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Genotype-phenotype pancreatic neuroendocrine tumor relationship in multiple endocrine neoplasia type 1 patients: A 23-year experience at a single institution

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Background. The aim of this study was to investigate the genotype-phenotype relationship of pancreatic neuroendocrine tumors in patients with multiple endocrine neoplasia type 1 treated at our institution.
Methods. We conducted a retrospective chart review of all patients with multiple endocrine neoplasia type 1 treated at our center from January 1993 to December 2015. Presence of a pancreatic neuroendocrine tumor was determined based on imaging performed at any time from presentation to conclusion of follow-up.
Results. We reviewed 188 patients. The most common site of multiple endocrine neoplasia type 1 mutation was in exon 2 (34/188; 18%). Of 188 patients, 125 had a pancreatic neuroendocrine tumor (61%). Among all patients, 30 of 34 (88%) with an exon 2 mutation had a pancreatic neuroendocrine tumor compared with 95 of 154 (62%) with a mutation in exons 3–10 (P = .002). In the age group of 20 to 40 years, 8 of 9 patients with an exon 2 mutation had a pancreatic neuroendocrine tumor, compared with 24 of 52 patients (46%) with a mutation in exons 3–10 (P = .028). Patients with an exon 2 mutation had a greater frequency of pancreatic neuroendocrine tumor distant metastasis (53% vs 23%, P = .049).
Conclusion. Young patients with multiple endocrine neoplasia type 1 and an exon 2 mutation appear to have a 2-fold greater risk for developing a pancreatic neuroendocrine tumor, and patients with an exon 2 mutation may be at greater risk for developing distant metastasis. Consideration should be given to more intensive screening and more liberal application of primary operative intervention in this potentially high-risk group.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease characterized by the presence of multiple neoplasms, primarily in the pancreas, parathyroid, and the anterior pituitary glands.[1] MEN1 is caused by heterozygous, germline mutations in the *MEN1* tumor-suppressor gene located on chromosome 11q13.[2,3] The *MEN1* gene consists of 10 exons, 9 of which are coding (exon 1 is noncoding).[4]

Parathyroid neoplasms are the most common feature of MEN1 (95% of patients); duodenal and pancreatic neuroendocrine tumors (PNETs) occur in about 40% to >50% of patients and are the second most frequently expressed clinical manifestation of MEN1.[4] Duodenal and pancreatic islet cell neoplasms often are functional and include gastrinomas (primarily of the duodenum), insulinomas, pancreatic polypeptidomas, glucagonomas, and vasoactive intestinal polypeptidomas.[5,6] The optimal surgical strategy for PNETs in patients with MEN1 is still debated and may differ according to multiple factors, including the functional status of the PNET and its size and growth characteristics.[7,8] Despite technologic advances and increased experience, MEN1-associated PNETs continue to be a major cause of morbidity and mortality for these patients, associated with a substantial risk for liver metastasis and associated decreased duration of survival.[9] PNETs and thymic carcinoids constitute the major causes of mortality for patients with MEN1.[10]

A number of studies have attempted to determine whether there is a specific correlation between genotype and phenotype in patients with MEN1, similar to what is observed in other familial diseases such as MEN2.[11] Thus far, published results have had limited

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success in identifying a relationship between the specific *MEN1* gene mutation present and an individual patient's clinical course.[12-17] Furthermore, data from the literature suggest that *MEN1* mutations are distributed throughout the entire coding region without any dominant mutational hot spot.[4]

In a prior investigation of a limited number of patients with MEN1, our data suggested that mutations in exon 2 might be related to a greater risk for distant PNET metastasis.[8] The aim of this study was to reassess this hypothesis in a larger cohort of patients with MEN1 and to investigate the genotype-phenotype relationship of PNETs in patients with MEN1 treated at our institution over the past 23 years.

Methods

The University of Texas MD Anderson Cancer Center Institutional Review Board approved this study. The patient population was identified by search of prospectively collected data in the Endocrine Surgery MEN1 database between 1993 and 2015. Patients included in this study fulfilled clinical, genetic, and/or familial criteria for MEN1 syndrome based on practice guidelines described by Thakker et al. in 2012.[1] Patients with only a suspected or possible diagnosis of MEN1 were excluded. Clinical information was obtained from the MEN1, disease-specific patient database and where necessary supplemented with data obtained directly from institutional medical records. Data extracted included demographic characteristics (sex and age), MEN1-related diseases, presenting symptomatology, preoperative diagnostic imaging and biochemical evaluation, types of operations performed, histopathologic results, germline *MEN1* genetic test results, follow-up details including timing of metastases (synchronous or metachronous) from PNETs and other MEN1-related primary tumors, recurrence, and survival. All patients had at least part of their evaluation and treatment at our institution.

The diagnosis of MEN1-related tumors followed the criteria developed at our institution and have been described previously.[15] Radiographic evidence was sufficient to determine the presence of a PNET; fine-needle aspiration biopsy or operative removal was not necessary to confirm the diagnosis. Lesions <0.7 cm in size on computed tomography (CT) or on magnetic resonance imaging (MRI) were considered equivocal, as were lesions not seen on 2 sequential imaging studies; such lesions were not counted as a definitive PNET. PNETs were classified as functioning when they were associated with a clinical syndrome or an increase in serum hormone levels (more than twice the upper limit of normal values). The diagnosis of an insulinoma was based on results obtained after a supervised fast with a serum glucose level <45 mg/dL and a concomitant insulin level >6 IU/mL. When there was no clinical picture associated with hormone hypersecretion and patients had mild increases (less than twice the normal limits) of hormones (gastrin, glucagon, VIP, PP), they were considered to have nonfunctioning tumors.[8] Histopathologic reports of the first operation performed for PNET were reviewed to identify tumor-related variables. The histopathologic staging of the tumor was reported according to American Joint Commission of Cancer guidelines (7th Edition).[18]

MEN1 gene mutational analysis was performed as part of standard clinical care through a Clinical Laboratory Improvement Amendments-approved assay or through a research assay as described previously.[15] Briefly, DNA was isolated from whole blood (QIAGEN blood or tissue kit; QIAGEN Inc, Chatsworth, CA). Polymerase chain reaction assays were performed targeting coding exons 2–10, with DNA sequence analysis performed by the Sanger method in the sequencing and microarray core facility.

Statistical analysis

Demographic, clinical, and *MEN1* genetic characteristics were summarized. The statistical associations of the site (exon) or the type of mutations with clinicopathologic variables were assessed by χ^2 and Fisher exact tests. Associations of continuous variables with different groups of mutations were assessed by the nonparametric Mann–Whitney *U* test. Overall survival (OS) was calculated as time from date of birth until death. Patients who had not died were censored at the date of last follow-up. Time-to-event analysis was conducted using the Kaplan-Meier method. The log-rank test was used to compare survival curves. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY).

Results

The Figure presents the flowchart of patients included in this study. *MEN1* genetic testing was performed as standard of care in 120 patients, with an additional 137 patients assessed by research assay.

Clinical characteristics of the patients are summarized in Table I. Hyperparathyroidism was the most common manifestation (83%), whereas PNETs were found in 59% of patients. There were 164 different MEN1 families, with 115 representing simplex cases and the remaining 49 families ranging from having between 2 and 10 family members. Of 239 patients, 206 (86%) with a deleterious mutation were identified. The mean follow-up (FU) was 5.4 years (SD 5.0), and 84% of patients were alive at the end of the FU period.

Supplementary Table I (available online only) presents a summary of tumor involvement (pituitary tumor, primary hyperparathyroidism [PHPT], and PNET) of patients with MEN1 according to their age group (<20, 20–40, 40–60, >60 years of age). The presence of tumors differed by age of presentation, with the 40 to 60 age group demonstrating the greatest frequency of PHPT, PNETs, and pituitary tumors ($P \leq .001$ each when compared with all other age groups).

Table I.
Summary of the clinical characteristics of patients included in the study

		n	%
Sex	Male	128	(45)
	Female	154	(55)
Diagnostic criteria	Clinical	53	(19)
	Genetic	80	(28)
	Clinical and genetic	149	(53)
Main tumor involvement	Pituitary	119	(42)
	PHPT	233	(83)
	PNET	167	(59)
Age at diagnosis, Mean (SD), Min–Max	Pituitary tumor	37 (16) 7.2–73.7	
	PHPT	35 (15) 7.3–75.8	
	PNET	42 (14) 7.8–76	
Carcinoid	Thymic	9	(3)
	Bronchial	20	(7)
	Gastric	7	(3)
	Duodenal	6	(2)
Adrenal lesion*		66	(23)
Family number size (164 different families)	1	115	(41)
	2	17	(12)
	3	17	(18)
	4	8	(11)
	5	1	(2)
	6	2	(4)
	7	1	(3)
	8	2	(6)
	10	1	(4)
Years of FU mean (SD)		5.4 (5)	
Min–Max		1–22	
Vital status	Alive	236	(84)
	Dead	46	(16)

* As confirmed on computed tomography.

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