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Britt Skogseid

Kjell Oberg

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Britt Skogseid,* and Kjell Oberg*

To assess the age of clinically detectable onset of multiple endocrine neoplasia type 1 (MEN 1), 88 members of four families were invited to participate in a ten-year biochemical screening program. Evidence for clinically detectable MEN 1 was found in adolescence. Pancreatic endocrine dysfunction constituted the presenting lesion in a majority of these individuals. The age at diagnosis of pancreatic endocrine tumors averaged 25 years and was lowered by almost two decades by prospective investigation. Furthermore, the penetrance of the pancreatic endocrine and parathyroid lesions equaled the penetrance found in autopsy studies. The use of a standardized meal stimulation test with the measurement of serum pancreatic polypeptide (PP) and gastrin responses resulted in diagnostic sensitivities of 75% and 100%, respectively. In addition to basal serum PP and insulin values, the proinsulin level was predictive for early pancreatic involvement in MEN 1. Serum gastrin was another useful tumor marker but only in the patients with pancreatic tumors diagnosed outside the prospective investigation. Two of the four MEN 1 kindreds selected for the screening investigation displayed homogeneity within families with respect to the profile of peptide excess and malignant potential of the pancreatic endocrine lesion, while the remaining kindreds demonstrated variable MEN 1 traits. (Henry Ford Hosp Med J 1992;40:167-70)

Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominantly inherited disorder encompassing neoplasia of the parathyroid glands, anterior pituitary, and endocrine pancreas (1). The MEN 1 gene (MEN1) has been mapped to chromosome 11q13 (2). The function of the gene seems to be masked by the existence of a normal counterpart (2-5). This suggests that MEN1 represents an inactivated suppressor gene (anti-oncogene), which could normally be involved in regulating differentiation of the endocrine pancreas, the parathyroids, and the anterior pituitary gland. The pituitary tumors in MEN 1 have not been evaluated, but loss of the wild-type allele in MEN 1 parathyroids and pancreatic micro- and macroadenomas has been demonstrated as well as loss of constitutional heterozygosity in about one-third of sporadic parathyroid adenomas (2-5).

Recent advances in mapping of the MEN 1 gene, which have narrowed the target region (6), now permit identification of individuals at risk for MEN 1 with a high degree of accuracy. It is therefore increasingly important to clarify the natural course of the syndrome, the early characteristics of the developing lesions, and the expected utility of available diagnostic measures in order to design an optimal screening program.

Material and Methods

All individuals above 10 years of age in four MEN 1 kindreds were offered repeated biochemical screening investigations for 10 years. The screening program and references to methods used (7-20) in analyzing different hormones are listed in Table 1. At the first investigation, 56 of 62 members participated (27 women and 29 men, mean age 33 years, range 10 to 75 years), while during the last screening 80 of 88 were subjected to the tests (37 women and 43 men, mean age 35 years, range 10 to 85 years). Patients with known MEN 1 trait prior to first screening and those with lesions recognized at the first screening were denoted as nonprospectively diagnosed patients. Individuals without biochemical abnormalities at the first screening who later developed evidence of MEN 1 were considered as prospectively diagnosed patients. A patient displaying an MEN 1 lesion at first screening, and therefore defined as a nonprospectively diagnosed patient, could develop a previously undetected or new lesion which would then be considered a prospectively diagnosed MEN 1 lesion.

Diagnostic criteria

Basal fasting hormone levels were considered elevated if the reference range was exceeded. The meal stimulation test was considered abnormal if the serum pancreatic polypeptide (PP) or gastrin response to the meal was more than two standard deviations higher than the mean response in control subjects (20). An MEN 1 family member was considered affected by hyperparathyroidism (HPT) if albumin-corrected serum calcium and/or serum parathyroid hormone were elevated. A diagnosis of pituitary tumor was made if an elevated serum prolactin or diurnal serum growth hormone and/or positive sella radiology were observed. An MEN 1 family member was considered affected by a pancreatic endocrine lesion if basal hormone markers and/or the meal test were abnormal in combination with radiological evidence of a pancreatic tumor. In the absence of positive radiol-

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*Department of Internal Medicine, University Hospital, Uppsala, Sweden.
Address correspondence to Dr. Skogseid, Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden.

Table 1
Biochemical Screening Program for MEN 1

Hematology (hemoglobin concentration, leukocyte and platelet count)
Sedimentation rate
Blood glucose
Albumin-corrected serum calcium
Serum creatinine
Serum sodium
Serum potassium
Serum aspartate aminotransferase
Serum alanine aminotransferase
Serum parathyroid hormone (7)
Serum prolactin (8)
Serum growth hormone (9)
Serum insulin (10)
Serum C-peptide (11)
Serum proinsulin (12)
Serum pancreatic polypeptide (13)
Serum gastrin (14)
Serum calcitonin (15)
Serum human chorionic gonadotrophin subunits α and β (16)
Plasma glucagon (17)
Plasma somatostatin (18)
Plasma vasoactive intestinal polypeptide (19)
Meal stimulation test (20)

References are noted in parentheses.

ogy, repeated and progressive elevation of hormonal markers was required for diagnosis of a pancreatic endocrine tumor.

Results and Comments

Total prevalence of MEN 1 lesions

The most common lesion was HPT, found in 90% of the patients. Pituitary tumors were detected in 19% of affected family members, a low figure compared to frequencies found in autopsy studies (60%) (1). Pancreatic endocrine involvement was, however, demonstrated biochemically in 75% of MEN 1 patients. This is the highest frequency reported in screening studies and nears the findings in autopsy materials (1).

Age at diagnosis of the trait

Seven individuals without biochemical evidence of MEN 1 at first investigation developed MEN 1 abnormalities during follow-up, at an age of 18 years ± 4 standard deviations (range 12 to 25 years). This contrasted with a nonprospectively diagnosed MEN 1 trait at a mean age of 36 ± 13 years (range 15 to 63 years). The age at diagnosis was lowered by approximately two decades by screening. In three of the seven patients the first detectable lesion was the pancreatic lesion; in two others parathyroid and pancreatic endocrine involvement was demonstrated concurrently. In contrast to previous reports (21,22), HPT was found to be the presenting lesion in only two of the patients.

Age at diagnosis of HPT and pituitary tumors

HPT was recognized prospectively in seven individuals at a mean age of 19 ± 5 years (range 12 to 28 years) (Table 2). The age of HPT diagnosis was significantly decreased by screening since the nonprospectively-made diagnoses averaged 38 ± 14 years. The age of diagnosis in the nonprospectively screened group was similar to that reported by others (21-23). Only one patient developed pituitary lesions during the 10-year follow-up; a 24-year-old male displayed biochemical signs of acromegaly. The five patients with nonprospectively detected pituitary lesions had a mean age at diagnosis of 39 ± 17 years in accord with previous reports (21-23) (Table 2).

Table 2
Number, Sex, and Age (Years) at Diagnosis of Primary Hyperparathyroidism (HPT), Pituitary Tumors, and Pancreatic Endocrine Tumors in Nonprospectively Diagnosed Patients and Prospectively Diagnosed Patients

	Number		Mean Age	Age Range
	Total	F/M	(Years)	(Years)
Nonprospectively Diagnosed:				
HPT	22	10/12	38	15-63
Pituitary tumor	5	4/1	39	16-59
Pancreatic lesion	15	5/10	44	25-71
Prospectively Diagnosed:				
HPT	7	1/6	19	12-28
Pituitary tumor	1	0/1	24	24
Pancreatic lesion	9	1/8	25	16-38

Nonprospectively diagnosed = diagnosed prior to or at the first screening; prospectively diagnosed = diagnosed during the subsequent 10-year investigation.

Age at diagnosis of pancreatic endocrine tumors

One of the most striking findings in this screening study was the young age at onset of the pancreatic endocrine lesion in nine individuals diagnosed by prospective screening. Six of these nine individuals have had pancreatic surgery in which pancreatic tumors were found (24). The age at biochemical diagnosis averaged 25 ± 8 years (range 16 to 38 years) which was significantly lower ($P < 0.005$) than in the 15 patients with nonprospectively-recognized pancreatic tumors (a mean of 44 ± 16 years of age [Table 2]). Others have found the mean age at penetrance of the pancreatic endocrine tumors of the MEN 1 syndrome to be the fourth and fifth decades of life (22,23).

Symptoms

In all cases of prospectively diagnosed lesions, the patients were asymptomatic except for one female with a pancreatic endocrine lesion who had experienced mild hypoglycemic symptoms and weight gain during breast feeding. The individuals with nonprospectively diagnosed lesions, however, showed clinical symptoms related to their MEN 1 lesions. The majority of patients with nonprospectively diagnosed HPT had histories of nephrolithiasis, and those with nonprospective pituitary lesions had amenorrhea and infertility as well as headaches, dizziness, and a reduction of their visual fields. Furthermore, the nonprospectively diagnosed pancreatic lesions caused tumor-related symptoms in 11 of the 15 patients. The most frequently displayed classical endocrine manifestations were the Zollinger-Ellison, hypoglycemia, and watery diarrhea syndromes. Nausea and/or abdominal pain was observed in three individu-

als. Transition from one syndrome to another occurred in three of the 15 patients during follow-up.

Biochemical markers for pancreatic endocrine tumors

The serum PP was elevated in 67% of both prospectively and nonprospectively diagnosed individuals (Table 3). The secretion of PP is subject to great intra- and interindividual variation (25) and increases with age (21,25). However, the upper reference range (0.4 ng/mL) for basal serum PP in our laboratory is based on measurements in 45 healthy individuals with a mean age of 39 years (range 20 to 60 years) (13) and is, therefore, comparable to the present MEN 1 study. Among the patients with nonprospectively diagnosed pancreatic endocrine tumors, basal serum gastrin and PP were equally useful. In patients with prospectively diagnosed lesions, however, serum gastrin was elevated in only two of nine individuals. Vasen et al (23) used serum gastrin as a screening marker for pancreatic involvement and their mean age at diagnosis was 38 years. Thus, gastrin production from pancreatic endocrine tumors could be a result of a long-standing cell proliferation or the development of duodenal neuroendocrine tumors with gastrin production (26). Serum insulin and proinsulin levels were elevated in approximately half of the patients, respectively, and constituted equally useful markers in the prospective and nonprospective patient groups. Serum hCG alpha and beta subunits have been considered indicative of malignant tumors in neuroendocrine tissue (16,27). In our series serum hCG alpha and/or beta was elevated more often (26% and 33%) among the patients with nonprospectively diagnosed pancreatic tumors in comparison to the individuals with prospectively diagnosed lesions (11% and 0%). Plasma glucagon had a sensitivity of 37% among the young tumor patients and was somewhat lower (27%) in the group with nonprospectively diagnosed lesions. All other pancreatic tumor markers were within normal limits in the group of patients with prospectively diagnosed pancreatic tumors.

In agreement with others (20,28) meal-stimulated serum PP distinguished MEN 1 pancreatic endocrine tumors better than measurements of basal serum PP alone (20). In one patient, both the serum gastrin and PP response to the test meal normalized after resection of three PP-producing tumors of the endocrine pancreas even though no gastrin immunoreactivity was demonstrated in the resected specimen. All 15 of the patients with nonprospectively diagnosed pancreatic tumors and 75% of those with prospectively recognized pancreatic lesions had abnormal peptide responses to the test meal. Thus, an abnormal meal stimulation test was the most useful marker for pancreatic endocrine involvement in the MEN 1 patients, making it appropriate for use in screening young asymptomatic individuals.

Morbidity, mortality, and familial entities

The individuals with prospectively diagnosed lesions were, with few exceptions, asymptomatic at diagnosis and during follow-up (mean 3.5 years). Among patients with nonprospectively diagnosed lesions, severe endocrine symptoms were common and one-third of the patients with pancreatic endocrine tumors had metastases at diagnosis. Only one of the nine patients with prospectively diagnosed pancreatic involvement had metastases, and this individual died at age 40 from tumor progression. Whether this apparent reduced morbidity in patients subjected to early diagnosis and intervention will persist during long-term follow-up remains to be evaluated. At present, no significant difference in survival (Kaplan–Meyer life-table method) between the two patient categories has been found, although the follow-up period is short.

Table 3
Sensitivity of Tumor Markers Among Patients with Nonprospectively and Prospectively Diagnosed Pancreatic Endocrine Tumors

	Nonprospective (%)	Prospective (%)
S-PP	67	67
S-gastrin	67	22
S-proinsulin	58	56
S-insulin	46	56
S-HCG α/β	26/33	11/0
P-glucagon	27	37
P-VIP	20	0
Meal test	100	75

In two of the kindreds, the peptide profile and malignant behavior of the tumors were homogeneous within families. In one of these families the MEN 1 trait was invariably benign and 75% of the patients with pancreatic involvement had the Zollinger-Ellison syndrome, whereas in the other family eight (89%) of the nine individuals with pancreatic endocrine lesions displayed insulin-proinsulin hypersecretion. This overrepresentation of a specific hormone secretion was significant ($P < 0.05$, Student t test). In the latter family three individuals died before the age of 55 and another two had metastases at the time of diagnosis. Within the remaining two kindreds peptide hormone excess and malignant potential in affected individuals were variable. These results suggest that in families with prominent malignant potential of the pancreatic lesions, surgery is indicated at early asymptomatic stages of the disease. In addition, peptide hormone excess alone is not satisfactory in selecting patients for surgery. Others have reported syndrome-dependent policies for surgical intervention (29,30).

Conclusion

The MEN 1 trait is clinically detectable in adolescents. The pancreatic endocrine dysfunction constitutes the presenting lesion in a majority of affected individuals and the penetrance of this lesion approximated findings in autopsy studies. Serum PP, insulin, proinsulin, and glucagon were the most useful basal markers for diagnosis of pancreatic tumors, but a meal test with measurements of serum PP and gastrin responses enhanced the detection of early endocrine pancreatic tumors in asymptomatic young individuals. Reliable markers for malignant transformation are still lacking and therefore the malignant potential must be evaluated for each family and each individual. A decision for surgical intervention in MEN 1 cannot be based on the hormone profile only.

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