned by 373 respondents (response rate 48.4%): 113 replied “yes” (30.3% of respondents), and 260 replied “no” (69.7% of respondents). We then mailed the second questionnaires (consists of 10 questions) to the 113 respondents who replied yes to the first questionnaire. Seventy-nine replies were returned (response rate 70.0%), and they were used in the analysis.

Results

Composition of respondents

Among the 79 respondents who completed the first and second questionnaires, 38 (48.1%) reported themselves to be surgeons (32 endocrine surgeons, 4 digestive system surgeons, and 2 general surgeons), and 25 (31.6%) to be internists (including clinical endocrinologists). The number of urologists and neurosurgeons was 10 (12.7%) and 2 (2.5%), respectively. Others were otolaryngologists or were working in a genetic counseling division (Fig. 1B). Fifty-four (68.4%) were working for either a university hospital or a research organization hospital, 15 (19.0%) for a general hospital, and 5 (6.3%) for a specialized hospital. The remaining 5 (6.3%) were in private practice (Fig. 1C).

Number of patients

Because only 6 respondents had experience with Carney complex and only 2 had experience with Cowden disease, we excluded these diseases from the analysis. Among the 373 respondents to the first questionnaire, 56 (15.0%), 54 (14.5%), and 23 (6.2%) respondents had experience with the clinical care of patients with MEN1, MEN2, and VHL, respectively (Fig. 2). The number of patients treated varied. For example, 37 respondents had treated 1 to 5 patients with MEN1, while 2 respondents had seen more than 30 MEN1 patients. Two respondents answered they had seen more than 10 VHL patients, but all others had seen five or fewer patients.

Methods of medical care

Patients with familial endocrine tumor syndromes...
and asymptomatic family members who have been found to carry the mutated gene are encouraged by attending physicians to undergo various periodic studies for early detection and early treatment of tumors. Also, physicians and surgeons in more than one specialty area participate in the treatment of each patient. Thus, the method of medical care provided to patients is an important element for better medical services. The questionnaire asked how each hospital periodically screens patients, and the results are shown in bar graphs.

**Table 1.** Questionnaire regarding methods of medical care

**Questionnaire:**
Since multiple tumors develop at different sites in familial endocrine tumor syndromes, more than one specialty department may participate in the treatment of a patient with such syndromes. What methods does your department take to periodically screen such patients? Choose only one.

1) One department performs all screenings and refers patients to other departments when necessary (eg., one department performs parathyroid, pituitary, and pancreatic screening for MEN1 patients).

2) More than one department in the same hospital performs screening in their specialty area (eg., the endocrine surgery department performs parathyroid screening and the neurosurgery department performs pituitary screening).

3) More than one department, in more than one hospital, perform screening in their specialty area (eg., the endocrine surgery department in one hospital performs parathyroid screening and the neurosurgery department in another hospital performs pituitary screening).

4) Either 1) or 2), depending on the disease.

5) None of the above.

Answers (numbers of respondents who chose each answer, and the percentage):
1) 45 (57.0%)
2) 23 (29.1%)
3) 5 (6.3%)
4) 3 (3.8%)
5) 3 (3.8%)

**Fig. 2.** Experience with the clinical care of patients with A. MEN1, B. MEN2 and C. VHL. Respondents with experience with the clinical care of patients with each syndrome were categorized according to the number of patients cared for, and the results are shown in bar graphs.

**Genetic tests**
Since genetic screening is now considered very useful or even mandatory for the diagnosis and family screening of MEN1, MEN2, and VHL [5–7], we next asked whether respondents had genetic tests performed for the diagnosis and/or screening of these syndromes in their hospitals (Table 2). Twenty-two respondents (27.9%) answered that they had genetic tests performed in their institution. Fifty-five respondents (69.6%) answered that they had genetic tests performed elsewhere. Only 11 respondents (13.9%) an-
In 2003, 10 genetic-medicine-related academic societies in Japan released “Guidelines for genetic testing”, and they are considered as a baseline when genetic tests are performed in Japan. The entire text of the guidelines can be read online at http://www.kuhp.kyoto-u.ac.jp/idennet/idensoudan/guideline/geneguide.doc (in Japanese). We asked if respondents knew and understood these guidelines (Table 4). Only one fourth of respondents knew about them and understood them, and another one fourth did not know of their existence.

Finally, we asked whether the respondent’s hospital had a clinical genetics division. Thirty-three (41.8%) answered that it does, and forty-six (58.2%) answered that it does not.

Discussion

Conditions of clinical care

The present study aimed to reveal the current status of clinical management of patients with familial endocrine tumor syndromes in Japan. Monitoring for familial endocrine tumors requires repetitive and costly studies, and multiple surgical procedures are usually needed. Thus, it is not surprising that most institutions caring for patients with such syndromes are university hospitals or general hospitals, where a variety of specialists are available (Fig. 1). However, since such patients need to be monitored for the rest of their life, some patients may consider it more convenient and have the periodic studies performed by a local physician. We may have missed such physicians in our survey, which was based on membership lists of specialist...
societies; and that may be a limitation of this study.

Our survey revealed that a considerable proportion of hospitals see patients with familial endocrine tumor syndromes, but that the number of patients seen in most hospitals is five or fewer (Fig. 2). It seemed obvious that the distribution of the patients depended on the availability of specialists rather than on geographic location.

Although many physicians see only a few patients, there is a debate about methods of medical examination, surgical procedures, and a follow-up programs between clinicians who have abundant experience with familial endocrine tumor syndromes. However, unfortunately, such discussion is not shared enough with many clinicians. It seems necessary to establish a patient registration system and accumulate epidemiologic data to establish a method of desirable management for Japanese patients.

Follow-up program

According to the responses to our questionnaire, more than half of the hospitals had adopted a follow-up program that burdens patients as little as possible: one attending physician performs all the periodic studies required and refers the patient to a specialty department when necessary. Cross-sectional cooperation is essential to the care of multidisciplinary diseases, such as familial endocrine tumor syndromes. Thus, the “hub and spoke” follow-up style seems appropriate, since at least one physician should be familiar with the overall health status of the patient, and the patient can undergo all necessary studies by visiting just one physician. However, some patients may prefer to be seen by experts in each clinical specialty, even if they have to visit more than one hospital, and that may be especially true in urban areas, where many experts are usually available. In such cases, patients’ demands should be carefully considered, but it is doubtlessly important that participating physicians share clinical information, and, preferably, one physician should play a central role as coordinator for effective follow-up.

Genetic medicine and familial endocrine tumor syndromes

Genetic testing for familial cancer syndromes should be considered when patients are suspected of having specific syndrome. Genetic testing is also performed to detect asymptomatic gene carriers among family members, if the mutation has already been detected in the family. Identification of carrier status helps in early diagnosis and intervention, and in MEN2, it can provide the rationale for performing preventive thyroidectomy in presymptomatic children [6]. On the other hand, once genetic testing has demonstrated that a family members is not a carrier, the costly studies can be discontinued. Genetic screening for MEN and VHL is considered highly appropriate and useful for diagnosis and family screening, because of its high sensitivity and specificity. A genotype-phenotype correlation has been established in MEN2, and genetic information is used for classification of the clinical entities (MEN2A, MEN2B, and familial medullary thyroid cancer) and to determine the clinical approach to the patient (i.e., timing of thyroidectomy) [6]. In a recent survey regarding Japanese patients with medullary thyroid cancer, about half of MEN2 patients were found to have been diagnosed through genetic testing [8].

Genetic testing requires careful handling of the information obtained. Because testing yields important genetic information that remains unchanged throughout the individual’s life time, it raises some important issues for discussion, such as informed consent to testing, protection of genetic information, handling of specimens used in testing, and genetic counseling before and after testing. Also, the individual’s genetic information is shared with relatives [9]. The “Guidelines for genetic testing” in 2003 were proposed by a consortium of 10 Japanese genetic-medicine-related societies and describe the need for genetic counseling before and after genetic testing. This principle has also been described in “A guideline for the appropriate handling of personal information in medical care/care-related businesses”, released by the Ministry of Health, Labour and Welfare of Japan in 2004. The entire text of the guideline can be read at http://www.mhlw.go.jp/houdou/2004/12/dl/h1227-6a.pdf (in Japanese). However, the present survey revealed that despite the fact that more than 80% of institutions performed genetic tests for MEN and VHL, less than half had a clinical genetics division. In the majority of hospitals, the explanation of genetic testing to obtain informed consent was provided by the attending physician. Furthermore, only 27.8% of respondents had read and understood the concept of the “Guidelines for genetic testing” (Table 4).

Genetic tests for neoplastic syndromes involve many ethicolegal and social issues [10], and a system of
genetic counseling is indispensable to resolving them. There is an urgent need to promote and enhance genetic medicine in this era of genetics, and all clinicians should be aware of the significance and possible misuse of genetic tests and of the need for appropriate genetic counseling. A clinical genetics training program should be included among the postgraduate training courses for all specialities as well as the core curriculum of medical education.

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