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Results of a Screening Program for Multiple Endocrine Neoplasia Type 2A: A Clinical Study of a Japanese Family

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A Japanese family of 87 members in five generations with multiple endocrine neoplasia type 2A (MEN 2A) is described regarding the utility of screening tests for early detection of medullary thyroid carcinoma and the potential for DNA diagnosis of MEN 2A gene carriers. The screening programs for family members in this series include measurements of plasma calcitonin concentrations after intravenous injection of pentagastrin (0.5 μg/kg/5 sec) and 24-hour urinary excretion of catecholamines. While 18 MEN 2A patients had been previously diagnosed, these screening programs revealed five additional patients with MEN 2A (aged 16, 19, 35, 37, and 57). Prediction of MEN 2A gene carriers by DNA analysis has been attempted but is not yet possible in this family. (Henry Ford Hosp Med J 1989;37:124-6)

Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant syndrome characterized by the association of medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism. A carrier of the MEN 2A gene often shows clinical signs or symptoms of these associated diseases, such as cervical nodes, hypertensive attacks, and repeated severe headaches in the third or fourth decade of life (1). However, in the kindred at high risk for MEN 2A, early diagnosis of MTC is possible even at an early stage, including "occult disease," by measuring plasma calcitonin (CT) concentrations after intravenous injection of calcium or pentagastrin (2). In recent years, prospective studies including children have been initiated in some institutions, and many young patients with MEN 2A have been diagnosed and treated surgically (3-5).

A Japanese family with MEN 2A was investigated regarding early diagnosis of MTC by screening tests in childhood and the possibility of DNA diagnosis of gene carriers.

Patients and Methods

The H-kindred is a Japanese family (currently 87 members) with MEN 2A. Members of this family had many episodes of cervical tumors and often experienced characteristic attacks such as repeated headache, sweating, and pale face. Some underwent thyroidectomies and/or adrenalectomies. However, most of the family members had been reluctant to consult physicians because of the surgery required for relatives and the severe hypertensive attacks which were sometimes fatal. Patients were also anxious about violation of the individual privacy of unaffected relatives. For these reasons, no systematic investigation had been performed on this family. The clinical complaints of cervical nodule and repeated severe headache in a 34-year-old male in this family in 1987 provided us the opportunity to approach this family.

Screening program

The medical history and cause of death of family members were investigated by interviewing their relatives or studying their medical records. The surviving patients were interviewed and their medical records reviewed.

Screening programs included biochemical measurements of specimens from the first- and second-degree relatives of the patients. For detection of MTC, plasma CT concentrations were measured following provocative agents. CT was determined by radioimmunoassay on blood samples collected before and at 2, 5, and 10 minutes following intravenous administration of pentagastrin (0.5 μg/kg/5 sec). For detection of pheochromocytomas, 24-hour urine specimens were collected for an estimation of the excretion of epinephrine and norepinephrine.

Genotype at RBP3 locus

DNA was extracted from leukocytes or lymphoblastoid cell lines of each member of the family. Restriction fragment length polymorphisms (RFLPs) were determined using H.4IRBP, containing the 3′ region of the cDNA of retinol binding protein 3 (6) as a probe after complete digestion of DNA with Bg1II.

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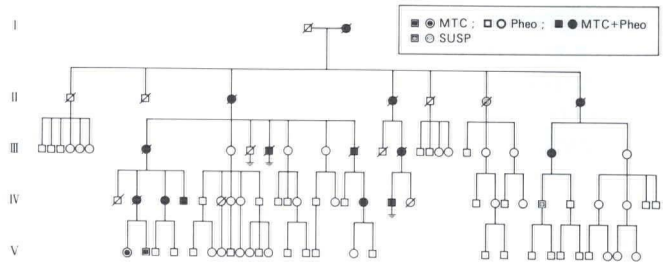

Fig 1—Pedigree of the H-kindred. A crossbar through the individual symbol indicates the patient is deceased. MTC = medullary thyroid carcinoma, pheo = pheochromocytoma, SUSP = suspected MTC, squares = males, circles = females.

Results

Eighteen patients with MEN 2A were confirmed by medical records or screening programs. This autosomal dominant syndrome is inherited with high penetrance (Fig 1). Screening tests are continued yearly until the age of 40 for the relatives whose data were negative for MEN 2A.

Results of screening program

Twenty-six family members (aged 3 to 62) were screened for the progression of C-cell abnormalities and pheochromocytomas. Abnormal responses of CT levels were observed in six subjects (aged 16, 19, 33, 35, 37, and 57) (Fig 2). Five underwent total thyroidectomy with regional lymph node dissection soon after the screening test, and in each case multicentric growth of MTC was found. The remaining patient, a 33-year-old male, was not operated on because of a less sharp response compared with that of the others, but he has been followed carefully. The two youngest patients, a 16-year-old boy and his 19-year-old sister, underwent total thyroidectomy for bilateral MTC (the largest diameters: 16 mm and 3 mm in the boy; 14 mm and 7 mm in the girl). Small metastatic foci of MTC were found in the cervical lymph nodes of the 16-year-old boy. The oldest patient, a 57-year-old female, had huge bilateral MTC. Her stimulated plasma CT level was more than 200,000 pg/mL (the normal upper limit of plasma CT level in our series was 150 pg/mL).

The 26 family members screened also had 24-hour urinary excretions of epinephrine and norepinephrine measured for detection of pheochromocytoma. Three of these subjects (aged 35, 37, and 57), who had been diagnosed as having MTC in the screening process, showed abnormal elevations (Fig 3). Adrenal pheochromocytomas were detected upon further examination, and a right adrenalectomy, a left adrenalectomy, and a bilateral adrenalectomy were performed in the 35-year-old, 37-year-old, and 57-year-old patients, respectively.

Prediction of the gene carrier by RFLPs at the RBP3 locus

Unfortunately, the RBP3 allele cosegregating with the disease could not be determined from the data obtained, and therefore DNA diagnosis of gene carriers was not possible in this family using this particular probe.

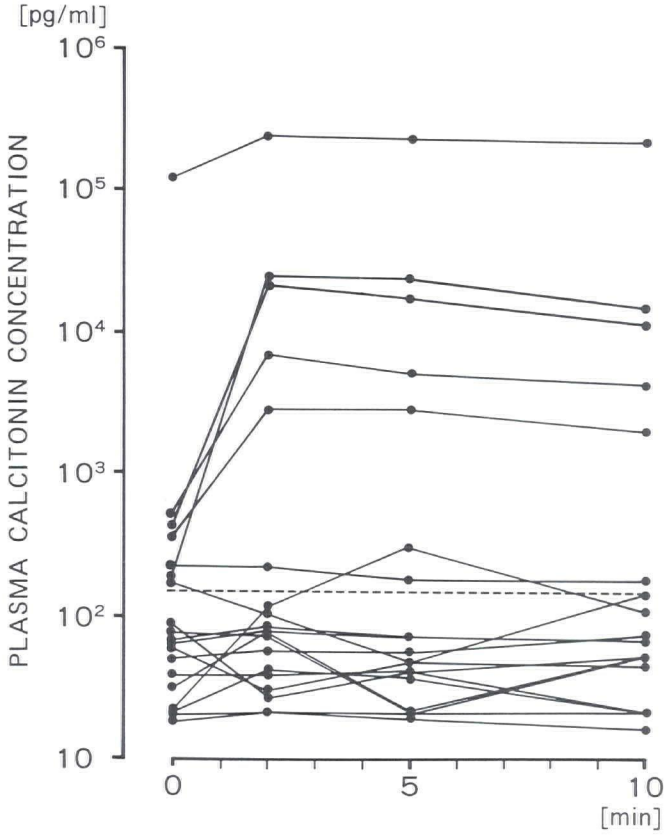

Fig 2—Results of screening with the measurement of plasma calcitonin concentration following an intravenous injection of pentagastrin (0.5 μg/kg/5 sec).

Discussion

Clinical screening programs for MEN 2A with stimulated plasma CT measurements have been utilized for early detection of MTC. The results of these screening programs have clarified the importance of early diagnosis of this hereditary malignant syndrome with the improvement of prognosis for affected patients (7).

Pediatric implications for MEN 2A have been discussed since the establishment of the value of measuring plasma CT for early diagnosis of MTC which has resulted in the initiation of periodic screening tests for young family members. Gagel et al (4) reported the results of a prospective screening program for MEN 2A in which periodic tests had been initiated at the age of 5. In their series half of the gene carriers were found before the age of 12, and in 80% of those patients the diagnosis of MEN 2A was made before the age of 20. Telander et al (5) reported the results of total thyroidectomy in 14 children with MEN 2A who were 12 years old or younger and recommended initiating the screening test at the age of 1 year and performing total thyroidectomy as soon as MTC or C-cell hyperplasia was diagnosed. In our series, two of the 11 members aged 19 or younger who received screening tests were diagnosed as having MEN 2A and were treated

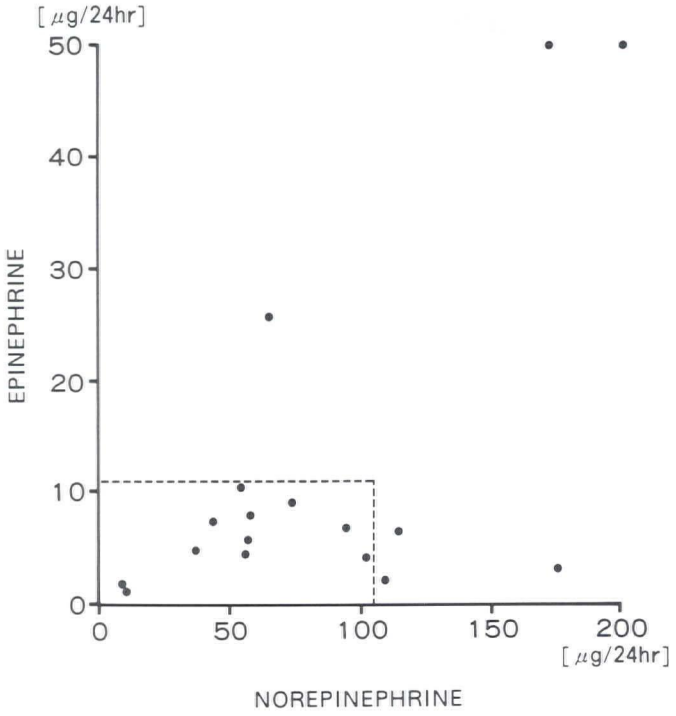

Fig 3—Results of screening with the measurement of 24-hour urinary excretion of epinephrine and norepinephrine. Pheochromocytoma was diagnosed in three members aged 35, 37, and 57.

surgically. Surgery has shown MTC metastases to the cervical lymph nodes in a 16-year-old male. Therefore, despite the troublesome procedures and the emotional strain burdening at-risk infants and children who have no clinical complaints, these screening programs must be started in childhood for improvement of the prognosis in this syndrome.

Recently the gene predisposing to MEN 2A was assigned to the pericentromeric region on chromosome 10 by the tight linkage with the RBP3 gene (8,9), and this linkage was confirmed in a Japanese family (10). DNA diagnosis may be possible in an informative family by determining genotypes at the RBP3 locus if the allele cosegregating with the disease can be determined. In our family, however, it has not been possible because the affected parents were deceased or homozygous at the RBP3 locus with Bg1II digestion. We are now trying other enzymes and other probes linked with MEN2A, and DNA diagnosis of gene carriers is expected to be possible in this family soon.

The early detection of MEN 2A gene carriers may prevent noncarriers of the MEN 2A gene from having periodic, troublesome screening tests. DNA can be obtained from peripheral blood samples at the initial screening test, from the umbilical cord blood samples at birth, or theoretically even from amniotic fluid or chorionic villus samples obtained before birth (11). What screening procedure is best within MEN 2A families? Perhaps screening programs should include DNA linkage analysis for detection of MEN 2A gene carriers in addition to the conventional screening tests as more informative markers are obtained closer to and flanking the MEN 2A gene.

Acknowledgment

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