Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)

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Objective: The aim was to provide guidelines for evaluation, treatment, and genetic testing for multiple endocrine neoplasia type 1 (MEN1).

Participants: The group, which comprised 10 experts, including physicians, surgeons, and geneticists from international centers, received no corporate funding or remuneration.

Process: Guidelines were developed by reviews of peer-reviewed publications; a draft was prepared, reviewed, and rigorously revised at several stages; and agreed-upon revisions were incorporated.

Conclusions: MEN1 is an autosomal dominant disorder that is due to mutations in the tumor suppressor gene *MEN1*, which encodes a 610-amino acid protein, menin. Thus, the finding of MEN1 in a patient has important implications for family members because first-degree relatives have a 50% risk of developing the disease and can often be identified by *MEN1* mutational analysis. MEN1 is characterized by the occurrence of parathyroid, pancreatic islet, and anterior pituitary tumors. Some patients may also develop carcinoid tumors, adrenocortical tumors, meningiomas, facial angiofibromas, collagenomas, and lipomas. Patients with MEN1 have a decreased life expectancy, and the outcomes of current treatments, which are generally similar to those for the respective tumors occurring in non-MEN1 patients, are not as successful because of multiple tumors, which may be larger, more aggressive, and resistant to treatment, and the concurrence of metastases. The prognosis for MEN1 patients might be improved by presymptomatic tumor detection and undertaking treatment specific for MEN1 tumors. Thus, it is recommended that MEN1 patients and their families should be cared for by multidisciplinary teams comprising relevant specialists with experience in the diagnosis and treatment of patients with endocrine tumors. *(J Clin Endocrinol Metab* 97: 2990–3011, 2012)

The optimal therapy of gastrinoma remains controversial. Surgery for a nonmetastasizing gastrinoma arising within the pancreas may be curative and should be considered, as long as it is performed by an experienced endocrine surgeon (2|⊕⊕○○). However, most MEN1 patients will have multiple small submucosal duodenal gastrinomas, and the management of such tumors remains controversial. We suggest medical management using proton-pump inhibitors for the majority of patients (2|⊕⊕○○). However, in experienced surgical centers local excision of these tumors with lymph node dissection, duodenectomy, or less commonly duodenopancreatectomy may also be considered together with patient preferences, because such approaches may improve the cure rate (2|⊕⊕○○). Although Whipple pancreaticoduodenectomy provides the greatest likelihood of cure for gastrinoma in MEN1 patients, we do not suggest it for the majority of patients because it is associated with an increased operative mortality and long-term morbidity and because lesser operations in these patients are associated with excellent long-term survival (2|⊕⊕⊕○).

Medical therapies include proton-pump inhibitors and somatostatin analogs to suppress hyperacidity (1|⊕⊕⊕⊕). Periodic gastroscopic surveillance is indicated in those with hypergastrinemia for the identification of peptic ulcer disease and gastric carcinoid (2|⊕⊕○○).

The role of surgery for nonfunctioning pancreatic tumors is controversial. We suggest considering surgery for tumors that are more than 1 cm in size and/or demonstrate significant growth over 6–12 months (2|⊕⊕○○).

A histopathologist with expertise in NET should review all tumor tissues. Tumors should be classified according to the World Health Organization 2010 classification, Union for International Cancer Control TNM (7th edition), and the European Neuroendocrine Tumor Society site-specific T-staging system (1|⊕⊕⊕⊕).

Treatment of nonresectable tumor mass includes somatostatin analogs, biotherapy, targeted radionuclide therapy, locoregional treatments, and chemotherapy (1|⊕⊕⊕○).

Chemotherapy may be used for inoperable or metastatic pancreatic NET (1|⊕⊕⊕○). Sunitinib and everolimus may be considered for patients with advanced (inoperable or metastatic) progressive well-differentiated pancreatic NET (1|⊕⊕⊕○).

Pituitary tumors

Diagnosis

Biochemical screening for pituitary tumors, which will depend on clinical judgment and local resources, could include an annual assessment of plasma prolactin and IGF-I levels (2|⊕⊕⊕○), as well as MRI of the pituitary every 3–5 yr (2|⊕⊕○○). In patients with abnormal results,

hypothalamic pituitary testing should be undertaken to characterize further the nature of the pituitary lesion and its effects on the secretion of other pituitary hormones (1|⊕⊕⊕○).

Treatment

Treatment of MEN1-associated pituitary tumors is similar to that for non-MEN1 pituitary tumors and consists of appropriate medical therapy (*e.g.* dopamine agonists for prolactinoma; octreotide or lanreotide for somatotrophinomas) or selective transsphenoidal surgical hypophysectomy, with radiotherapy reserved for residual unresectable tumor tissue (1|⊕⊕⊕⊕).

Thymic, bronchopulmonary, and gastric NET

Diagnosis

Biochemical evaluation with urinary 5-hydroxyindoleacetic acid and chromogranin A is not helpful (1|⊕⊕⊕⊕).

CT or MRI of the chest every 1–2 yr is recommended for detection of thymic and bronchopulmonary carcinoid tumors (2|⊕○○○).

Gastroscopic examination (with biopsy) every 3 yr in those with hypergastrinemia for detection of peptic ulcer disease and gastric carcinoid type II is recommended (2|⊕⊕○○). Endoscopic ultrasound and somatostatin receptor scintigraphy may aid the diagnosis (1|⊕⊕⊕⊕).

Treatment

Curative surgery, where possible, is the treatment of choice for thymic and bronchial carcinoid tumors (1|⊕⊕⊕⊕).

Where disease is advanced and curative surgery is not possible, additional therapies include radiotherapy and chemotherapy (2|⊕○○○).

The optimal treatment of type II gastric carcinoids has not been established. Small (<10 mm) lesions may remain under endoscopic surveillance. Larger tumors require endoscopic resection or local resection with partial or total gastrectomy. Indications for somatostatin analogs in the treatment of type II gastric carcinoids are not defined (2|⊕⊕○○).

Adrenal tumors

Diagnosis

Minimal screening should comprise abdominal imaging by CT or MRI every 3 yr (2|⊕⊕○○). Adrenal lesions should remain under radiological surveillance and should be assessed for malignant features (1|⊕⊕⊕○).

Images should be reviewed by a radiologist with expertise in adrenal imaging (1|⊕⊕⊕○).

TABLE 1. MEN syndromes and their characteristic tumors and associated genetic abnormalities

Type (chromosome location)	Tumors (estimated penetrance)	Gene, most frequently mutated codons
MEN1 (11q13)	Parathyroid adenoma (90%) Enteropancreatic tumor (30–70%): gastrinoma (40%), insulinoma (10%), nonfunctioning and PPoma (20–55%), glucagonoma (<1%), VIPoma (<1%) Pituitary adenoma (30–40%): prolactinoma (20%), somatotropinoma (10%), corticotropinoma (<5%), nonfunctioning (<5%) Associated tumors: adrenal cortical tumor (40%), pheochromocytoma (<1%), bronchopulmonary NET (2%), thymic NET (2%), gastric NET (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (8%)	*MEN1* 83/84, 4-bp del (≈4%) 119, 3-bp del (≈3%) 209–211, 4-bp del (≈8%) 418, 3-bp del (≈4%) 514–516, del or ins (≈7%) Intron 4 ss, (≈10%)
MEN2 (10 cen-10q11.2) MEN2A	MTC (90%) Pheochromocytoma (50%) Parathyroid adenoma (20–30%)	*RET* 634, missense e.g. Cys→Arg (~85%)
MTC only	MTC (100%)	*RET* 618, missense (>50%)
MEN2B (also known as MEN3)	MTC (>90%) Pheochromocytoma (40–50%) Associated abnormalities (40–50%) Mucosal neuromas Marfanoid habitus Medullated corneal nerve fibers Megacolon	*RET* 918, Met→Thr (>95%)
MEN4 (12p13)	Parathyroid adenoma[a] Pituitary adenoma[a] Reproduction organ tumors (e.g. testicular cancer, neuroendocrine cervical carcinoma)[a] ?Adrenal + renal tumors[a]	*CDKN1B* No common mutations identified to date

Autosomal-dominant inheritance of the MEN syndromes has been established. del, Deletion; ins, insertion; PPoma, pancreatic polypeptide-secreting tumor. [Adapted from R. V. Thakker: Multiple endocrine neoplasia—syndromes of the twentieth century. *J Clin Endocrinol Metab* 83: 2617–2620, 1998 (6), with permission. © The Endocrine Society.]

[a] Insufficient numbers reported to provide prevalence information.

1). Parathyroid tumors, resulting in primary hyperparathyroidism, are the most common feature of MEN1 and occur in approximately 95% of MEN1 patients (1, 4, 5). Pancreatic islet tumors, also referred to as pancreatic NET, consist of gastrinomas, insulinomas, glucagonomas, vasoactive intestinal polypeptidomas (VIPomas), and nonfunctioning pancreatic NET, and these occur in approximately 40–70% of MEN1 patients (1, 8–10); and anterior pituitary tumors, consisting of prolactinomas, somatotrophinomas, corticotrophinomas, and nonfunctioning adenomas, occur in approximately 30–40% of patients (1, 11–13). In addition, some MEN1 patients may also develop adrenocortical tumors, lipomas, carcinoid tumors, facial angiofibromas, collagenomas, and meningiomas (Table 1) (1, 14). Combinations of these affected glands and their respective pathological features (for example, hyperplasia or single or multiple adenomas of the parathyroid glands) may differ in members of the same

family and even between identical twins (15). MEN1 is inherited as an autosomal-dominant disorder in such families, but a nonfamilial (*i.e.* sporadic) form may have developed in 8 to 14% of patients with MEN1, and molecular genetic studies have confirmed the occurrence of *de novo* mutations of the MEN1 gene in approximately 10% of all patients with MEN1 (4, 16). In the absence of treatment, endocrine tumors are associated with an earlier mortality in patients with MEN1. Thus, untreated patients with MEN1 have a decreased life expectancy with a 50% probability of death by the age of 50 yr, and the cause of death in 50–70% of patients with MEN1 is usually a malignant tumor process or sequelae of the disease (17–20). Although the prognosis of patients with MEN1 improved considerably after the introduction of acid-suppressive therapies for the treatment of gastrinoma and the Zollinger-Ellison syndrome (ZES), results of a multicenter study from France and Belgium have suggested that ap-

Treatment

Surgical removal of the abnormally overactive parathyroid glands in patients with MEN1 is the definitive treatment, but it is controversial whether to perform subtotal (3.5 glands) or total parathyroidectomy and whether surgery should be performed at an early or late stage of the disease. Open bilateral neck exploration is recommended, as opposed to minimally invasive parathyroidectomy, because all four parathyroid glands are usually affected with multiple adenomas or hyperplasia, although this histological distinction may be difficult; parathyroid carcinoma is rarely found in patients with MEN1, and to date only three patients with germline *MEN1* mutations have been reported to have parathyroid carcinoma (31, 32). Subtotal parathyroidectomy (*i.e.* removal of ≤3.5 glands) has resulted in persistent or recurrent hypercalcemia within 10 to 12 yr after surgery in 40 to 60% of patients, and in hypocalcemia requiring long-term therapy with vitamin D or its active metabolite calcitriol in 10 to 30% of patients with MEN1 (26, 27, 33, 34). These recurrence rates are markedly higher than those observed after parathyroidectomy in patients who do not have MEN1, in whom recurrent hypercalcemia occurs in 4 to 16% and hypocalcemia in 1 to 8% of patients. For total parathyroidectomy with autotransplantation, both fresh and cryopreserved parathyroid tissue has been used. However, this procedure is dependent on the vitality of cryopreserved cells, which decreases with the time interval from cryopreservation to autotransplantation (35). An alternate approach is intraoperative monitoring of PTH by rapid assay during surgery to determine successful removal of hyperfunctioning parathyroid tissue and to help with the decision to implant parathyroid tissue in the forearm (35). The presence of functioning autotransplanted parathyroid tissue leads to recurrent hypercalcemia in more than 50% of patients with MEN1, and surgical removal of the transplanted grafts is not always successful. To improve the outcome of parathyroid autotransplantation, one study has reported that the use of less tissue (*e.g.* approximately 10 fresh parathyroid pieces 1 mm^3 in size) helps to reduce both the recurrence of hypercalcemia and the hypoparathyroidism rates (35). Autotransplantation of parathyroid tissue to the forearm may be beneficial over subtotal parathyroidectomy because it avoids the necessity for vitamin D medication for the patient. If hypercalcemia recurs, the transplanted parathyroid tissue can be removed under local anesthesia, and reoperation of the neck under general anesthesia can be avoided (35). Subtotal parathyroidectomy is suggested as the initial treatment of primary hyperparathyroidism in MEN1, but total parathyroidectomy with autotransplantation may also be considered in some cases. Total parathyroidectomy may be reserved for those with extensive disease either at first or at repeat surgery. Persistent hypocalcemia is treated with oral calcitriol (1,25-dihydroxyvitamin D), although management of hypoparathyroidism can be challenging in some patients, even with the use of vitamin D and calcium replacement. One recommendation is that parathyroidectomy be reserved for symptomatic hypercalcemic patients with MEN1 and that asymptomatic hypercalcemic patients with MEN1 do not undergo parathyroid surgery but have regular assessment for symptom onset and complications, at which time subtotal parathyroidectomy with transcervical thymectomy should be undertaken (34, 36). However, the timing of surgery requires careful consideration, and factors such as surgical experience, availability of facilities for long-term regular serum calcium monitoring, accessibility of calcitriol (or vitamin D analogs), and patient preference should be taken into account. Calcimimetics (*e.g.* cinacalcet) that act via the calcium-sensing receptor have been used to treat primary hyperparathyroidism in some patients in whom surgery had either failed or was contraindicated (37).

Pancreatic islet cell tumors (NET)

The incidence of pancreatic NET in patients with MEN1 varies from 30 to 80% in different series (1, 4, 8, 9, 38, 39). Many of these tumors (Table 1) secrete excessive amounts of hormone [for example, gastrin, insulin, or vasoactive intestinal polypeptide (VIP)] and are associated with distinct clinical syndromes, although some (for example, those secreting pancreatic polypeptide) may not be associated with clinical manifestations or may be nonsecretory (*i.e.* nonfunctioning). These pancreatic NET have an earlier age of onset in patients with MEN1 than in patients without MEN1 (1, 7, 40, 41). Given that MEN1-associated pancreatic NET are frequently multiple and their behavior uncertain, their accurate diagnosis and management presents significant challenges. For example, it cannot be assumed that tumor visualization on imaging studies correlates with the site of hormone excess in functioning tumor syndromes (*e.g.* gastrinoma, insulinoma).

Gastrinoma

Clinical manifestations and diagnosis

Gastrin-secreting tumors (gastrinomas) are associated with marked gastric acid production and recurrent peptic ulcerations, a combination also referred to as the ZES. Gastrinomas represent more than 50% of all neuroendocrine duodenopancreatic tumors in patients with MEN1 (Table 1), and approximately 20% of patients with gastrinomas will have MEN1 (1, 23, 38, 42, 43). Gastrinomas frequently appear as small (<5 mm in diameter), multiple nodular lesions arising deep in the mucosa. Gastrinomas

tin analogs, octreotide or lanreotide; hepatic artery embolization; administration of human leukocyte interferon; and removal of all resectable tumor have been occasionally successful (4).

Insulinoma

Clinical manifestations and diagnosis

Insulinomas, β-islet cell tumors that secrete insulin, represent 10 to 30% of all pancreatic tumors in patients with MEN1 (Table 1). Insulinomas are usually a single lesion more than 5 mm in diameter, but they can be associated with other neuroendocrine pancreatic tumors at the time of diagnosis in 10% of patients with MEN1, and the two tumors may arise at different times. Insulinomas occur more often in patients with MEN1 who are younger than 40 yr, and many of them arise in individuals younger than 20 yr, whereas in patients without MEN1, insulinomas generally occur in those older than 40 yr (1, 4, 7, 50, 51). Insulinomas may be the first manifestation of MEN1 in 10% of patients, and approximately 4% of patients with insulinomas will have MEN1 (1, 4). Patients with an insulinoma present with hypoglycemic symptoms that develop after a fast or exertion and improve after glucose intake. The most reliable test is a supervised 72-h fast, during which increased plasma insulin concentration in association with hypoglycemia is demonstrated. Elevated circulating C-peptide and proinsulin concentrations may establish the diagnosis (1, 4). It also is important to exclude the presence of oral hypoglycemic agents (*e.g.* sulfonylureas) in plasma and urine samples obtained during hypoglycemia evaluation. Preoperative localization with endoscopic ultrasonography, MRI, CT scanning, or celiac axis angiography, selective intraarterial stimulation with hepatic venous sampling, and intraoperative direct pancreatic ultrasonography is likely to improve the success rate of surgery (1, 4, 45).

Treatment

Medical treatment, which consists of frequent carbohydrate meals and diazoxide or octreotide, is not always successful, and surgery is the optimal treatment (1, 4). Surgical treatment, which ranges from enucleation of a single tumor to distal pancreatectomy or partial pancreatectomy, or excision of all the macroscopic pancreatic tumors with enucleation of nodules in the remaining pancreas has been curative in many patients. In addition, monitoring the insulin/glucose ratio during surgery has been reported to be of value in assessing successful removal of the insulinoma (52). Chemotherapy consisting of streptozotocin, 5-flurouracil, and doxorubicin or hepatic artery embolization has been used for metastatic disease (1, 4).

Glucagonoma

Clinical manifestations and diagnosis

Glucagonomas, glucagon-secreting pancreatic tumors, occur in fewer than 3% of patients with MEN1, although some nonfunctioning pancreatic NET may immunostain for glucagon (Table 1) (1, 4, 39, 52). The characteristic clinical manifestations of a skin rash (necrolytic migratory erythema), weight loss, anemia, and stomatitis may be absent, and the presence of the tumor may have been detected in an asymptomatic patient with MEN1 undergoing pancreatic imaging or detected by glucose intolerance and hyperglucagonemia.

Treatment

The tail of the pancreas is the most frequent site for glucagonomas, and surgical removal is the treatment of choice. However, treatment may be difficult because approximately 50 to 80% of patients have metastases at the time of diagnosis (28). Medical treatment with somatostatin analogs (*e.g.* octreotide or lanreotide), or chemotherapy with streptozotocin, and 5-fluorouracil, or dimethyltriazeno-imidazole carboxamide has been successful in some patients, and hepatic artery embolization has been used to treat metastatic disease (1, 4).

VIP-secreting tumors (VIPomas)

Clinical manifestations and diagnosis

VIPomas have been reported in only a few patients with MEN1 (Table 1) who develop watery diarrhea, hypokalemia, and achlorhydria (WDHA). This clinical syndrome has been referred to as the Verner-Morrison syndrome, the WDHA syndrome, or the VIPoma syndrome (28). The diagnosis is established by excluding laxative and diuretic abuse, by confirming a stool volume in excess of 0.5 to 1.0 liters/d during a fast, and by documenting a markedly increased plasma VIP concentration.

Treatment

Surgical management of VIPomas, which are mostly located in the tail of the pancreas, has been curative (1, 4). However, in patients with unresectable tumor, treatment with somatostatin analogs such as octreotide and lanreotide, streptozotocin with 5-fluorouracil, corticosteroids, indomethacin, metoclopramide, and lithium carbonate has proved beneficial, and hepatic artery embolization has been useful for the treatment of metastases (1, 4).

Nonfunctioning pancreatic NET

Clinical manifestations and diagnosis

Nonfunctioning pancreatic tumors are not associated with a clinical syndrome. These include those associated

proach requires an informed patient choice. In addition, when considering these recommendations, it is important to consider that occult metastatic disease (*i.e.* tumors not detected by imaging investigations) may be present in a substantial proportion of these patients at the time of initial presentation, and that after surgery further tumors are likely to recur in remnant pancreatic tissue (39, 58).

Inhibitors of tyrosine kinase receptors (TKR) and of the mammalian target of rapamycin (mTOR) signaling pathway have been reported to be effective in treating pancreatic NET (59, 60). Pancreatic NET may express TKR, vascular endothelial growth factor receptor, and platelet-derived growth factor receptors; some tumors may exhibit IGF-mediated autocrine activation of the mTOR signaling pathway, a serine-threonine kinase that stimulates cell growth proliferation and angiogenesis. Treatment of patients with advanced, well-differentiated pancreatic NET with sunitinib malate, which inhibits TKR, led to increased overall survival and a doubling in progression-free survival when compared with patients receiving placebo (11.4 *vs.* 5.5 months; $P < 0.001$). Treatment of patients with advanced, low-grade or intermediate-grade pancreatic NET with everolimus, an mTOR inhibitor, also led to a doubling of median progression-free survival when compared with patients receiving placebo (11.0 *vs.* 4.6 months; $P < 0.001$) (59). These two studies mainly included non-MEN1 patients; for example, in the sunitinib study, which comprised 171 patients, there were only two MEN1 patients, and none were in the treatment arm (60); in the everolimus study, which had 410 patients, details of MEN1 status were not provided. Nevertheless, these two studies represent major advances in treatment of malignant pancreatic NET in non-MEN1 patients, and it seems highly plausible that these results can be extrapolated to MEN1 patients harboring pancreatic NET.

Other pancreatic NET

NET secreting GHRH, or GHRHomas, have been reported in some patients with MEN1, and approximately 33% of patients with GHRHomas will have other MEN1-related tumors (4, 61). GHRHomas may be diagnosed by finding elevated circulating concentrations of GH and GHRH. More than 50% of GHRHomas arise in the lung, 30% arise in the pancreas, and 10% are found in the small intestine. Surgical removal is the treatment of choice for these tumors. Somatostatinomas, which secrete somatostatin that inhibits GH secretion, result in hyperglycemia, cholelithiasis, low acid output, steatorrhea, diarrhea, abdominal pain, anemia, and weight loss, also referred to as the somatostatinoma syndrome. Although 7% of pancreatic NET in patients with MEN1 secrete somatostatin, the somatostatinoma syndrome does not appear to have been reported in a patient with MEN1 (4, 17).

Pituitary tumors

Clinical manifestations and diagnosis

The incidence of pituitary tumors in patients with MEN1 varies from 15 to 50% in different series (Table 1) (11, 12, 50, 62, 63). These occur as early as 5 yr of age or as late as the ninth decade, and the mean ± sd age of onset has been reported to be 38.0 ± 15.3 yr (12, 64). MEN1 pituitary adenomas have been reported to occur more frequently in women than men, and significantly more of these were macroadenomas, *i.e.* diameter greater than 1 cm (MEN1 *vs.* non-MEN1 macroadenomas = 85 *vs.* 42%; $P < 0.001$) (12). Moreover, about one third of these pituitary tumors showed at histology invasive features such as infiltration of tumor cells through surrounding normal juxtatumoral pituitary tissue. However, no specific histological parameters were reported to differentiate between MEN1 and non-MEN1 pituitary tumors (11). Despite the apparent larger size, more aggressive behavior and reduced response to therapy, no increased prevalence of pituitary carcinoma is observed in MEN1 (63). Approximately 60% of MEN1-associated pituitary tumors secrete prolactin, fewer than 25% secrete GH, 5% secrete ACTH, and the remainder appear to be nonfunctioning, with some secreting glycoprotein subunits (Table 1) (11, 62, 63), although the occurrence of nonfunctioning adenomas has been reported to be higher at approximately 25% in a large kindred from Tasmania (65). However, pituitary tumors derived from MEN1 patients may exhibit immunoreactivity to several hormones, and in particular there is a higher occurrence of somatolactotrophinomas (11). Indeed, plurihormonal expression is more frequently observed in MEN1-associated pituitary tumors compared with non-MEN1 pituitary tumors (11, 12). Pituitary tumors, which are usually prolactinomas, may be the first manifestation of MEN1 in approximately 15% of patients, and somatotrophinomas occur more often in patients older than 40 yr (4, 12, 50), although there does not appear to be any clear genotype-phenotype correlation (11). Fewer than 3% of patients with anterior pituitary tumors will have MEN1 (63, 66). Clinical manifestations of these tumors in patients with MEN1 are similar to those in patients with sporadic pituitary tumors without MEN1 and depend on the hormone secreted and the size of the pituitary tumor. Thus, patients may have symptoms of hyperprolactinemia (*e.g.* amenorrhea, infertility, and galactorrhea in women, and impotence and infertility in men) or have acromegaly or Cushing's disease. In addition, enlarging pituitary tumors may compress adjacent structures such as the optic chiasm or normal pituitary

as octreotide or lanreotide, has resulted in regression of these ECLomas (72, 74, 75).

Adrenocortical tumors

Clinical manifestations and diagnosis

The incidence of asymptomatic adrenocortical tumors in patients with MEN1 is reported to be 20–73%, depending on the radiological screening methods employed (Table 1) (45, 76–78). Most of these tumors, which include cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, or carcinomas, are nonfunctioning (76). Indeed, less than 10% of patients with enlarged adrenal glands have hormonal hypersecretion, and among these, primary hyperaldosteronism and ACTH-independent Cushing's syndrome are the most commonly encountered (76). Occasionally, hyperandrogenemia may occur in association with adrenocortical carcinoma, and the occurrence of pheochromocytoma in association with MEN1 is rare. Biochemical investigation (*e.g.* plasma renin and aldosterone concentrations, low-dose dexamethasone suppression test, urinary catecholamines and/or metanephrines) should be undertaken for those with symptoms or signs suggestive of functioning adrenal tumors, or for those with tumors larger than 1 cm. The incidence of adrenocortical carcinoma is reported to be approximately 1% in MEN1 patients but increases to approximately 13% in MEN1 patients with adrenal tumors larger than 1 cm (76). Thus, it is important that MEN1 patients with adrenal tumors are offered an annual imaging screen (Table 2) (76–78), and tumors that display atypical radiological characteristics (*e.g.* increased Hounsfield unit on unenhanced CT scan), significant growth, or are larger than 4 cm are considered for surgical removal.

Treatment

Consensus has not been reached about the management of MEN1-associated nonfunctioning tumors because the majority of nonfunctioning adrenal tumors are benign. However, the risk of malignancy is increased if the tumor has a diameter greater than 4 cm, although adrenocortical carcinomas have been identified in tumors of less than 4 cm in patients with MEN1. We therefore suggest surgery for adrenal tumors that: are more than 4 cm in diameter; have atypical or suspicious radiological features and are 1–4 cm in diameter; or show significant measurable growth over a 6-month interval (76–78). The treatment of functioning (*i.e.* secreting) adrenal tumors in MEN1 patients is similar to that for tumors occurring in non-MEN1 patients.

Meningioma

Central nervous system tumors including ependymomas, schwannomas, and meningiomas have been reported in MEN1 patients (Table 1) (14). Meningiomas were found in less than 10% of MEN1 patients (Table 1) who had other clinical manifestations of MEN1 (*e.g.* primary hyperparathyroidism) for more than 15 yr. The majority of meningiomas were not associated with symptoms, and 60% did not enlarge (14). The treatment of MEN1-associated meningiomas is similar to that occurring in non-MEN1 patients.

Cutaneous manifestations of MEN1

Lipomas

Subcutaneous lipomas may occur in more than 33% of patients with MEN1 (Table 1) and are frequently multiple. In addition, visceral, pleural, or retroperitoneal lipomas may occur in patients with MEN1 (1). Management is conservative. However, when surgically removed for cosmetic reasons, they typically do not recur.

Facial angiofibromas and collagenomas

Studies of patients with MEN1 have revealed that the occurrence of multiple facial angiofibromas may range from 22 to 88%, and occurrence of collagenomas may range from 0 to 72% (Table 1) (4, 79). These cutaneous findings, which occur with a higher frequency in patients with MEN1, may provide a useful means for possible presymptomatic diagnosis of MEN1 in the relatives of a patient with MEN1. Treatment for these cutaneous lesions is usually not required.

Thyroid tumors

Thyroid tumors comprising adenomas, colloid goiters, and carcinomas have been reported to occur in more than 25% of patients with MEN1. However, the prevalence of thyroid disorders in the general population is high, and it has been suggested that the association of thyroid abnormalities in patients with MEN1 may be incidental and not significant. The treatment of thyroid tumors in MEN1 patients is similar to that for non-MEN1 patients.

Genetic testing and screening in MEN1

MEN1 gene

The *MEN1* gene is located on chromosome 11q13 and consists of 10 exons, which encode a 610-amino acid protein, menin (80, 81), that regulates transcription, genome stability, cell division, and proliferation (4, 16). However, the precise role of menin in tumorigenesis as well as new therapeutic targets, remains to be established. Inheritance of a germline *MEN1* mutation predisposes an individual to developing a tumor that arises after a somatic mutation, which may be a point mutation or more commonly a deletion, leading to loss of heterozygosity (LOH) in the tumor DNA, consistent with the Knudson two-hit hypothesis and a

FIHP patients and particularly deletions, such as the 4 bp, involving codons 83–84, which are identical to those observed in MEN1 patients, makes it difficult to establish an unequivocal phenotype-genotype correlation. However, the sole occurrence of parathyroid tumors in these FIHP families that harbor *MEN1* mutations, similar to those found in other families with MEN1, is remarkable, and mechanisms that determine the altered phenotypic expressions of these mutations remain to be elucidated. MEN1 families with the Burin or prolactinoma variant, which are characterized by a high occurrence of prolactinomas and a low occurrence of gastrinomas (85–87), harbor nonsense mutations (Tyr312Stop and Arg460Stop), and a MEN1 kindred from Tasmania, in whom there was an absence of somatotrophinomas (88), has been reported to have a splice site mutation (c.446−3c→g).

MEN1 phenocopies and mutation in other genes

Approximately 5 to 25% of patients with MEN1 may not have mutations of the *MEN1* gene. This variability in detecting *MEN1* mutations may partly be attributable to differences in methods used to identify the mutations; for example, most studies do not systematically examine for large gene deletions, which may be found in up to 33% of patients who do not have coding region mutations (89). In addition, this variability may be due to phenotype ascertainment because some studies have included nonfamilial (*i.e.* sporadic) patients who may have developed only two (or fewer) endocrine tumors, and the detection rate for *MEN1* mutations in these patients was found to be less than 5% (82). Such patients with MEN1-associated tumors but without *MEN1* mutations may represent phenocopies or have mutations involving other genes. Phenocopy refers to the development of disease manifestations usually associated with mutations of a particular gene but instead are due to another etiology, and the occurrence of phenocopies has been reported in 5–10% of MEN1 kindreds (21, 88, 90). These phenocopies occurred in two settings—first, in the context of familial MEN1 (Fig. 1), in which a patient with one MEN1-associated tumor, *e.g.* a prolactinoma, did not have the familial mutation; and second, in the context of clinical MEN1, in which patients with two MEN1-associated tumors, who did not have an *MEN1* mutation, were demonstrated to have involvement of other genes. These genes may include: *CDC73*, which encodes parafibromin, whose mutations result in the hyperparathyroid-jaw tumor (HPT-JT) syndrome; the *CaSR*, whose mutations result in familial benign hypocalciuric hypercalcemia (FBHH) (90); and the aryl hydrocarbon receptor-interacting protein (*AIP*), a tumor suppressor located on chromosome 11q13 whose mutations are associated with fa-

milial isolated pituitary adenomas (FIPA) (91). FIPA, which may account for approximately 2.5% of all pituitary adenomas, constitutes a heterogeneous disorder characterized by familial pituitary adenomas that are most commonly somatotrophinomas, but may also be prolactinomas, ACTH-secreting and nonfunctioning pituitary adenomas (92, 93); and *AIP* mutations may occur in approximately 20% of FIPA patients and approximately 30–50% of those with familial acromegaly (94–96). The occurrence of MEN1 phenocopies may confound the diagnosis of MEN1 (Fig. 1) in an individual, and it therefore appears advisable to offer genetic testing to determine the *MEN1* mutation status to symptomatic family members within a MEN1 kindred, as well as to all index cases (*i.e.* patient) with two or more endocrine tumors. If a *MEN1* mutation is not identified in the index case with two or more endocrine tumors, then clinical and genetic tests for other disorders such as HPT-JT, FBHH, or FIPA should be considered because these patients may represent phenocopies for MEN1 (Fig. 2).

The involvement of another gene, *CDKN1B*, which encodes the 196-amino acid cyclin-dependent kinase inhibitor p27kip1, has also been reported by studies of unrelated patients who did not have *MEN1* mutations but did have MEN1-associated tumors (66, 97, 98). *CDKN1B* mutations have been reported in approximately 1.5% of these patients and their families, and this condition has been referred to as MEN4 (Table 1). In addition, germline mutations of the cyclin-dependent kinase inhibitors p15, p18, and p21 may be probable causes of MEN1 in approximately 1, 0.5, and 0.5% of patients, respectively (99).

MEN1 *mutational analysis in clinical practice*

MEN1 mutational analysis is helpful in clinical practice in several ways that include: 1) confirmation of the clinical diagnosis; 2) identification of family members who harbor the *MEN1* mutation and require screening for tumor detection and early/appropriate treatment; and 3) identification of the 50% of family members who do not harbor the familial germline *MEN1* mutation and can therefore be reassured and alleviated of the anxiety burden of developing future tumors. This latter aspect cannot be overemphasized because it helps to reduce the cost to the individuals and their children and also to the health services in not having to undertake unnecessary biochemical and radiological investigations (Table 2) (21). Thus, *MEN1* mutational analysis can be useful in clinical practice (Table 3).

Indications for MEN1 *mutational analysis*

MEN1 mutational analysis should be undertaken in: 1) an index case with two or more MEN1-associated endocrine tumors (*i.e.* parathyroid, pancreatic, or pituitary tu-

TABLE 3. Suggested approach for *MEN1* mutational analysis in a clinical setting

Value in clinical setting
  Aid in confirming the diagnosis
  Identify mutation carriers in a family for screening and
    development of tumors, thereby facilitating early
    treatment
  Identify the 50% of family members who do not harbor the
    MEN1 mutation, thereby alleviating the anxiety and
    burden of disease from them and their progeny
Who should be tested?
  In an index case
    Meeting the clinical criteria for MEN1 (*i.e.* two or more
      MEN1-associated tumors or a diagnosis of familial
      MEN1)
    Suspicious (*i.e.* multiple parathyroid adenomas before the
      age of 40 yr; recurrent hyperparathyroidism; gastrinoma
      or multiple pancreatic NET at any age) or atypical for
      MEN1 (*i.e.* development of two nonclassical MEN1-
      associated tumors, *e.g.* parathyroid and adrenal tumor)
  A first-degree relative of family member with known *MEN1*
    mutation
    Asymptomatic first-degree relative
    First-degree relative with familial MEN1 (*i.e.* one MEN1-
      associated tumor)
When should testing be undertaken?
  As early as possible (*e.g.* before 5 yr of age for asymptomatic
    individuals)
Where should test be performed?
  In accredited department/laboratory undertaking DNA
    testing of *MEN1* gene

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the diagnosis (Fig. 1), and therefore we suggest that MEN1 family members with one MEN1-associated tumor should be offered MEN1 mutation analysis.

MEN1 *mutational analysis in young patients with nonfamilial single endocrine tumors*

MEN1 germline mutational analysis should be considered in those presenting at an early age with a single, apparently sporadic MEN1-associated tumor (Table 3). The occurrence of germline *MEN1* mutations in all patients with sporadic, nonfamilial parathyroid adenomas is 1%; in gastrinomas, 5%; in prolactinomas, 1%; and in foregut carcinoids, 2%. Investigations by two studies (100, 101) for germline *MEN1* mutations in patients developing nonfamilial (*i.e.* sporadic) parathyroid tumors before the age of 40 yr has found the occurrence of such mutations in only three of 36 patients. All three of these patients had multigland parathyroid disease, whereas the majority (~95%) of the patients without *MEN1* mutations had solitary parathyroid adenomas. We suggest performing *MEN1* mutational testing in patients who are below 40 yr of age and have primary hyperparathyroidism due to multigland disease. The occurrence rates of germline *MEN1* mutations in individuals presenting with a single apparent nonfamilial (*i.e.* sporadic) pancreatic NET at similarly

younger age has not been established, and we suggest that *MEN1* mutational analysis should also be considered in those with gastrinoma or multiple pancreatic NET.

Detection of MEN1 tumors

Biochemical screening for the development of MEN1 tumors in asymptomatic members of families with MEN1 is likely to be of benefit in as much as earlier diagnosis and treatment of these tumors may help reduce morbidity and mortality (Fig. 2). Age-related penetrance (*i.e.* the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) has been ascertained, and the mutation appears to be nonpenetrant in those younger than 5 yr (1, 4, 64). Thereafter, the mutant *MEN1* gene has a high penetrance, more than 50% penetrant by 20 yr of age and more than 95% by 40 yr (1, 4, 7). Screening for MEN1 tumors is difficult because clinical and biochemical manifestations in members of any one family are not uniformly similar. Attempts to screen for development of MEN1 tumors in the asymptomatic relatives of an affected individual have depended largely on measuring serum concentrations of calcium, gastrointestinal hormones (*e.g.* gastrin), prolactin, and IGF-I, as well as on abdominal and pituitary imaging (Table 2). Parathyroid overactivity causing hypercalcemia is almost invariably the first manifestation of the disorder and has become a useful and easy biochemical screening investigation. In addition, hyperprolactinemia, which may be asymptomatic, may represent the first manifestation in approximately 15% of patients and may thus also be a helpful and easy biochemical screening investigation. Pancreatic involvement in asymptomatic individuals has been detected by measuring fasting plasma concentrations of gastrin, pancreatic polypeptide, glucagon, and chromogranin A and by abdominal imaging (4, 102).

We suggest that individuals at high risk for MEN1 (*i.e.* mutant gene carriers) undergo biochemical screening (Fig. 2) at least once per annum and also have baseline pituitary and abdominal imaging (*e.g.* MRI or CT), which should then be repeated at 1- to 3-yr intervals (Table 2). Screening should possibly commence in early childhood because the disease has developed in some individuals by the age of 5 yr, and it should be repeated throughout life because the disease may not manifest in some individuals until the eighth decade. Screening history and physical examination should be directed toward eliciting symptoms and signs of hypercalcemia, nephrolithiasis, peptic ulcer disease, neuroglycopenia, hypopituitarism, galactorrhea and amenorrhea in women, acromegaly, Cushing's disease, and visual field loss and the presence of sc lipomas, angiofibromas, and collagenomas. We suggest that biochemical screening should include estimations of serum calcium, PTH, gastrointestinal hormones (*e.g.* gastrin,

site with MLL (105, 106). Such further studies may help to identify other analogs that could represent future pharmacological treatments for MEN1 tumors. Another possible approach is to undertake molecular phenotyping of tumors because this may provide important insights that could guide treatment; for example, molecular phenotyping of pancreatic NET could identify those tumors with an activated mTOR pathway and which are reported to be associated with a poor prognosis, so that earlier treatment with mTOR inhibitors may be started and its effect on clinical outcomes assessed. In addition, non-MEN1 patients whose pancreatic NET have MEN1 or DAXX/ATRX mutations have a better prognosis than those with mutations of genes within the mTOR signaling pathway (83), and this finding requires a prospective evaluation in MEN1 patients. Thus, it is important that research efforts are encouraged, including the establishment of biobanks of MEN1-associated tumors. Finally, patients should be made aware of the importance of ongoing research and encouraged to engage in these studies, consistent with the goal of providing personalized therapies.

Web sites of centers offering MEN1 genetic testing

Contact information for some centers offering genetic testing for MEN1 can be found on the following web sites: http://www.ncbi.nlm.nih.gov/sites/GeneTests/ (giving details of centers in Canada, Denmark, Greece, Israel, Japan, and United States); http://www.orpha.net/consor/cgi-bin/index.php or www.eddnal.com (giving details of centers in Austria, Belgium, Denmark, Finland, France, Germany, Holland, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom).

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