Asymptomatic Children with Multiple Endocrine Neoplasia Type 1 Mutations May Harbor Nonfunctioning Pancreatic Neuroendocrine Tumors

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Context: Multiple endocrine neoplasia type 1 (MEN1) is characterized by the occurrence of parathyroid, pituitary, and pancreatic tumors. MEN1, an autosomal dominant disorder, has a high degree of penetrance, such that more than 95% of patients develop clinical manifestations by the fifth decade, although this is lower at approximately 50% by age 20 yr. However, the lower penetrance in the younger group, which is based on detecting hormone-secreting tumors, may be an underestimate because patients may have nonfunctioning tumors and be asymptomatic.

Objective: The aim of the study was to evaluate the occurrence of nonfunctioning pancreatic neuroendocrine tumors in asymptomatic children with MEN1.

Patients: Twelve asymptomatic Northern European children, aged 6 to 16 yr, who were known to have *MEN1* mutations were studied.

Results: Two asymptomatic children, who were aged 12 and 14 yr, had normal plasma fasting gastrointestinal hormones and were found to have nonfunctioning pancreatic neuroendocrine tumors that were more than 2 cm in size. Surgery and immunostaining revealed that the tumors did not have significant expression of gastrointestinal hormones but did contain chromogranin A and synaptophysin, features consistent with those of nonfunctioning pancreatic neuroendocrine tumors. The tumors had a loss of menin expression. The 14 yr old also had primary hyperparathyroidism and a microprolactinoma, and the 12 yr old had a nonfunctioning pituitary microadenoma. Three other children had primary hyperparathyroidism and a microprolactinoma.

Conclusion: Nonfunctioning pancreatic neuroendocrine tumors may occur in asymptomatic children with *MEN1* mutations, and screening for such enteropancreatic tumors in MEN1 children should be considered earlier than the age of 20 yr, as is currently recommended by the international guidelines. **(*J Clin Endocrinol Metab* 94: 3640–3646, 2009)**

Multiple endocrine neoplasia type 1 (MEN1) is characterized by the combined occurrence of parathyroid, anterior pituitary, and pancreatic neuroendocrine tumors (PETs) (1–3). Some patients may also develop adrenal cortical tumors, thoracic and thymic carcinoid tumors, facial angiofibromas, collagenomas, and lipomas (1, 2). MEN1, an autosomal dominant disorder, is due to mutations of the *MEN1* gene, which is located on chro-

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Abbreviations: H&E, Hematoxylin and eosin; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PET, pancreatic neuroendocrine tumor.

mosome 11q13 and encodes a 610-amino acid protein, menin, that belongs to the class of tumor suppressors (4). *MEN1* mutations have a high degree of penetrance such that more than 95% of patients develop clinical manifestations of the disorder by the fifth decade (1, 2, 5). However, the penetrance at the age of 20 yr is lower at approximately 50%, and this may represent an underestimate since many children and young adults may be asymptomatic because they may have either a smaller tumor burden or hormonally inactive (*i.e.* nonfunctioning) tumors (1, 2, 5). Hormonally active (*i.e.* functioning) tumors do occur in children, and primary hyperparathyroidism, insulinoma, and prolactinoma have been reported to occur as early as 8, 5, and 5 yr, respectively (6–8). However, nonfunctioning tumors, *e.g.* PETs, are likely to have not been reported in asymptomatic children with *MEN1* mutations because guidelines for MEN1 recommend radiological screening for PETs from the age of 20 yr (1). We report two asymptomatic children with *MEN1* mutations, in whom nonfunctioning PETs were identified at the ages of 12 and 14 yr.

Patients and Methods

Northern European children and adults less than 20 yr of age who were relatives of MEN1 patients with known mutations of the *MEN1* gene (Figs. 1 and 2) were ascertained. Twelve children (five males, seven females) with *MEN1* mutations were assessed annually for symptoms associated with MEN1 tumors and plasma measurements that included calcium, PTH, IGF-I, prolactin, fasting glucose, fasting gut hormones (glucagon, pancreatic polypeptide, gastrin, vasoactive-intestinal peptide, and somatostatin), chromogranin A, and chromogranin B. Interval magnetic resonance imaging (MRI), at 1 to 2 yr, of the pituitary and abdomen was undertaken. MEN1-associated tumors were diagnosed on the basis of either persistent plasma abnormalities or radiological and/or surgical evidence of a tumor. The age at diagnosis was that at which plasma and/or radiological abnormalities were first detected. Informed consent was obtained from the individuals and their relatives, and where appropriate the parents and guardians of children, using protocols approved by local and national ethics committees.

MEN1 mutation analysis

DNA sequence analysis of the *MEN1* gene was undertaken using leukocyte DNA and abnormalities confirmed by restriction endonuclease analysis and agarose gel electrophoresis as previously described (5, 9, 10).

Histological analysis

Tumors were fixed in formalin. Sections were stained for hematoxylin and eosin (H&E) and immunostained for gastrin, glucagon, insulin, somatostatin, MIB-1 (Ki-67), chromogranin A, PTH, synaptophysin, pancreatic polypeptide, and calcitonin. Immunohistochemistry was performed for menin using a rabbit polyclonal antibody (Abcam ab2605, 1:500; Abcam plc, Cambridge, UK).

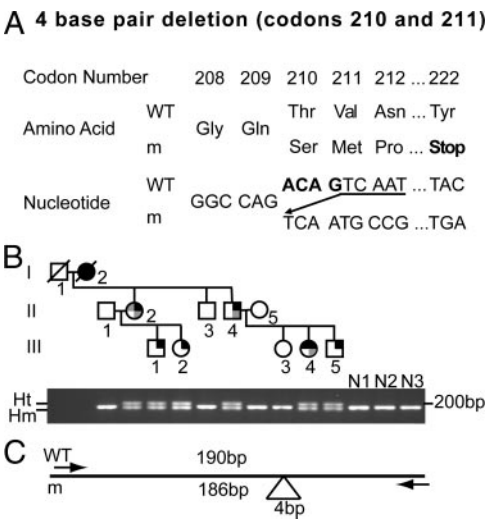

FIG. 1. Details of case 1 (individual III.4) from family with MEN1. The family was known to have a *MEN1* mutation, which consisted of a 4-bp deletion (ACAG) involving codons 210 and 211 that resulted in a frameshift with incorporation of 12 missense amino acids followed by a stop codon (A) (5). Cosegregation of this deletion with MEN1 in the family and its absence in 110 alleles from 55 unrelated normal individuals (N1-3 shown) was demonstrated (B) by the use of gene-specific primers (C). This deletion results in the formation of homoduplexes (Hm) (WT/WT or m/m of 190 and 186bp respectively) or heteroduplexes (Ht) (WT/m), which have a decreased electrophoretic mobility. Individuals are represented as male (*squares*), female (*circles*), unaffected (*open symbols*), affected with parathyroid tumor (*blackened right upper quadrant*), affected with nonfunctioning pituitary tumor (*gray left upper quadrant*), affected with prolactinoma (*blackened left upper quadrant*), affected with gastrinoma (*blackened lower right quadrant*), affected with nonfunctioning pancreatic tumor (*gray lower right quadrant*), affected but deceased and clinical details not available (*all blackened*). WT, Wild-type; m, mutant.

Results

Two of the 12 children developed nonfunctioning PETs and are described in detail below.

Case 1

A 14-yr-old girl (individual III.4; Fig. 1) known to have a family history of MEN1 was found to have inherited a deletional-frameshift *MEN1* mutation. Her father (individual II.4, Fig. 1) was noted to have facial angiofibromas, but she did not have any cutaneous abnormalities, *e.g.* facial angiofibromas, collagenomas, or lipomas, which have been reported in association with MEN1 (2). She denied symptoms, but detailed questioning revealed that she had oligomenorrhea. She was found to have hyperprolactinemia (plasma prolactin, 3676 mU/liter; normal range in females, 60–620 mU/liter) and mild hypercalcemia [plasma calcium, 10.56 mg/dl (2.64 mmol/liter)] with an inappropriately normal PTH of 3.0 pmol/liter (normal range, 1.3–7.6 pmol/liter). Fasting plasma gut hormones were not elevated. MRI of the abdomen revealed a less than 2-cm mass in the neck of the pancreas in keeping with a PET, and given its size (<2 cm) and lack of symptoms,

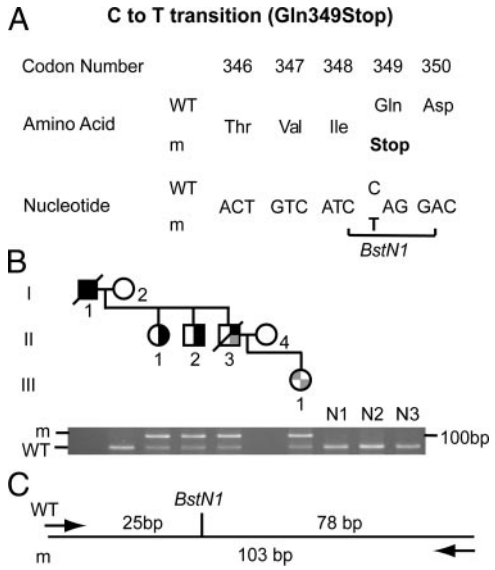

FIG. 2. Details of case 2 (individual III.1) from family with MEN1. The family was known to have a nonsense mutation due to a C to T transition at the first position of codon 349 in exon 7 of the *MEN1* gene (A) (5). This C to T transition alters the wild-type (WT) sequence, CAG encoding a glutamine (Gln) to the mutant (m) sequence, TAG, encoding a stop signal. This nonsense mutation (Gln349Stop) also results in the loss of a *BstN1* restriction enzyme site (CC/AGG) in the mutant sequence, and this has facilitated the confirmation of the mutation in the family (B). PCR amplification and *BstN1* digestion results in two products (78 and 25 bp) from the WT sequence (25-bp product not shown), but only one product (103 bp) from the mutant sequence (C). Cosegregation of this Gln349Stop (Q349X) mutation with MEN1 in the family and its absence in 110 alleles from 55 unrelated normal individuals was demonstrated (N1-3 shown). Individuals are represented by symbols as detailed in the legend to Fig. 1.

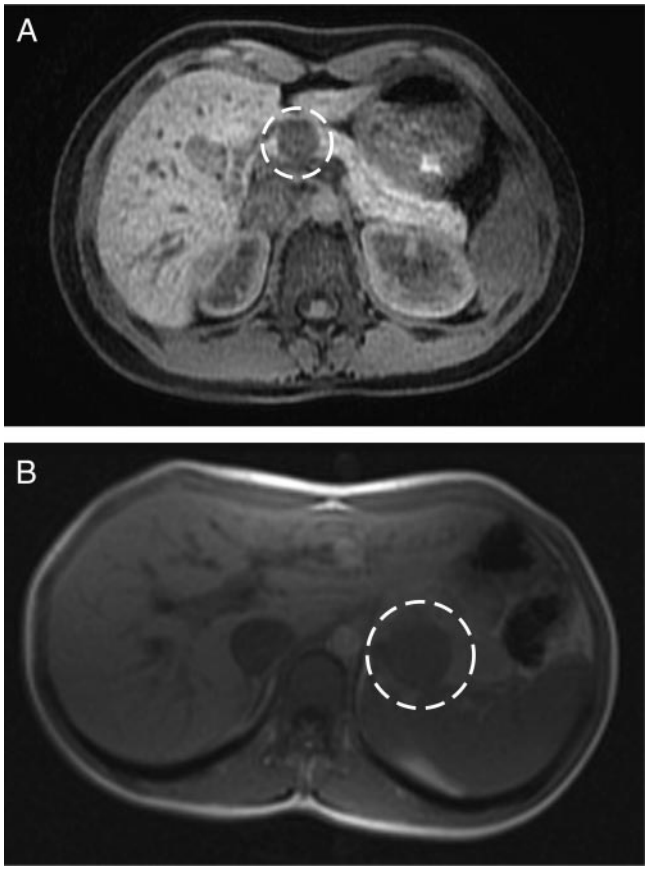

FIG. 3. Abdominal MRI scans showing pancreatic tumors. A, In case 1, a T1-weighted axial MRI of the pancreas demonstrated a low intensity 2.1 cm (anteroposterior maximal diameter) tumor within the neck of pancreas. There was no evidence of invasion of adjacent structures. B, In case 2, an abdominal MRI (Short T1 Inversion Recovery (STIR) image) demonstrated a 3.8-cm (maximal diameter) tumor lying anterior to the spleen and likely located within the distal body of the pancreas. No other abnormalities were identified. The tumors are indicated by *white interrupted circles*. The pancreatic origin of the tumors was confirmed at surgery and by immunohistochemistry (see Fig. 4).

it was decided not to proceed to surgery but to continue surveillance. Two years later, she remained asymptomatic with normal plasma fasting gut hormones, but the pancreatic tumor had grown to 2.0 × 2.1 cm in size (Fig. 3A) and surgery was undertaken. A partial pancreatectomy was performed, without complications. Histology revealed features consistent with a PET of uncertain malignant potential (Fig. 4, A and B). Detailed immunostaining of the main tumor (Fig. 4, E, F, and I) was consistent with a nonfunctioning PET in which immunostaining for insulin and gastrin was absent, and less than 1% of cells showed immunostaining for glucagon, somatostatin, and pancreatic polypeptide. However, strong immunostaining for chromogranin A (Fig. 4I) and synaptophysin was observed. The tumor had loss of menin expression when compared with normal surrounding islets (Fig. 4, M and N), consistent with biallelic inactivation of the *MEN1* gene in the tumor cells. The remaining pancreas was found to contain microadenomas, which immunostained predominantly for glucagon, and to a lesser extent somatostatin, pancreatic polypeptide, and insulin, consistent with the complex multihormonal expression pattern previously reported in pancreatic microadenomas in MEN1 patients (11, 12). The patient remains well at 12 months of follow-up with normal glucose tolerance. MRI of the pituitary was consistent with a right-sided pituitary adenoma, and treatment with cabergoline restored a regular menstrual cycle and normoprolactinemia.

Case 2

A 7-yr-old girl (individual III.1; Fig. 2) known to have a family history of MEN1 was found to have inherited a nonsense *MEN1* mutation, Gln349Stop. Her father (individual II.3; Fig. 2) had died from a metastatic pancreatic tumor at age 33 yr. She was asymptomatic, and her height and weight were on the 25th and 10th centile, respectively. Cutaneous abnormalities associated with MEN1 were not observed. She was assessed annually, and at age 12 yr she remained asymptomatic and normocalcemic with normal plasma PTH concentrations and fasting plasma gut hor-

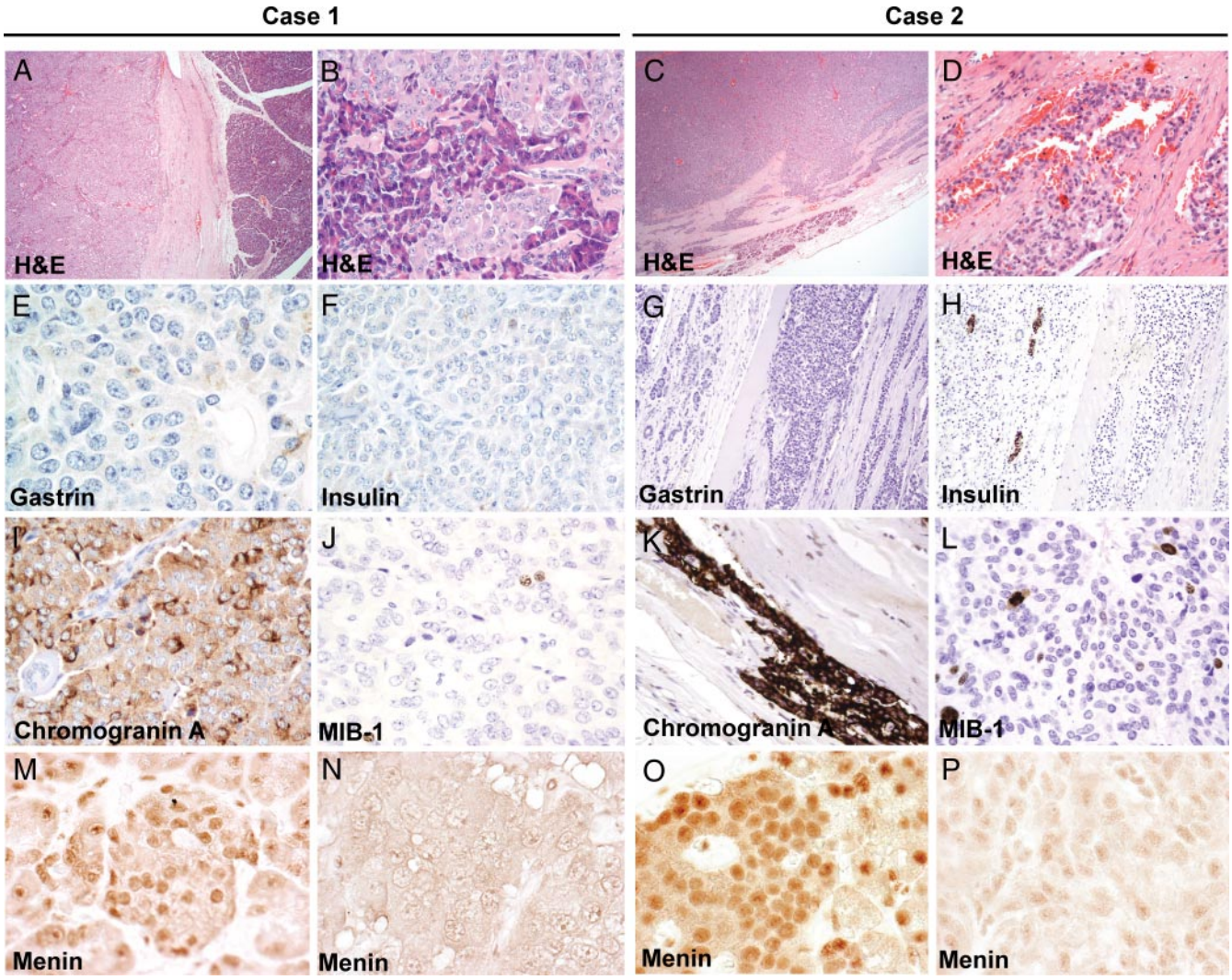

FIG. 4. Histology and immunostaining of pancreatic tumors from cases 1 and 2. H&E analysis (A–D) and immunostaining (E–P) are shown for case 1 (A, B, E, F, I, J, M, N) and case 2 (C, D, G, H, K, L, O, P). A, H&E examination of tumor from case 1 demonstrated a PET that was largely well circumscribed, but (B) focally the margin between tumor (paler cells) and normal pancreas was poorly defined. Immunostaining was consistent with a nonfunctioning PET because the tumor did not have significant expression of gastrointestinal peptides (results for gastrin and insulin are shown in panels E and F), but did contain chromogranin A (I). The proliferative index measured by MIB-1 (Ki-67) was low (J). Loss of menin expression was demonstrated in the PET; in the adjacent nontumorous pancreatic tissue nuclear menin expression is evident within pancreatic islets (M), whereas nuclear menin expression is lost within the tumor (N). C, In case 2, H&E examination revealed a well-differentiated and circumscribed PET within a capsule. D, A few tumor cells were seen within the endothelial lined spaces that were likely to be blood vessels. Immunostaining was consistent with a nonfunctioning PET because the tumor contained chromogranin A (K), but not gastrointestinal peptides (results for gastrin and insulin are shown in panels G and H). Proliferative index was focally up to 5% (L). Marked reduction of menin expression was evident in the tumor (P), when compared with surrounding pancreatic islets from adjacent nontumorous tissue (O).

mone concentrations in the normal range. However, interval MRI of the abdomen revealed a $3.8 \times 3.6 \times 3.3$ cm mass that was likely located in the distal body of the pancreas (Fig. 3B). MRI of the pituitary demonstrated a pituitary microadenoma, and this was not associated with elevations in serum prolactin, GH, IGF-I, ACTH, TSH, T_3, T_4, LH, FSH, or α- and β-subunits, consistent with a nonfunctioning pituitary microadenoma. There was no radiological evidence of local or distant spread of the pancreatic tumor, and a distal pancreatectomy with splenectomy was performed without complication. Histology demonstrated a well-differentiated PET (Fig. 4, C and D) within the distal pancreas, but with a mitotic rate of more than two mitoses per 10 high-power fields, which indicated the tumor to be of uncertain malignant potential (Fig. 4, C, D, and L). Immunostaining of the main tumor (Fig. 4, G, H, and K) was consistent with a nonfunctioning PET in which immunostaining for gastrin and insulin was absent, and less than 1% of cells showed immunostaining for glucagon, pancreatic polypeptide, and somatostatin. However, immunostaining for chromogranin A (Fig. 4K) and synaptophysin was observed. Menin immunostaining was markedly reduced in the tumor when compared with normal surrounding islets in the pancreas (Fig. 4, O and P).

Investigation of the remaining pancreas showed it to contain microadenomas, which immunostained predominantly for glucagon and pancreatic polypeptide, consistent with previous reports of microadenoma occurrence with multihormonal expression in pancreases from MEN1 patients (11, 12). The patient remains well postoperatively with a normal glucose tolerance and no evidence of tumor recurrence or distant metastases at the 12-month follow-up.

Thus, nonfunctioning PETs (Fig. 3, A and B) were found in two unrelated asymptomatic girls, cases 1 and 2, who had normal plasma fasting gut hormones and chromogranin A and B. Histology (Fig. 4, A–D) and immunohistochemical assessment (Fig. 4, E–P) of the tumors confirmed that these did not contain gastrointestinal hormones but did contain chromogranin A and synaptophysin in keeping with the neuroendocrine origin of these tumors (Fig. 4, E–L). In addition, menin expression was lost or markedly reduced in these tumors (Fig. 4, M–P). The occurrence of nonfunctioning PETs in such a young age group has not been previously reported.

Three other children (one male, two females) were found to have the following MEN1-associated tumors: a 14-yr-old girl had primary hyperparathyroidism and a prolactinoma; and a 12-yr-old girl and 14-yr-old boy had primary hyperparathyroidism. Seven children (four males, three females), with an age range of 6–16 yr remain tumor free. Thus, of the nine MEN1 associated tumors, six are hormonally active and result in primary hyperparathyroidism (n = 4) or microprolactinoma (n = 2), whereas three are nonfunctioning and comprised PETs (n = 2) and a pituitary microadenoma (n = 1).

Discussion

Our study has identified the occurrence of nonfunctioning PETs in young (<15 yr) patients with *MEN1* mutations. Previously, only functioning PETs, which include insulinoma and gastrinoma, have been reported in young children with *MEN1* mutations, with the earliest reported ages being 5 and 8 yr, respectively (8). These findings are of clinical importance because gastroenteropancreatic tumors have been reported to be the commonest cause of death in patients with MEN1, and these deaths occur at a considerably younger age than deaths from other causes (3, 13, 14). Furthermore, nonfunctioning PETs, have been reported to be associated with a poorer prognosis than other MEN1-associated PETs (*i.e.* insulinoma and gastrinoma) (8), although one study has reported that both nonfunctioning and functioning PETs rarely metastasize (11). Thus, the identification of nonfunctioning PETs in children and young adults is likely to be of clinical significance and may indicate a revision of the current consensus guidelines that recommend screening for enteropancreatic tumors, other than insulinoma, from the age of 20 yr (1).

The reported frequency of gastroenteropancreatic tumors in MEN1 varies considerably and is dependent on the populations studied and the diagnostic methods employed to identify them. Previous studies have reported the prevalence to be 30–80% (2), with functioning tumors being the most common. However, the prevalence of nonfunctioning PETs has been underestimated. The widespread implementation of screening programs has led to nonfunctioning PETs being diagnosed more frequently, with recent studies indicating that these tumors are the most common gastroenteropancreatic tumor associated with MEN1 (15–17). For example, one study identified 19% of MEN1 patients as having nonfunctioning PETs with an age-related penetrance of 3, 34, and 53% at the ages 20, 50, and 80 yr, respectively (15), and another study employing endoscopic ultrasonography has reported that 55% of asymptomatic MEN1 patients have nonfunctioning PETs (16). It is likely that nonfunctioning PETs constitute a heterogeneous group of tumors, although, to date, it has not been possible to define separate clinical behaviors within this group. Moreover, microadenomas (*i.e.* tumors smaller than 5 mm) that express multiple hormones, which include glucagon and pancreatic polypeptide, have been found in more than 90% of pancreases from MEN1 patients, and these are not associated with a clinical syndrome (11, 12), as observed in cases 1 and 2. Asymptomatic individuals with minor elevations of pancreatic peptides (*i.e.* 2-fold above the upper normal limit) and a radiologically identifiable tumor have typically been considered to have nonfunctioning PETs (8, 15, 18). Although some of these biochemical abnormalities may be attributable to small secretory tumors diagnosed before the presence of a clinically apparent syndrome, it is important to note that such biochemical abnormalities are common in MEN1 both in the presence and absence of identifiable PETs (16). Elevations of plasma pancreatic polypeptide have also been reported to occur frequently in asymptomatic individuals with PETs, and it remains unclear as to whether these have a prognosis different from other nonfunctioning PETs (17, 19, 20).

The goal of screening patients with MEN1 is to identify MEN1-associated tumors at an early stage and thereby reduce both the morbidity and mortality associated with these tumors. Biochemical and radiological abnormalities may precede the onset of clinical symptoms by 5–10 yr (19). The early identification of tumors may be of importance because up to 46% of deaths in patients with MEN1 have been reported to be due to MEN1-associated tumors, and these occurred by a mean age of 47 yr (3, 13, 14, 17).

Furthermore, the most common cause of death is reported to be PETs, which also account for some of the youngest deaths (3, 14, 17, 21). Life expectancy in MEN1 patients with nonfunctioning PETs is similarly reduced compared with those without PETs (43 *vs.* 61 yr) (15). In addition, the 10-yr survival rate for nonfunctioning PETs (62%) has been reported to be significantly less than both gastrinoma (82%) and insulinoma (91%) (16), although it is important to note that some metastases from occult duodenal microgastrinomas may have been incorrectly attributed to originate from nonfunctioning PETs (22, 23).

The optimum management of MEN1-associated nonfunctioning PETs remains controversial. The absence of accurate markers of malignancy makes the timing of surgical intervention difficult. One study has reported that larger primary tumors are associated with an increased risk of metastasis with 43% of patients with nonfunctioning tumors larger than 3 cm demonstrating synchronous metastases, 18% with tumors 2.1–3.0 cm, 10% with tumors 1.1–2.0 cm, and only 4% with tumors less than 10 cm (15). However, other studies have not found an association between the size of the PET and the presence of metastases (24, 25). Although such conflicting results might suggest a case for earlier intervention, the potential benefits of surgery in MEN1 patients must be weighed against the risks associated with pancreatic resection, which include a mortality rate of 4.8% and a significant rate of impaired glucose tolerance requiring antidiabetic medication postoperatively (26, 27). In addition, recent studies have reported that surgery for nonfunctioning PETs 2 cm or less may not be beneficial and that the rates of progression in tumors of 2 cm or less were similar between those who underwent surgery and those who did not (28), and that tumors less than 1.5 cm usually grow slowly and are associated with a low risk of metastasis (29). Furthermore, life expectancy in those with tumors of 2 cm or less was similar to that in MEN1 patients without PETs (28). Such studies (28, 29) suggest that surveillance as opposed to surgery for smaller tumors may be more appropriate. However, until further evidence is obtained, many centers have adopted a balance of the two approaches, suggesting surgical intervention for tumors of more than 2 cm or those demonstrating evidence of rapid tumor growth (15, 30).

In summary, our study has identified two unrelated children with nonfunctioning PETs associated with MEN1. Nonfunctioning PETs have previously not been reported in such a young age group with MEN1, but are increasingly recognized and are reported to be associated with malignancy and a poorer prognosis than other functioning PETs (13–17, 21). Our study suggests that appropriate radiological screening for PETs in children with MEN1 should be undertaken earlier than currently indicated by the guidelines and should be commenced by the age of 10 yr as opposed to the recommended 20 yr (1).

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