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MEN-2 Syndrome: The Value of Screening and Central Registration; A Study of Six Kindreds in The Netherlands

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Since 1975, six families with the MEN-2A syndrome including 66 patients have been identified in The Netherlands. All these patients underwent thyroidectomy for C-cell hyperplasia and/or medullary thyroid carcinoma (MTC); eight were symptomatic (Group A), 51 were relatives of patients found to be affected (Group B), and seven had had a negative screening test that became positive (Group C). To assess the effect of screening, we compared these groups with respect to the occurrence of metastatic MTC at thyroidectomy and the results of the postoperative calcitonin (CT) tests. We found that 87% of Group A, 37% of Group B; and none of Group C had metastatic disease at surgery. The "cure rates" in these three groups with MEN-2A, as determined by stimulated CT measurement, was 0%, 51%, and 100%, respectively. From these results it may be concluded that screening can lead to the detection of MTC at an earlier stage which in turn could permit curative treatment and improvement of both prognosis and life expectancy. The need for supervision of affected families by central registration to guarantee the continuity of screening is stressed. (Henry Ford Hosp Med J 1987;35:101-3)

The occurrence of medullary thyroid carcinoma (MTC) in combination with pheochromocytoma and hyperparathyroidism is a well-known hereditary syndrome (multiple endocrine neoplasia syndrome type 2A [MEN-2A] or Sipple's syndrome) characterized by autosomal dominant inheritance with a high degree of penetrance but varying expression (1-4).

The only way to recognize patients with the MEN-2A syndrome at a curable stage is periodic examination of close relatives of known patients (3,5-9). Potentially life-threatening tumors can be identified and removed at an early stage of development (3,5-9). These advantages of periodic screening may counterbalance the disadvantages, which include psychological burden and violation of privacy. However, it has yet to be ascertained whether or not large-scale screening of families with hereditary tumors meets the criteria for epidemiologic screening programs described by Wilson and Jungner in 1968 (10). Their most important criterion is that early treatment should improve prognosis and offer the prospect of prolonged life expectancy.

In 1983 the Foundation for the Detection of Hereditary Tumors was established in The Netherlands. The objectives of this foundation include the promotion of early detection, the establishment and maintenance of a registration system, and the guarantee of continuity of screening programs (11). Since 1983 the data on six families with the MEN-2A syndrome have been collected in the registration center, including 66 patients with MTC with or without pheochromocytomas. To assess the effect of screening on the prognosis, we reviewed the data from these families. Also the importance of central registration to guarantee the continuity of screening is discussed.

Materials and Methods

Patients

Clinical and genetic studies were performed in six kindreds with the MEN-2A syndrome.

To investigate the effect of screening we divided the patients into three groups, A, B, and C. Group A comprised patients who came for advice because they had symptoms caused by the MEN-2A syndrome (mainly probands). Group B was reserved for examined relatives of patients found to be affected (call-up group), and group C comprised patients with a previously negative screening test that became positive (converters). We compared the occurrence of metastatic MTC at thyroidectomy in each group. Since the level of plasma calcitonin (CT) following postoperative provocative testing is probably the most sensitive indicator of curative thyroidectomy (9,12,13), we compared these groups with respect to the results of such testing.

Screening program

Screening programs applied in The Netherlands include a medical history, clinical examination, and measurement of calcium and phosphate levels in the first-degree relatives of patients. For the detection of MTC, the short calcium or pentagastrin infusion test is used. CT levels were determined

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Table 1
Pattern of Expression of the MEN-2A Syndrome in 66 Patients

	Number of Cases
Medullary thyroid carcinoma	43
Medullary thyroid carcinoma + pheochromocytoma	15
Medullary thyroid carcinoma + pheochromocytoma + hyperparathyroidism	6
Medullary thyroid carcinoma + hyperparathyroidism	2

by specific radioimmunoassay (4). For the detection of pheochromocytoma, 24-hour urine was collected for estimation of adrenalin, noradrenalin, and their metabolites (4). The screening program in families with the MEN-2A syndrome starts between five and ten years of age and is continued on a yearly basis until the age of 35. After that age less frequent screening is sufficient, ie, once every three years.

When the value of CT after stimulation is more than three times the baseline value and exceeds 1,000 pg/mL, diffuse C-cell hyperplasia or MTC is likely. In patients with an abnormal CT response in at least two separate provocative tests, surgery is indicated. The operation of choice for MTC is total thyroidectomy with exploration of the central region of the neck. For the surgical treatment of pheochromocytoma, the bilateral extraperitoneal laterolumbar approach is used (14).

National registry

A registration center supervised by a multihospital committee was set up in The Netherlands in 1983 (11,15). This center is responsible for maintaining the continuity of the investigation by periodic assessment of the screening results. Annually, a reminder is sent to the physicians to screen the family members at risk.

Because this project is concerned with registration of very sensitive data on large groups of patients and their families, much attention is paid to the protection of privacy. Persons to be registered have several rights: the right to refuse such registration, the right of access to their own data, and even the right to order destruction of such data. Furthermore, their data may not be given to third parties without their permission. A supervisory committee, composed of patients and persons with nonmedical backgrounds, was set up. Two genetic field workers (social workers with special training in genealogy) assist in the collection of data, the working out of pedigrees, and providing the relatives with information on request. In addition, pamphlets containing information about the objectives of the registration center and the syndrome itself were made available to the relatives.

Results

Since 1983 the data of 18 families with the MEN-2 syndrome were collected in the registration center. The data on six families with the MEN-2A syndrome are complete, including 66 patients, 32 men and 34 women. The pattern of expression of the disease is shown in Table 1. Six patients with MEN-2A had all three components of the syndrome, 15 had MTC and pheochromocytoma, two had MTC and hyperparathyroidism, and the remaining 43 had only MTC.

Table 2
Metastatic MTC at Diagnosis of the MEN-2A Syndrome: Postoperative Calcitonin Test Results

	GROUPS A Symptomatic	B Call-up	C Converter
Number of Cases (66)	8	51	7
Average Age	41.7	29.4	13.4
Metastatic MTC	87%	37%	0%
Postoperative conversion of calcitonin tests to normal			
Basal	25%	70%	100%
After stimulation	0%	51%	100%

Sixty-six patients with abnormal test results had surgery, and thyroid abnormalities (MTC and/or C-cell hyperplasia) were confirmed in all of these. Seven of the eight patients in Group A, 19 of the 51 patients in Group B, and none of the seven patients in Group C had metastatic disease at the time of thyroidectomy (Table 2). The basal CT value became normal in two of the eight patients in Group A, 36 of the 51 patients in Group B, and in each of the seven patients in Group C. The CT value after provocative testing became normal in none of the eight patients in Group A, 26 of the 51 patients in Group B, and in each of the seven patients in Group C.

Discussion

The best way to assess the effect of periodic examination in families with the MEN-2A syndrome would be to perform a randomized controlled trial. However, because there is substantial evidence in the literature for a favorable effect of treatment (3,5-9), this would seem to be excluded on ethical grounds. Another way to assess the effect of screening is to divide the patients into three groups—a symptomatic group (group A), a call-up group (group B), and a converter group (group C)—and compare them with respect to the stage of the thyroid tumor at surgery and the effect of surgery on the results of the postoperative CT test.

We found that 87% of the symptomatic group, 37% of the call-up group, and none of the converters had metastatic MTC at the time of surgery. The "cure rates" in the three groups, as determined by stimulated CT measurement, were 0%, 51%, and 100%, respectively.

From these findings we concluded that screening led to detection of MTC at an earlier stage, which permitted curative treatment and improvement of both prognosis and life expectancy. However, the ultimate value of screening must be based on the long-term cumulative experience with survival rates. We expect to find that the life expectancy of prospectively screened families will not differ from that of the general population.

The responsibility for the continuity of periodic examination is a heavy burden on the family physician or general internist, and experience has shown that periodic control cannot be adequately guaranteed in this way. Continuity was found to be interrupted (for example, by completion of short-term research programs, loss of funding, departure or death of the coordinating physician, or moving away of the patients), which led to unnecessary morbidity and mortality.

One way to solve the practical problems involved might be to have the administrative work organized centrally and to have the family physician perform the main screening work. A study group was set up in 1981 to assess the feasibility of central registration and decentralized screening of large groups of patients with the MEN-2A syndrome and their relatives. To assure the continuity of this project, a foundation called Foundation for the Detection of Hereditary Tumors was established in 1983. After three years, our experience has shown that large groups of patients and their close relatives can be handled properly by the registration center and that the privacy of patients and relatives can be guaranteed. Patients and physicians have been generally enthusiastic about participating and extremely helpful with the family studies. At present, the activities of this foundation are limited to the MEN-2 syndromes and polyposis coli. Perhaps, if sensitive tests and curative treatment become available, other hereditary tumor syndromes could be included.

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