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Multiple Endocrine Neoplasia Type 2 Syndromes in Japan

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Multiple Endocrine Neoplasia Type 2 Syndromes in Japan

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and Yuichi Kumahara, MD*

Through nationwide surveys, we collected and analyzed 242 patients of medullary thyroid carcinoma (MTC). Included were 40 patients with multiple endocrine neoplasia type 2A (MEN-2A), six patients with MEN-2B, and 36 patients with only MTC having a positive family history (82 total patients in the hereditary group). Ten-year survival rates were 81.5% for all cases, and 91.8% and 76.1% for the hereditary and the sporadic group, respectively.

Epinephrine/norepinephrine ratio in the urine was found to be a good indicator of the adrenomedullary hyperfunction in patients with hereditary MTC. At least one patient in each family with hereditary MTC had overt pheochromocytoma or latent hyperfunction of adrenal medulla.

Doubling times of plasma calcitonin levels correlated with life expectancy and recurrence rates.

We carried out linkage analysis between the MEN-2 locus and several genetic markers in our MEN-2 families, but so far we have been unable to demonstrate or exclude a linkage.

In Japan, medullary thyroid carcinoma (MTC) is so rare that it accounts for only 1.5% of all thyroid malignancies. In order to learn about the clinicopathological features of MTC and of multiple endocrine neoplasia type 2 (MEN-2) in our country, we carried out nationwide surveys on two occasions.

Methods

The questionnaire for clinical and laboratory data on all patients with MTC was prepared in the Second Department of Surgery, Osaka University Medical School, and sent out to all member institutions of the Japanese Society of Thyroid Surgery.

In the first survey carried out in 1975-76, 122 histologically proved cases were registered. Five years later, in the second survey, which was performed to follow the patients registered in the previous survey, 120 new patients were found.

Our own cases consisted of 66 patients with MTC operated on and followed in either the Second Department of Surgery, Osaka University Medical School, or in Kuma Hospital, Kobe, Japan. Details of urinary catecholamines determination and of calcitonin assay have been published elsewhere (1,2).

Twenty-six genetic markers listed below were determined by standard laboratory methods in the Department of Forensic Medicine, Osaka Medical School. The markers determined were nine blood groups: ABO, MNS, P, Rh, Kell, Kidd, Duffy, Lutheran and Diego, and 17 serum protein and enzyme markers: haptoglobin, transferrin, group specific component, Gm, Km, alpha-1-antitrypsin, acid phosphatase, PGM, ADA, PGD, ESD, GPT, GOT, phosphohexose isomerase, LDH, UMPK and GLO.

Results

Studies on the cases collected by nationwide surveys

Among 242 patients with MTC, 67 patients belonged to 31 kindreds at high risk. These 67 patients consisted of 36 patients with MTC only, 30 with MEN-2A, and one patient with MEN-2B. This MEN-2B patient was reported to have siblings whose phenotypes were normal, but whose plasma calcitonin levels were elevated (3). We also found 10 patients with MEN-2A and five patients...

with MEN-2B in whom no family history was elicited. Of all patients with a positive family history and/or MEN-2, the hereditary group accounted for 33.9% of all MTC in Japan (Fig. 1).

Breakdown of patients with medullary thyroid carcinoma in Japan. Average ages were calculated from ages at the first operation.

Six patients with MEN-2A had all three components of this syndrome, 28 had MTC and pheochromocytoma, and the remaining six had MTC and parathyroid adenoma.

Three patients with MEN-2B manifested the complete syndrome. The remaining three patients of MEN-2B initially were reported to have only mucosal neuromas and MTC, but bilateral pheochromocytomas developed later in two patients.

Of the 82 hereditary patients, 72 (87.8%) had bilateral MTC, while the remaining 10 patients had unilateral thyroidectomy only by the time of the survey. Pheochromocytomas were bilateral in 33 (84.6%) of 39 patients who had this component of MEN-2.

Postoperative survival curves for the hereditary and sporadic groups of MTC are shown in Fig. 2. Five- and 10-year survival rates were 90.5% and 81.5% for all cases, 94.7% and 91.8% for the hereditary group, and 88.1% and 76.1% for the sporadic group, respectively. In the sporadic group, a sharp decrease in the survival curve was noted in the first two postoperative years, with the curve later becoming almost parallel to that for the hereditary group (Fig. 2).

Involvement of cervical lymph nodes at the time of surgery did not seem to affect the survival of patients in the hereditary group but was associated with a marked decrease in the survival rate of patients in the sporadic group. Specifically, the five- and 10-year survival rates for the hereditary group were 95.9% and 95.9% in patients without node involvement, and 96.2% and 96.2% in patients with positive nodes, respectively. For the sporadic group, those rates were 98.5% and 94.5% in patients without node involvement, and 82.4% and 61.6% in patients with positive nodes.

By the time of the second survey, 28 patients in the sporadic group had died, 24 dying of MTC and four of unrelated causes. In the hereditary group, four died of MTC, two died of pheochromocytoma, and four of unrelated causes. Most patients dying of unrelated causes had recurrent MTC. All six patients with MEN-2B were alive at the time of the second survey.

Studies on our own patients
Sixty-six patients of our own included 50 patients who had been reported in the nationwide survey and 16 patients treated more recently. Among the 66 patients, 29 were hereditary patients, four of whom had MEN-2 without positive family histories. The remaining 25 hereditary patients, derived from 12 kindreds at high risk for MTC, consisted of 16 patients with MEN-2A and nine patients with MTC only.
TABLE I

Catecholamines Excreted in 24-hour Urine and in Single-voided Urine of Patients with Medullary Thyroid Carcinoma (1,2)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Patients with MTC + Pheo</th>
<th>Patients with MTC-H</th>
<th>Patients with MTC-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (µg/day)</td>
<td>14.1 ± 1.2</td>
<td>162.0 ± 33.1</td>
<td>23.4 ± 3.7</td>
<td>10.4 ± 1.3</td>
</tr>
<tr>
<td>Norepinephrine (µg/day)</td>
<td>125.0 ± 7.8</td>
<td>274.3 ± 87.1</td>
<td>94.8 ± 11.5</td>
<td>82.7 ± 6.2</td>
</tr>
<tr>
<td>E/N ratio</td>
<td>0.12 ± 0.01</td>
<td>0.85 ± 0.10</td>
<td>0.26 ± 0.03</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>Single-voided urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/N ratio</td>
<td>0.14 ± 0.02</td>
<td>0.99 ± 0.27</td>
<td>0.43 ± 0.06</td>
<td>0.15 ± 0.01</td>
</tr>
</tbody>
</table>

MTC-H: hereditary MTC  
MTC-S: sporadic MTC  
Mean ± S.E.M.

Bilateral lesions of MTC were found in all these hereditary patients except for two in whom bilateral C-cell hyperplasia and unilateral MTC were seen. Pheochromocytomas or increased urinary catecholamine excretion was found in 19 of 20 patients with MEN-2. Bilateral total adrenalectomy was carried out in eight patients with bilateral pheochromocytomas. Unilateral adrenalectomy was performed in three patients who had unilateral pheochromocytoma and apparently normal-sized adrenal glands on the other side. Adrenal surgery was not performed in eight patients who had no clinical signs and symptoms of pheochromocytoma, despite slightly increased catecholamine excretion. Two of these eight patients died later (one from MTC and another from hepatocellular carcinoma) and proved to have bilateral pheochromocytomas at autopsy.

We have published our studies of urinary excretion of catecholamines in 36 patients with MTC and their relatives (1). Table I summarizes these findings. A marked increase in both the excretion of epinephrine and epinephrine/norepinephrine ratio (E/N ratio) with a less prominent increase in norepinephrine characterized the 24-hour urine of patients with pheochromocytomas. A statistically significant increase in epinephrine excretion and in E/N ratio was observed in patients with hereditary MTC in the absence of any clinical signs and symptoms of pheochromocytoma. Norepinephrine excretion by this group was no different from that of the control group. No significant difference was recognized in epinephrine and norepinephrine excretion, or in E/N ratio between patients of the sporadic group and the control group.

The E/N ratio of 24-hour urine of the sporadic MTC was always less than 0.3, while an E/N ratio greater than 0.3 was observed in five of 10 patients (eight of 21 urine specimens tested) with hereditary MTC without clinical signs and symptoms of pheochromocytoma. Essentially the same results were obtained in single-voided urine collected in the outpatient clinic. These results suggest that most patients of hereditary MTC even without clinical pheochromocytoma, have hyperfunction of adrenal medulla, probably resulting from adrenal medullary hyperplasia.

In all urine samples tested among 10 patients with hereditary MTC without clinical pheochromocytoma, only four patients had consistently normal epinephrine, norepinephrine excretion, and E/N ratio less than 0.3. Of these four patients with hereditary MTC and normal urinary catecholamines, two had relatives with MTC and pheochromocytomas, while a third patient had relatives proved to have adrenal medullary hyperfunction. The remaining patient, a 14-year-old girl when diagnosed to have MTC, had MEN-2B. She developed bilateral pheochromocytomas and underwent bilateral adrenalectomy five years after the neck surgery. Thus, at least one patient in each family with hereditary MTC had proven pheochromocytoma or latent adrenal medullary hyperfunction, leaving no family with only hereditary MTC in our series.

Serial measurements of plasma calcitonin levels are important in following MTC patients. We have found that the doubling time of plasma calcitonin levels correlates significantly with three-year survival, recurrence within five years, and time interval between surgery and clinical recurrence of the tumor (2). All five patients whose doubling time of basal calcitonin levels was shorter than 0.5 year died of MTC within three years,
whereas none of 13 patients with doubling times longer than 0.5 year died within three years. The doubling time of calcitonin levels was less than 0.5 year for only one of 10 hereditary patients but for four of 13 sporadic patients. We could not measure the doubling time of calcitonin in the patient with MEN-2B because her postoperative plasma calcitonin levels were normal even after provocation by calcium or gastrin. In the linkage study we could calculate lod scores for only seven genetic markers (Table II).

### Table II

<table>
<thead>
<tr>
<th>Markers</th>
<th>Lod score at θ = 0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidd</td>
<td>-1.553</td>
</tr>
<tr>
<td>Gm</td>
<td>-0.841</td>
</tr>
<tr>
<td>Km</td>
<td>-0.208</td>
</tr>
<tr>
<td>Pi</td>
<td>-0.720</td>
</tr>
<tr>
<td>PGM</td>
<td>-1.117</td>
</tr>
<tr>
<td>ADA</td>
<td>-0.673</td>
</tr>
<tr>
<td>PGD</td>
<td>-1.331</td>
</tr>
</tbody>
</table>

Discussion

Furihata and Maruchi (4) reported that 60 patients of thyroid cancer were found among 46,037 inhabitants examined, giving a prevalence rate of 0.13% in the general population in Japan. Miyauchi (5) reported that MTC accounted for 1.5% of all thyroid malignancies treated in Kuma Hospital. Data from the thyroid cancer registry in Japan also revealed 58 MTC (1.55%) of 3,742 patients with thyroid malignancies registered from 1977 through 1980. Therefore, we can estimate the prevalence rate of MTC in Japan to be approximately two patients per 10^5 of the general population. It is difficult to compare this rate with that in other countries because the prevalence rate of thyroid cancer in the general population is not known in other countries.

According to Hakama’s paper (6) based on the monograph *Cancer Incidence in Five Continents*, the prevalence of thyroid cancer in Japan (1.1 per 10^5 in males, 2.6 per 10^5 in females) is very close to those in the United States and in Canada, slightly higher than in Norway (1.0 and 2.0 per 10^5 in males and females, respectively), and twice as much as in England and Wales (0.5 and 1.2 per 10^5).

The proportion of MTC among all thyroid malignancies was reported to be 8.2% (7) and 9.4% (8) in the United States, 3.4% in Norway (9), and 1.5% in Japan (5). Therefore, MTC seems to be less frequent in Japan than in other countries.

Survival rates of MTC in Japan were better than those reported by Chong, et al in the United States (7). In our series, only six patients had MEN-2B and 40 patients had MEN-2A, while in Chong’s series, 14 patients had MEN-2B and 15 had MEN-2A. This difference in 2B/2A ratio is highly significant (P < 0.01). Since MTC in MEN-2B is very aggressive (10), the small number of MEN-2B in our series could be a factor for better survival. However, all MEN-2B patients were alive at the time of the survey (2-13 years, mean: 7.3 years after surgery), so that MTC of MEN-2B in our country may not be as aggressive as that in the United States.

The growth rate of a tumor must be one of the most important factors determining its aggressiveness. Jackson, et al (11), estimating the maximum volume doubling times of MTC in MEN-2 by measuring the size of tumors in each patient, found that MTC in MEN-2B had shorter doubling times than in MEN-2A. Measuring plasma calcitonin levels, we found good correlation between the calcitonin doubling time and life expectancy. These results suggest that measurement of doubling times (either tumor volume or calcitonin concentration) may be useful in comparing aggressiveness of MTC in different countries.

Gagel, et al (12) reported that epinephrine was the major secretory product of pheochromocytomas in the J-kindred and that E/N ratios are useful in the early detection of pheochromocytoma in MEN-2. Sato, et al (13) and Hamilton, et al (14) reported similar results, and we have confirmed these findings. In addition, the measurements of catecholamines in single-voided urine are useful in an outpatient clinic.

We are more conservative in treatment policy for pheochromocytomas in MEN-2 than Sizemore, et al (15) and Lips, et al (16) who advocate bilateral total adrenalectomy for all MEN-2 patients with pheochromocytoma. We do not hesitate to perform bilateral total adrenalectomy for patients with symptomatic bilateral pheochromocytomas. We recommend unilateral adrenalectomy for patients with unilateral pheochromocytoma and a normal-sized adrenal gland on the other side, and we perform the indicated thyroid surgery for patients who have biochemical evidence for adrenal hyperplasia without pheochromocytoma symptoms. Tibblin, et al (17) advocate a treatment policy similar to ours.

Linkage analysis is very important in the search for the genetic basis of MEN-2. Jackson, et al (18) and Emmertsen, et al (19) reported linkage studies on their large kindreds but could not demonstrate linkage of the MEN-2 locus to any genetic markers tested. They both excluded close linkage to ABO, Rh, MNS (18,19). In addition, HLA was excluded in Jackson’s study, and Gm and PGM, were excluded in Emmertsen’s study. Our data could neither demonstrate nor exclude the close linkage of the MEN-2 locus but will be useful when combined with data of other families, assuming that
heterogeneity among families can be excluded. The possibility of finding a genetic marker closely linked to the MEN-2 locus will be greatly increased by using DNA markers (restriction fragment length polymorphisms). We have initiated this study as well as chromosome analyses in members of MEN-2 families.

Acknowledgments
The authors thank all the surgeons and physicians who reported their cases in the nationwide surveys.

References