14 - 400 Multiple Endocrine Neoplasia Syndromes

400 Multiple Endocrine Neoplasia Syndromes

TABLE 399-3 Patterns of Occurrence in Inherited Pheochromocytoma and Paraganglioma–Associated Syndromes EXTRA-ADRENAL RETROPERITONEAL OR PELVIC TUMORS MUTATED GENE ADRENAL TUMORS HEAD AND NECK TUMORS MAX +++++ <x + <x +++++ ++++ ++ +++ NF1 +++++ <+ + <+ + ++ + ++ RET +++++ <+ <+ <+ ++++ ++++ <+ + SDHA ++ ++++ ++ + + <+ + + SDHB ++++ +++ +++ + ++ <+ +++ ++ SDHC <+ +++++ <+ + + <+ <+ ++ SDHD ++ +++++ + + ++++ <+ + +++ VHL +++++ <+ + + ++++ +++ + ++++ TMEM127 +++++ + + + ++ ++ <+ + Note: Frequencies in percentage (<+: 0–4%; +: 5–19%; ++: 20–39%; +++: 40–59%; ++++: 60–79%; +++++: 80–100%) of clinical characteristics of pheochromocytomas/ paragangliomas of patients with germline mutations of the genes MAX, NF1, RET, SDHA, SDHB, SDHC, SDHD, VHL, and TMEM127; for other genes, the data are too limited to include in this summary. A single adrenal pheochromocytoma in a patient with an otherwise unremarkable history may still be associated with mutations of VHL, RET, SDHB, or SDHD (in decreasing order of frequency). Two-thirds of extra-adrenal tumors are associated with one of these syndromes, and multifocal tumors occur with decreasing frequency in carriers of RET, SDHD, VHL, SDHB, and MAX mutations. About 30% of head and neck paragangliomas are associated with germline mutations of one of the SDH subunit genes (most often SDHD) and are rare in carriers of VHL, RET, MAX, and TMEM127 mutations. Immunohistochemistry is helpful in the preselection of hereditary pheochromocytoma. Negative immunostaining with antibodies to SDHB (Fig. 399-5F), TMEM127, and MAX may predict mutations of the SDHx (PGL1-5), TMEM127, and MAX genes, respectively. Once the underlying syndrome is diagnosed, the benefit of genetic testing can be extended to relatives. For this purpose, it is necessary to identify the germline mutation in the proband and, after genetic counseling, to perform DNA sequence analyses of the responsible gene in relatives to determine whether they are affected. Other family mem bers may benefit when individuals who carry a germline mutation are biochemically screened for paraganglial tumors. ■ ■FUTURE PERSPECTIVES About 15% of sporadic PPGLs present with recurrence, including some ocurring >10 years after initial management; this rate is higher in genetically determined PPGL. Defining the clinical outcome of a PPGL remains difficult, and machine learning models including several fac tors might be helpful in the future to personalize the follow-up of these patients. The recent American Joint Committee on Cancer tumornode-metastasis classification could help select patients at risk of recur rence. The pathogenesis of PPGL remains imperfectly understood, and as

for other endocrine tumors, microenvironment and immune cells might influence PPGL aggressiveness or metastatic behavior; they could also constitute some new therapeutic targets in the future. ■ ■FURTHER READING Al Subhi AR et al: Systematic review: Incidence of pheochromocy toma and paraganglioma over 70 years. J Endocr Soc 6:bvac105, 2022. Amar L et al: International consensus on initial screening and followup of asymptomatic SDHx mutation carriers. Nat Rev Endocrinol 17:435, 2021. Bancos I et al: Maternal and fetal outcomes in pheochromocytoma and pregnancy: A multi-center retrospective cohort study and sys tematic review of literature. Lancet Diabetes Endocrinol 2021; 9:13. Calsina B et al: Genomic and immune landscape of metastatic pheo chromocytoma and paraganglioma. Nat Commun 14:1122, 2023. Castinetti F et al: Controversies about the systematic preoperative pharmacological treatment before pheochromocytoma or paragan glioma surgery. Eur J Endocrinol 186:D17, 2022. Horton C et al: Universal germline panel testing for individuals with pheochromocytoma and paraganglioma produces high diagnostic yield. J Clin Endocrinol Metab 107:e1917, 2022.

BILATERAL ADRENAL TUMORS FAMILY HISTORY IN PROBANDS FOR COMPONENTS OF THE GIVEN SYNDROME THORACIC TUMORS MULTIPLE

TUMORS METASTATIC TUMORS Multiple Endocrine Neoplasia Syndromes CHAPTER 400 Lenders JW et al: Genetics, diagnosis, management and future direc tions of research of phaeochromocytoma and paraganglioma: A posi tion statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. J Hypertens 38:1443, 2020. Lopez AG et al: Expression of LHCGR in pheochromocytomas unveils an endocrine mechanism connecting pregnancy and epi nephrine overproduction. Hypertension 79:1006, 2022. Neumann HPH et al: Comparison of pheochromocytoma-specific morbidity and mortality among adults with bilateral pheochromocy tomas undergoing total adrenalectomy vs cortical-sparing adrenalec tomy. JAMA Netw Open 2:e198898, 2019. Pamporaki C et al: Prediction of metastatic pheochromocytoma and paraganglioma: A machine learning modelling study using data from a cross-sectional cohort. Lancet Digit Health 5:e551, 2023. Taïeb D et al: European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromo cytoma and paraganglioma. Eur J Nucl Med Mol Imaging 46:2112, 2019. Taïeb D et al: Clinical consensus guideline on the management of phaeochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants. Lancet Diabetes Endocrinol 11:345, 2023. Rajesh V. Thakker

Multiple Endocrine

Neoplasia Syndromes Multiple endocrine neoplasia (MEN) is characterized by a predilection for tumors involving two or more endocrine glands. Five major forms of MEN are recognized and referred to as MEN types 1–5 (MEN 1–5) (Table 400-1). Each type of MEN is inherited as an autosomal domi nant syndrome or may occur sporadically, that is, without a family history. However, this distinction between familial and sporadic forms is often difficult because family members with the disease may have died before symptoms developed. In addition to MEN 1–5, at least six other syndromes are associated with multiple endocrine and other organ neoplasias (MEONs) (Table 400-2). These MEONs include the hyperparathyroidism-jaw tumor (HPT-JT) syndrome, Carney com plex, von Hippel–Lindau disease (Chap. 399), neurofibromatosis

TABLE 400-1 Multiple Endocrine Neoplasia (MEN) Syndromes TYPE (CHROMOSOMAL LOCATION) GENE AND MOST FREQUENTLY MUTATED CODONS TUMORS (ESTIMATED PENETRANCE) MEN 1 (11q13) Parathyroid adenoma (90%) Enteropancreatic tumor (30–70%) • Gastrinoma (>50%) • Insulinoma (10–30%) • Nonfunctioning and PPoma 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%) (20–55%) • Glucagonoma (<3%) • VIPoma (<1%) Pituitary adenoma (15–50%) • Prolactinoma (60%) • Somatotrophinoma (25%) • Corticotrophinoma (<5%) • Nonfunctioning (<5%) Associated tumors • Adrenal cortical tumor (20–70%) • Pheochromocytoma (<1%) • Bronchopulmonary NET (2%) • Thymic NET (2%) • Gastric NET (10%) • Lipomas (>33%) • Angiofibromas (85%) • Collagenomas (70%) • Meningiomas (8%) PART 12 Endocrinology and Metabolism MEN 2 (10 cen-10q11.2) MEN 2A MTC (90%) Pheochromocytoma (>50%) Parathyroid adenoma (10–25%) RET 634, e.g., Cys → Arg (~85%) MTC only MTC (100%) RET 618, missense (>50%) MEN 2B (also MTC (>90%) Pheochromocytoma (>50%) Associated abnormalities (40–50%) • Mucosal neuromas • Marfanoid habitus • Medullated corneal nerve RET 918, Met → Thr (>95%) known as MEN 3) fibers • Megacolon MEN 4 (12p13) Parathyroid adenomaa CDKN1B; no common mutations identified to date Pituitary adenomaa Reproductive organ tumorsa (e.g., testicular cancer, neuroendocrine cervical carcinoma) ?Adrenal + renal tumorsa MEN5 (14q23.3) Pheochromocytomaa MAX; no common mutations identified to date Pituitary adenomaa Parathyroid adenomas?a Neural crest tumors (e.g., ganglioneuroma, neuroblastoma) (other tumors? – renal cell carcinoma, renal oncocytoma, pancreatic NETs, chondrosarcoma) aInsufficient numbers reported to provide prevalence information. Note: Autosomal dominant inheritance of the MEN syndromes has been established. Abbreviations: del, deletion; ins, insertion; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; PPoma, pancreatic polypeptide–secreting tumor; VIPoma, vasoactive intestinal polypeptide–secreting tumor. Source: Adapted with permission from Thakker RV. Multiple endocrine neoplasia– syndromes of the twentieth century. J Clin Endocrinol Metab 83:2617, 1998.

TABLE 400-2 Multiple Endocrine and Other Organ Neoplasia (MEON) Syndromes CHROMOSOMAL LOCATION DISEASEa GENE PRODUCT Hyperparathyroidism-jaw tumor (HPT-JT) Parafibromin 1q31.2 Carney complex CNC1 PRAKAR1A 17q24.2 CNC2 ?b 2p16 von Hippel–Lindau disease (VHL) pVHL (elongin) 3p25 Neurofibromatosis type 1 (NF1) Neurofibromin 17q11.2 Cowden's syndrome (CWS) CWS1 PTEN 10q23.31 CWS2 SDHB 1p36.13 CWS3 SDHD 11q23.1 CWS4 KLLN 10q23.31 CWS5 PIK3CA 3q26.32 CWS6 AKT1 14q32.33 CWS7 SEC23B 20p11.23 McCune-Albright syndrome (MAS) Gsα 20q13.32 aThe inheritance for these disorders is autosomal dominant, except MAS, which is due to mosaicism that results from the postzygotic somatic cell mutation of the GNAS1 gene, encoding Gsα. b?, unknown. type 1 (Chap. 95), Cowden's syndrome (CWS), and McCune-Albright syndrome (MAS) (Chap. 424); all of these are inherited as autoso mal dominant disorders, except for MAS, which is caused by mosaic expression of a postzygotic somatic cell mutation (Table 400-2). A diagnosis of a MEN or MEON syndrome may be established in an individual by one of three criteria: (1) clinical features (two or more of the associated tumors [or lesions] in an individual); (2) familial pattern (one of the associated tumors [or lesions] in a firstdegree relative of a patient with a clinical diagnosis of the syndrome); and (3) genetic analysis (a germline mutation in the associated gene in an individual, who may be clinically affected or asymptomatic). Mutational analysis in MEN and MEON syndromes is helpful in clinical practice to (1) confirm the clinical diagnosis; (2) identify family members who harbor the mutation and require screening for relevant tumor detection and early/appropriate treatment; and (3) identify the ~50% of family members who do not harbor the germline mutation and can, therefore, be alleviated of the anxiety of

developing associated tumors. This latter aspect also helps to reduce health care costs by reducing the need for unnecessary biochemical and radio logic investigations. ■ ■MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 Clinical Manifestations MEN type 1 (MEN 1), which is also referred to as Wermer's syndrome, is characterized by the triad of tumors involving the parathyroids, pancreatic islets, and anterior pituitary. In addition, adrenal cortical tumors, carcinoid tumors usually of the fore gut, meningiomas, facial angiofibromas, collagenomas, and lipomas may also occur in some patients with MEN 1. Combinations of the affected glands and their pathologic features (e.g., hyperplastic adenomas of the parathyroid glands) may differ in members of the same family and even between identical twins. In addition, a nonfamilial (e.g., sporadic) form occurs in 8–14% of patients with MEN 1, and molecular genetic studies have confirmed the occurrence of de novo mutations of the MEN1 gene in ~10% of patients with MEN 1. The prevalence of MEN 1 is ~0.25% based on randomly chosen postmortem studies but is 1–18% among patients with primary hyperparathyroidism, 16–38% among patients with pancreatic islet tumors, and <3% among patients with pituitary tumors. The disorder affects all age groups, with a reported age range of 5–81 years, with clinical and biochemical manifestations developing in the vast majority by the fifth decade. The clinical manifestations of MEN 1 are related to the sites of tumors and their hormonal products. In the absence of treatment, endocrine tumors are associated with an earlier

TABLE 400-3 Biochemical and Radiologic Screening in Multiple Endocrine Neoplasia Type 1 TUMOR AGE TO BEGIN (YEARS) BIOCHEMICAL TEST (PLASMA OR SERUM) ANNUALLY IMAGING TEST (TIME INTERVAL) Parathyroid

Calcium, PTH None Pancreatic NETs Gastrinoma

Gastrin (± gastric pH) None Insulinoma

Fasting glucose, insulin None Other pancreatic NET <10 Chromogranin A; pancreatic polypeptide, glucagon, vasoactive intestinal peptide Anterior pituitary

Prolactin, IGF-I MRI (every 3 years) Adrenal <10 None unless symptoms or signs of functioning tumor and/or tumor >1 cm identified on imaging Thymic and bronchial carcinoid

None CT or MRI (every 1–2 years) Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; IGF-I, insulin-like growth factor I; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PTH, parathyroid hormone. Source: Data from PJ Newey, RV Thakker: Role of multiple endocrine neoplasia type 1 mutational analysis in clinical practice. Endocr Pract 17, 2011 and RV Thakker: Multiple endocrine neoplasia type 1 (MEN1). Translational Endocrinology and Metabolism, Vol 2. Chevy Chase, MD: The Endocrine Society; 2011. mortality in patients with MEN 1, with a 50% probability of death by the age of 50 years. The cause of death is usually a malignant tumor, often from a pancreatic neuroendocrine tumor (NET) or foregut carcinoid. In addition, the treatment outcomes of patients with MEN 1–associated tumors are not as successful as those in patients with non–MEN 1 tumors. This is because MEN 1–associated tumors, with the exception of pituitary NETs, are usually multiple, making it difficult to achieve a successful surgical cure. Occult metastatic disease is also more prevalent in MEN 1, and the tumors may be larger, more aggressive, and resistant to treatment. Parathyroid Tumors (See also Chap. 422) Primary hyper parathyroidism occurs in ~90% of patients and is the most common feature of MEN 1. Patients may

have asymptomatic hypercalcemia or vague symptoms associated with hypercalcemia (e.g., polyuria, poly dipsia, constipation, malaise, or dyspepsia). Nephrolithiasis and osteitis fibrosa cystica (less commonly) may also occur. Biochemical investiga tions reveal hypercalcemia, usually in association with elevated circu lating parathyroid hormone (PTH) (Table 400-3). The hypercalcemia is usually mild, and severe hypercalcemia or parathyroid cancer is a rare occurrence. Additional differences in the primary hyperparathy roidism of patients with MEN 1, as opposed to those without MEN 1, include an earlier age at onset (20–25 vs 55 years) and an equal maleto-female ratio (1:1 vs 1:3). Preoperative imaging (e.g., neck ultrasound with 99mTc-sestamibi parathyroid scintigraphy) is of limited benefit because all parathyroid glands may be affected, and neck exploration may be required irrespective of preoperative localization studies. TREATMENT Parathyroid Tumors Surgical removal of the abnormally overactive parathyroids in patients with MEN 1 is the definitive treatment, and most special ist centers recommend performing a subtotal (e.g., removal of 3.5 glands) parathyroidectomy. Minimally invasive parathyroidec tomy is not recommended because all four parathyroid glands are usually affected with multiple adenomas or hyperplasia. Surgical experience should be taken into account given the variability in pathology in MEN 1. Calcimimetics (e.g., cinacalcet), which act via the calcium-sensing receptor, have been used to treat primary hyperparathyroidism in some patients when surgery is unsuccessful or contraindicated. Pancreatic Tumors (See also Chap. 89) The incidence of pancreatic islet cell tumors, which are NETs, in patients with MEN 1 ranges from 30 to 80% in different series. Most of these tumors (Table 400-1) produce excessive amounts of hormone (e.g., gastrin, insulin, glucagon, vasoactive intestinal polypeptide [VIP]) and are associated with distinct clinical syndromes, although some are nonfunctioning or

 nonsecretory. These pancreatic islet cell tumors have an earlier age at onset in patients with MEN 1 than in patients without MEN 1. Gastrinoma Gastrin-secreting tumors (gastrinomas) are associated with marked gastric acid production and recurrent peptic ulcerations, a combination referred to as Zollinger-Ellison syndrome. Gastrinomas occur more often in patients with MEN 1 who are aged >30 years. Recurrent severe multiple peptic ulcers, which may perforate, and cachexia are major contributors to the high mortality. Patients with Zollinger-Ellison syndrome may also suffer from diarrhea and steat orrhea. The diagnosis is established by demonstration of an elevated fasting serum gastrin concentration in association with increased basal gastric acid secretion (Table 400-3). However, the diagnosis of Zollinger-Ellison syndrome may be difficult in hypercalcemic MEN 1 patients because hypercalcemia can also cause hypergastrinemia. Ultrasonography, endoscopic ultrasonography, computed tomography (CT), nuclear magnetic resonance imaging (MRI), selective abdominal angiography, venous sampling, and somatostatin receptor scintigraphy (SRS) are helpful in localizing the tumor prior to surgery. Gastrinomas represent >50% of all pancreatic NETs in patients with MEN 1, and ~20% of patients with gastrinomas will be found to have MEN 1. Gas trinomas, which may also occur in the duodenal mucosa, are the major cause of morbidity and mortality in patients with MEN 1. TREATMENT Gastrinoma Medical treatment of patients with MEN 1 and Zollinger-Ellison syndrome is directed toward reducing basal acid output to <10 mmol/L. Parietal cell H+-K+-adenosine triphosphatase (ATPase) inhibitors (e.g., omeprazole or lansoprazole) reduce acid output and are the drugs of choice for gastrinomas. Some patients may also require additional treatment with the histamine H2 receptor antagonists cimetidine or ranitidine. The role of surgery in the treatment of gastrinomas in patients with MEN 1 is controversial. The goal of surgery is to reduce the risk of distant metastatic

disease and improve survival. For a nonmetastatic gastrinoma situated in the pancreas, surgical excision is often effective. However, the risk of hepatic metastases increases with tumor size, such that 25–40% of patients with pancreatic NETs >4 cm develop hepatic metastases, and 50–70% of patients with tumors 2–3 cm in size have lymph node metastases. Survival in MEN 1 patients with gastrinomas <2.5 cm in size is 100% at 15 years, but 52% at 15 years, if metastatic disease is present. The presence of lymph node metastases does not appear to adversely affect survival. Surgery for gastrinomas that are >2–2.5 cm has been recommended, because the disease-related survival in these patients is improved following surgery. In addition, duodenal gastrinomas, which occur more frequently in patients with MEN 1, have been treated successfully with surgery. However,

in most patients with MEN 1, gastrinomas are multiple or extrapan creatic, and with the exception of duodenal gastrinomas, surgery is rarely successful. For example, the results of one study revealed that only ~15% of patients with MEN 1 were free of disease immediately after surgery, and at 5 years, this number had decreased to ~5%; the respective outcomes in patients without MEN 1 were better, at 45 and 40%. Given these findings, most specialists recommend a nonsurgical management for gastrinomas in MEN 1, except as noted earlier for smaller, isolated lesions. Treatment of dissemi nated gastrinomas is difficult. Chemotherapy with streptozotocin and 5-fluorouracil; hormonal therapy with octreotide or lanreotide, which are human somatostatin analogues (SSAs); selected internal radiation therapy (SIRT); radiofrequency ablation; peptide radio receptor therapy (PRRT); hepatic artery embolization; administra tion of human leukocyte interferon; and removal of all resectable tumor have been successful in some patients.

PART 12 Endocrinology and Metabolism Insulinoma These β islet cell insulin-secreting tumors represent 10–30% of all pancreatic tumors in patients with MEN 1. Patients with an insulinoma present with hypoglycemic symptoms (e.g., weakness, headaches, sweating, faintness, seizures, altered behavior, weight gain) that typically develop after fasting or exertion and improve after glucose intake. The most reliable test is a supervised 72-h fast. Biochemical inves tigations reveal increased plasma insulin concentrations in association with hypoglycemia (Table 400-3). Circulating concentrations of C pep tide and proinsulin, which are also increased, are useful in establishing the diagnosis. It also is important to demonstrate the absence of sulfo nylureas in plasma and urine samples obtained during the investigation of hypoglycemia (Table 400-3). Surgical success is greatly enhanced by preoperative localization by endoscopic ultrasonography, CT scanning, or celiac axis angiography. Additional localization methods may include preoperative and perioperative percutaneous transhepatic portal venous sampling, selective intraarterial stimulation with hepatic venous sam pling, and intraoperative direct pancreatic ultrasonography. Insulinomas occur in association with gastrinomas in 10% of patients with MEN 1, and the two tumors may arise at different times. Insulinomas occur more often in patients with MEN 1 who are aged <40 years, and some arise in individuals aged <20 years. In contrast, in patients without MEN 1, insu linomas generally occur in those aged >40 years. Insulinomas may be the first manifestation of MEN 1 in 10% of patients, and ~4% of patients with insulinomas will have MEN 1. TREATMENT Insulinoma Medical treatment, which consists of frequent carbohydrate meals and diazoxide or octreotide, is not always successful, and surgery is the optimal treatment. Surgical treatment, which ranges from enucleation of a single tumor to a distal pancreatectomy or partial pancreatectomy, has been curative in many patients. Chemotherapy (streptozotocin, 5-fluorouracil, and doxorubicin), PRRT (e.g., with 177Lu-DOTATATE), or hepatic artery embolization has been used for metastatic disease.

Glucagonoma These glucagon-secreting pancreatic NETs occur in <3% of patients with MEN 1. The characteristic clinical manifestations of a skin rash (necrolytic migratory erythema), weight loss, anemia, and stomatitis may be absent. The tumor may have been detected in an asymptomatic patient with MEN 1 undergoing pancreatic imaging or by the finding of glucose intolerance and hyperglucagonemia. TREATMENT Glucagonoma Surgical removal of the glucagonoma is the treatment of choice. However, treatment may be difficult because ~50–80% of patients have metastases at the time of diagnosis. Medical treatment with SSAs (e.g., octreotide or lanreotide) or chemotherapy with

streptozotocin and 5-fluorouracil has been successful in some patients, and hepatic artery embolization has been used to treat metastatic disease. Vasoactive Intestinal Peptide (VIP) Tumors (VIPomas)

VIPomas have been reported in only a few patients with MEN 1. This clinical syndrome is characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome), which is also referred to as the Verner-Morrison syndrome, or the VIPoma syndrome. The diagnosis is established by excluding laxative and diuretic abuse, confirming a stool volume in excess of 0.5–1.0 L/d during a fast, and documenting a markedly increased plasma VIP concentration. TREATMENT VIPomas Surgical management of VIPomas, which are mostly located in the tail of the pancreas, can be curative. However, in patients with unresectable tumor, SSAs, such as octreotide and lanreotide, may be effective. Streptozotocin with 5-fluorouracil may be ben eficial, along with hepatic artery embolization for the treatment of metastases. Pancreatic Polypeptide-Secreting Tumors (PPomas) and Nonfunctioning Pancreatic NETs PPomas are found in a large number of patients with MEN 1. No pathologic sequelae of excessive polypeptide (PP) secretion are apparent, and the clinical significance of PP is unknown. Many PPomas may have been unrecognized or clas sified as nonfunctioning pancreatic NETs, which likely represent the most common enteropancreatic NET associated with MEN 1 (Fig. 400-1). The absence of both a clinical syndrome and specific biochemical abnormalities may result in a delayed diagnosis of nonfunctioning pancreatic NETs, which are associated with a worse prognosis than other functioning tumors, including insulinoma and gastrinoma. The optimum screening method and its timing interval for nonfunctioning pancreatic NETs remain to be established. At present, endoscopic ultra sound likely represents the most sensitive method of detecting small pancreatic tumors, but SRS is the most reliable method for detecting metastatic disease (Table 400-3). FIGURE 400-1 Pancreatic nonfunctioning neuroendocrine tumor (NET) in a 32-year-old patient with multiple endocrine neoplasia type 1 (MEN 1). An abdominal magnetic resonance imaging (MRI) scan revealed a low-intensity >3.0 cm (anteroposterior maximal diameter) tumor within the body of pancreas. There was no evidence of invasion of adjacent structures or metastases. The tumor is indicated by white dashed circle.

TREATMENT PPomas and Nonfunctioning Pancreatic NETs The management of nonfunctioning pancreatic NETs in the asymp tomatic patient is controversial. One recommendation is to under take surgery irrespective of tumor size after biochemical assessment is complete. Alternatively, other experts recommend surgery based on tumor size, using either >1 cm or >2 cm at different centers. Pan creatoduodenal surgery is successful in removing the tumors in 80% of patients, but >40% of patients develop complications, including diabetes mellitus, frequent steatorrhea, early and late dumping syn dromes, and other gastrointestinal symptoms. However, ~50–60% of

patients treated surgically survive >5 years. When considering these recommendations, it is important to consider that occult met astatic disease (e.g., tumors not detected by imaging investigations) is likely to be present in a substantial proportion of these patients at the time of presentation. Inhibitors of tyrosine kinase receptors (TKRs) and of the mammalian target of rapamycin (mTOR) signal ing pathway have been reported to be effective in treating pancre atic NET metastases and in doubling the progression-free survival time. Additional treatments for metastatic disease include PRRT using 177Lu-DOTATATE, chemotherapy, radiofrequency ablation, transarterial chemoembolization, and SIRT. Other Pancreatic NETs NETs secreting growth hormone–releasing hormone (GHRH), GHRHomas, have been reported rarely in patients with MEN 1. It is estimated that ~33% of patients with GHRHomas have other MEN 1–related tumors. GHRHomas may be diagnosed by demonstrating elevated serum concentrations of growth hormone and GHRH. More than 50% of GHRHomas occur in the lung, 30% occur in the pancreas, and 10% are found in the small intestine. Somatostati nomas secrete somatostatin, a peptide that inhibits the secretion of a variety of hormones, resulting in hyperglycemia, cholelithiasis, low acid output, steatorrhea, diarrhea, abdominal pain, anemia, and weight loss. Although 7% of pancreatic NETs secrete somatostatin, the clinical fea tures of somatostatinoma syndrome are unusual in patients with MEN 1. Pituitary Tumors (See also Chap. 392) Pituitary tumors occur in 15–50% of patients with MEN 1 (Table 400-1), and ~75% of these are microadenomas (<1 cm diameter). The tumors occur as early as 5 years of age or as late as the ninth decade. MEN 1 pituitary adenomas are more frequent in women than men, in whom they are often macroad enomas (>1 cm diameter). There are no specific histologic parameters that differentiate between MEN 1 and non–MEN 1 pituitary tumors. Approximately 60% of MEN 1–associated pituitary tumors secrete pro lactin, <25% secrete growth hormone, 5% secrete adrenocorticotropic hormone (ACTH), and the remainder appear to be nonfunctioning, with some secreting glycoprotein subunits (Table 400-1). However, pituitary tumors derived from MEN 1 patients may exhibit immunore activity to several hormones. In particular, there is a greater frequency of somatolactotrope tumors. Prolactinomas are the first manifestation of MEN 1 in ~15% of patients, whereas somatotrope tumors occur more often in patients aged >40 years. Fewer than 3% of patients with anterior pituitary tumors will have MEN 1. Clinical manifestations are similar to those in patients with sporadic pituitary tumors without MEN 1 and depend on the hormone secreted and the size of the pitu itary tumor. Thus, patients may have symptoms of hyperprolactinemia (e.g., amenorrhea, infertility, and galactorrhea in women, or impotence and infertility in men) or have features of acromegaly or Cushing’s disease. In addition, enlarging pituitary tumors may compress adjacent structures such as the optic chiasm or normal pituitary tissue, causing visual disturbances and/or hypopituitarism. In asymptomatic patients with MEN 1, periodic biochemical monitoring of serum prolactin and insulin-like growth factor 1 (IGF-1) levels, as well as MRI of the pitu itary, can lead to early identification of pituitary tumors (Table 400-3). In patients with abnormal results, hypothalamic-pituitary testing should characterize the nature of the pituitary lesion and its effects on the secretion of other pituitary hormones.

TREATMENT Pituitary Tumors Treatment of pituitary tumors in patients with MEN 1 consists of therapies similar to those used in patients without MEN 1 and includes appropriate medical therapy (e.g., bromocriptine or caber goline for prolactinoma; or octreotide or lanreotide for somatotrope tumors) or selective transsphenoidal adenomectomy, if feasible, with radiotherapy reserved for residual unresectable tumor tissue. Multiple Endocrine Neoplasia Syndromes CHAPTER 400 Associated Tumors Patients with MEN 1 may also develop carci noid tumors, adrenal cortical

tumors, facial angiofibromas, collageno mas, thyroid tumors, and lipomatous tumors. Carcinoid Tumors (See also Chap. 89) Carcinoid tumors occur in >3% of patients with MEN 1 (Table 400-1). The carcinoid tumor may be located in the bronchi, gastrointestinal tract, pancreas, or thymus. At the time of diagnosis, most patients are asymptomatic and do not have clinical features of the carcinoid syndrome. Impor tantly, no hormonal or biochemical abnormality (e.g., plasma chro mogranin A) is consistently observed in individuals with thymic or bronchial carcinoid tumors. Thus, screening for these tumors is depen dent on radiologic imaging. The optimum method for screening has not been established. Low-dose CT and MRI are sensitive for detecting thymic and bronchial tumors (Table 400-3), although repeated CT scanning raises concern about exposure to repeated doses of ionizing radiation. Octreotide scintigraphy may also reveal some thymic and bronchial carcinoids, although there is insufficient evidence to recom mend its routine use. Gastric carcinoids, of which the type II gastric enterochromaffin-like (ECL) cell carcinoids (ECLomas) are associated with MEN 1 and Zollinger-Ellison syndrome, may be detected inci dentally at the time of gastric endoscopy for dyspeptic symptoms in MEN 1 patients. These tumors, which may be found in >10% of MEN 1 patients, are usually multiple and sized <1.5 cm. Bronchial carcinoids in patients with MEN 1 occur predominantly in women (male-tofemale ratio, 1:4). In contrast, thymic carcinoids in European patients with MEN 1 occur predominantly in men (male-to-female ratio, 20:1), with cigarette smokers having a higher risk for these tumors; thymic carcinoids in Japanese patients with MEN 1 have a less marked sex dif ference (male-to-female ratio 2:1). The course of thymic carcinoids in MEN 1 appears to be particularly aggressive. The presence of thymic tumors in patients with MEN 1 is associated with a median survival after diagnosis of ~9.5 years, with 70% of patients dying as a direct result of the tumor. TREATMENT Carcinoid Tumors If resectable, surgical removal of carcinoid tumors is the treatment of choice. For patients with unresectable tumors and those with metastatic disease, treatment with SSAs, radiotherapy, chemothera peutic agents (e.g., fluorouracil, temozolomide, cisplatin, etopo side), mTOR inhibitors (e.g., everolimus), or PRRT therapy has resulted in symptom improvement and regression of some tumors. Little is known about the malignant potential of gastric type II ECLomas, but treatment with SSAs has resulted in regression of these ECLomas. Adrenocortical Tumors (See also Chap. 398) Asymptom atic adrenocortical tumors occur in 20–70% of patients with MEN 1 depending on the radiologic screening methods used (Table 400-1). Most of these tumors, which include cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, and carcinomas, are nonfunctioning. Indeed, <10% of patients with enlarged adrenal glands have hormonal hypersecretion, with primary hyperaldosteronism and ACTH-independent Cushing’s syndrome being encountered most commonly. Occasionally, hyperandrogenemia may occur in association with adrenocortical carcinoma. Pheochromocytoma in association

with MEN 1 is rare. Biochemical investigation (e.g., plasma renin and aldosterone concentrations, low-dose dexamethasone suppression test, urinary catecholamines, and/or metanephrines) should be undertaken in those with symptoms or signs suggestive of functioning adrenal tumors or in those with tumors >1 cm. Adrenocortical carcinoma occurs in ~1% of MEN 1 patients but increases to >10% for adrenal tumors >1 cm.

TREATMENT Adrenocortical Tumors PART 12 Endocrinology and Metabolism Consensus has not been reached about the management of MEN 1–associated nonfunctioning adrenal tumors, because the majority are benign. However, the risk of malignancy increases with size, particularly for tumors with a diameter >4 cm. Indications for surgery for adrenal tumors include size >4 cm in

diameter, atypical or suspicious radiologic features (e.g., increased Hounsfield unit on unenhanced CT scan) and size of 1–4 cm in diameter, or significant measurable growth over a 6-month period. The treatment of func tioning (e.g., hormone-secreting) adrenal tumors is similar to that for tumors occurring in non–MEN 1 patients. Meningioma Central nervous system (CNS) tumors, including ependymomas, schwannomas, and meningiomas, have been reported in MEN 1 patients (Table 400-1). Meningiomas are found in <10% of patients with other clinical manifestations of MEN 1 (e.g., primary hyperparathyroidism) for >15 years. The majority of meningiomas are not associated with symptoms, and 60% do not enlarge. The treatment of MEN 1–associated meningiomas is similar to that in non–MEN 1 patients. Lipomas Subcutaneous lipomas occur in >33% of patients with MEN 1 (Table 400-1) and are frequently multiple. In addition, visceral, pleural, or retroperitoneal lipomas may occur in patients with MEN 1. Management is conservative. However, when surgically removed for cosmetic reasons, they typically do not recur. Facial Angiofibromas and Collagenomas The occurrence of multiple facial angiofibromas in patients with MEN 1 may range from

> 20 to >90%, and occurrence of collagenomas may range from 0 to 70% (Table 400-1). These cutaneous findings may allow presymp tomatic diagnosis of MEN 1 in the relatives of a patient with MEN 1. Treatment for these cutaneous lesions is usually not required. Thyroid Tumors Thyroid tumors, including adenomas, colloid goiters, and carcinomas, have been reported to occur in >25% of patients with MEN 1. 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 MEN 1 may be incidental. The treatment of thyroid tumors in MEN 1 patients is simi lar to that for non–MEN 1 patients. Genetics and Screening The MEN1 gene is located on chromo some 11q13 and consists of 10 exons, which encode a 610–amino acid protein, menin, that regulates transcription, genome stability, cell division, and proliferation. The pathophysiology of MEN 1 follows the Knudson two-hit hypothesis with a tumor-suppressor role for menin. Inheritance of a germline MEN1 mutation predisposes an individual to developing a tumor that arises following a somatic mutation, which may be a point mutation or more commonly a deletion, leading to loss of heterozygosity (LOH) in the tumor DNA. The germline mutations of the MEN1 gene are scattered throughout the entire 1830-bp coding region and splice sites, and there is no apparent correlation between the location of MEN1 mutations and clinical manifestations of the disor der, in contrast with the situation in patients with MEN 2 (Table 400-1). More than 10% of MEN1 germline mutations arise de novo and may be transmitted to subsequent generations. Some families with MEN 1 mutations develop parathyroid tumors as the sole endocrinopathy, and this condition is referred to as familial isolated hyperparathyroid ism (FIHP). However, between 5 and 25% of patients with MEN 1 do

not harbor germline mutations or deletions of the MEN1 gene. Such patients with MEN 1–associated tumors but without MEN1 mutations may represent phenocopies or have mutations involving other genes. Other genes associated with MEN 1–like features include CDKN1B, which encodes p27kip1;

mutations result in MEN4 (see below) (Table 400-1). Mutations in CDC73, which encodes parafibromin, result in the HPT-JT syndrome; mutations in the calcium-sensing receptor gene (CaSR) result in familial benign hypocalciuric hypercalcemia (FBHH); mutations in MAX, which encodes Myc-associated factor X, result in MEN5, and mutations in the aryl hydrocarbon receptor interacting protein gene (AIP), a tumor suppressor located on chromosome 11q13, are associated with familial isolated pituitary adenomas (FIPA). Genetic testing to determine the MEN1 mutation status in symptomatic family members within a MEN 1 kindred, as well as in all index cases (e.g., patients) with two or more endocrine tumors, is advisable. If a MEN1 mutation is not identified in the index case with two or more endocrine tumors, clinical and genetic tests for other disorders such as HPT-JT syn drome, FBHH, FIPA, MEN 2, or MEN 4 should be considered because these patients may represent phenocopies for MEN 1. The current guidelines recommend that MEN1 mutational analysis should be undertaken in (1) an index case with two or more MEN 1– associated endocrine tumors (e.g., parathyroid, pancreatic, or pituitary tumors); (2) asymptomatic first-degree relatives of a known MEN1 mutation carrier; and (3) first-degree relatives of a MEN1 mutation carrier with symptoms, signs, or biochemical or radiologic evidence for one or more MEN 1–associated tumors. In addition, MEN1 mutational analysis should be considered in patients with suspicious or atypical MEN 1. This would include individuals with parathyroid adenomas before the age of 30 years or multigland parathyroid disease; individuals with gastrinoma or multiple pancreatic NETs at any age; or individuals who have two or more MEN 1–associated tumors that are not part of the classical triad of parathyroid, pancreatic islet, and anterior pituitary tumors (e.g., parathyroid tumor plus adrenal tumor). Family members, including asymptomatic individuals who have been identified to harbor a MEN1 mutation, will require biochemical and radiologic screening (Table 400-3). In contrast, relatives who do not harbor the MEN1 muta tion have a risk of developing MEN 1–associated endocrine tumors that is similar to that of the general population; thus, relatives without the MEN1 mutation do not require repeated screening. Mutational analysis in asymptomatic individuals should be under taken at the earliest opportunity and, if possible, in the first decade of life because tumors have developed in some children by the age of 5 years. Appropriate biochemical and radiologic investigations (Table 400-3) aimed at detecting the development of tumors should then be under taken in affected individuals. Mutant gene carriers should undergo biochemical screening 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-year intervals (Table 400-3). Screening should commence after 5 years of age and should continue for life because the disease may develop as late as the eighth decade. The screening history and physical examination elicit the 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 subcutane ous lipomas, angiofibromas, and collagenomas. Biochemical screening should include measurements of serum calcium, PTH, gastrointestinal hormones (e.g., gastrin, insulin with a fasting glucose, glucagon, VIP, PP), chromogranin A, prolactin, and IGF-1 in all individuals. More specific endocrine function tests should be undertaken in individuals who have symptoms or signs suggestive of a specific clinical syndrome. Biochemical screening for the development of MEN 1 tumors in asymptomatic members of families with MEN 1 is of great importance to reduce morbidity and mortality from the associated tumors. ■ ■MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 AND TYPE 3 Clinical Manifestations MEN type 2 (MEN 2), which is also called Sipple’s syndrome, is characterized by the association of medullary

TABLE 400-4 Recommendations for Tests and Surgery in MEN 2 and MEN 3a RET MUTATION, EXON (EX) LOCATION, AND CODON INVOLVED RISKb RET MUTATIONAL ANALYSIS Ex8 (533)c; Ex10 (609, 611, 618, 620)c; Ex11 (630, 631, 666)c; Ex13 (768, 790)c; Ex14 (804)c; Ex15 (891)c; EX16 (912)c + <3–5

<5d 16e

Ex11 (634)c; Ex15 (883)c ++ <3 <3 <5f 11e

Ex15 (883)g; Ex16 (918)g +++ ASAP and by <1 ASAP and by <0.5–1 ASAP and by <1 11e —h aData from American Thyroid Association Guidelines Task Force, RT Kloos et al: Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 19:565, 2009 and revised from SA Wells Jr et al: Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 25:567, 2015. bRisk for early development of metastasis and aggressive growth of medullary thyroid cancer: +++, highest; ++, high; and + moderate. cMutations associated with MEN 2A (or medullary thyroid carcinoma only). dTiming of surgery to be based on elevation of serum calcitonin and/or joint discussion with pediatrician, surgeon, and parent/family. Later surgery may be appropriate if serum calcitonin and neck ultrasound are normal. ePresence of pheochromocytoma must be excluded prior to any surgical intervention and also in women with RET mutation who are planning pregnancy or are pregnant. fSurgery earlier than 5 years based on elevation of serum calcitonin. Optimal timing of surgery should be decided by the surgeon and pediatrician, in consultation with the child’s parent. gMutations associated with MEN 2B (MEN 3). hNot required because PHPT is not a feature of MEN 2B (MEN 3). Abbreviations: ASAP, as soon as possible; MEN, multiple endocrine neoplasia; PHPT, primary hyperparathyroidism. thyroid carcinoma (MTC), pheochromocytomas, and parathyroid tumors (Table 400-1). Three clinical variants of MEN 2 are recognized: MEN 2A, MEN 2B, and MTC only. MEN 2A, which is often referred to as MEN 2, is the most common variant. In MEN 2A, MTC is associated with pheochromocytomas in 50% of patients (may be bilateral) and with parathyroid tumors in 20% of patients. MEN 2A may rarely occur in association with Hirschsprung’s disease, caused by the absence of autonomic ganglion cells in the terminal hindgut, resulting in colonic dilatation, severe constipation, and obstruction. MEN 2A may also be associated with cutaneous lichen amyloidosis, which is a pruritic lichenoid lesion that is usually located on the upper back. MEN 2B, which is also referred to as MEN 3, represents 5% of all cases of MEN 2 and is characterized by the occurrence of MTC and pheochromocy toma in association with a Marfanoid habitus; mucosal neuromas of the lips, tongue, and eyelids; medullated corneal fibers; and intestinal autonomic ganglion dysfunction leading to multiple diverticulae and megacolon. Parathyroid tumors do not usually occur in MEN 2B. MTC only (FMTC) is a variant in which MTC is the sole manifestation of the syndrome. However, the distinction between FMTC and MEN 2A is difficult and should only be considered if there are at least four family members aged >50 years who are affected by MTC but not pheochro mocytomas or primary hyperparathyroidism. All of the MEN 2 vari ants are due to mutations of the rearranged during transfection (RET) protooncogene, which encodes a TKR. Moreover, there is a correlation between the locations of RET mutations and MEN 2 variants. Thus, ~95% of MEN 2A patients have mutations involving the cysteine-rich extracellular domain, with mutations of codon 634 accounting for ~85% of MEN 2A mutations; FMTC patients also have mutations of the cysteine-rich extracellular domain, with most mutations occurring in codon 618. In contrast, ~95% of MEN 2B/MEN 3 patients have mutations of codon 918

of the intracellular tyrosine kinase domain (Table 400-1 and Table 400-4). Medullary Thyroid Carcinoma MTC is the most common feature of MEN 2A and MEN 2B and occurs in almost all affected individuals. MTC represents 5–10% of all thyroid gland carcinomas, and 20% of MTC patients have a family history of the disorder. The use of RET mutational analysis to identify family members at risk for hereditary forms of MTC has altered the presentation of MTC from that of symptomatic tumors to a preclinical disease for which prophylactic thyroidectomy (Table 400-4) is undertaken to improve the prognosis and ideally result in cure. However, in patients who do not have a known family history of MEN 2A, FMTC, or MEN 2B, and therefore have not had RET mutational analysis, MTC may present as a palpable mass in the neck, which may be asymptomatic or associated with symptoms of pressure or dysphagia in >15% of patients. Diar rhea occurs in 30% of patients and is associated either with elevated circulating concentrations of calcitonin or tumor-related secretion of serotonin and prostaglandins. Some patients may also experience flushing. In addition, ectopic ACTH production by MTC may cause

RECOMMENDED AGE (YEARS) FOR TEST/INTERVENTION FIRST SERUM CALCITONIN AND NECK ULTRASOUND PROPHYLACTIC THYROIDECTOMY SCREENING FOR PHEOCHROMOCYTOMA SCREENING FOR PHPT Multiple Endocrine Neoplasia Syndromes CHAPTER 400 Cushing’s syndrome. The diagnosis of MTC relies on the demonstra tion of hypercalcitoninemia (>90 pg/mL in the basal state); stimula tion tests using IV pentagastrin (0.5 mg/kg) and or calcium infusion (2 mg/kg) are rarely used now, reflecting improvements in the assay for calcitonin. Neck ultrasonography with fine-needle aspiration of the nodules can confirm the diagnosis. Radionucleotide thyroid scans may reveal MTC tumors as “cold” nodules. Radiography may reveal dense irregular calcification within the involved portions of the thyroid gland and in lymph nodes involved with metastases. Positron emis sion tomography (PET) may help to identify the MTC and metastases (Fig. 400-2). Metastases of MTC usually occur to the cervical lymph nodes in the early stages and to the mediastinal nodes, lung, liver, trachea, adrenal, esophagus, and bone in later stages. Elevations in serum calcitonin concentrations are often the first sign of recurrence or persistent disease, and the serum calcitonin doubling time is useful for determining prognosis. MTC can have an aggressive clinical course, with early metastases and death in ~10% of patients. A family history of aggressive MTC or MEN 2B may be elicited. TREATMENT Medullary Thyroid Carcinoma Individuals with RET mutations who do not have clinical mani festations of MTC should be offered prophylactic surgery between the ages of <1 and 5 years. The timing of surgery will depend on the type of RET mutation and its associated risk for early develop ment, metastasis, and aggressive growth of MTC (Table 400-4). Such patients should have a total thyroidectomy with a systematic central neck dissection to remove occult nodal metastasis, although the value of undertaking a central neck dissection has been sub ject to debate. Prophylactic thyroidectomy, with lifelong thyroxine replacement, has dramatically improved outcomes in patients with MEN 2 and MEN 3, such that ~90% of young patients with RET mutations who had a prophylactic thyroidectomy have no evidence of persistent or recurrent MTC at 7 years after surgery. In patients with clinically evident MTC, a total thyroidectomy with bilateral central resection is recommended, and an ipsilateral lateral neck dissection should be undertaken if the primary tumor is >1 cm in size or there is evidence of nodal metastasis in the central neck. Surgery is the only curative therapy for MTC. The 10-year survival in patients with metastatic MTC is ~20%. For inoperable MTC or metastatic disease, TKR inhibitors (e.g., vandetanib, cabozantinib, selpercatinib) have improved the progression-free survival times. Among these, selpercatinib is more selective for the RET kinase and is most effective. PRRT with 177Lu-DOTATATE has been reported to be beneficial for metastatic MTCs that were found by SRS

to express somatostatin receptors. Other types of chemotherapy are of limited efficacy, but radiotherapy may help to palliate local disease.

[H] FDG avid MTC in neck PART 12 Endocrinology and Metabolism Metastatic MTC in liver FDG avid adrenal pheochromocytoma [F] FIGURE 400-2 Fluorodeoxyglucose (FDG) positron emission tomography scan in a patient with multiple endocrine neoplasia type 2A, showing medullary thyroid cancer (MTC) with hepatic and skeletal (left arm) metastasis and a left adrenal pheochromocytoma. Note the presence of excreted FDG compound in the bladder. (Reproduced with permission from A Naziat et al: Confusing genes: A patient with MEN2A and Cushing's disease. Clin Endocrinol (Oxf) 78:966, 2013.) Pheochromocytoma (See also Chap. 399) These noradrena line- and adrenaline-secreting tumors occur in >50% of patients with MEN 2A and MEN 2B and are a major cause of morbidity and mortal ity. Patients may have symptoms and signs of catecholamine secretion (e.g., headaches, palpitations, sweating, poorly controlled hyperten sion), or they may be asymptomatic with detection through biochemi cal screening based on a history of familial MEN 2A, MEN 2B, or MTC. Pheochromocytomas in patients with MEN 2A and MEN 2B differ significantly in distribution when compared with patients with out MEN 2A and MEN 2B. Extra-adrenal pheochromocytomas, which occur in 10% of patients without MEN 2A and MEN 2B, are observed rarely in patients with MEN 2A and MEN 2B. Malignant pheochromo cytomas are much less common in patients with MEN 2A and MEN 2B. The biochemical and radiologic investigation of pheochromocy toma in patients with MEN 2A and MEN 2B is similar to that in non– MEN 2 patients and includes the measurement of plasma (obtained from supine patients) and urinary free fractionated metanephrines (e.g., normetanephrine and metanephrines measured separately), CT or MRI scanning, radionuclide scanning with meta-iodo-(123I or 131I)- benzyl guanidine (MIBG), and PET using (18F)-fluorodopamine or (18F)-fluoro-2-dexoxy-D-glucose (Fig. 400-2). TREATMENT Pheochromocytoma Surgical removal of pheochromocytoma, using α and β adreno receptor blockade before and during the operation, is the rec ommended treatment. Other antihypertensive agents, including calcium channel blockers, are sometimes required for adequate blood pressure control. Endoscopic adrenal-sparing surgery, which

decreases postoperative morbidity, hospital stay, and expense, as opposed to open surgery, has become the method of choice. Parathyroid Tumors (See also Chap. 422) Parathyroid tumors occur in 10–25% of patients with MEN 2A. However, >50% of these patients do not have hypercalcemia. The presence of abnormally enlarged parathyroids, which are unusually hyperplastic, is often seen in the normocalcemic patient undergoing thyroidectomy for MTC. The biochemical investigation and treatment of hypercalcemic patients with MEN 2A is similar to that of patients with MEN 1. Genetics and Screening To date, ~50 different RET muta tions have been reported, and these are located in exons 5, 8, 10, 11, 13, 14, 15, and 16. RET germline mutations are detected in

> 95% of MEN 2A, FMTC, and MEN 2B families, with Cys634Arg being most common in MEN 2A, Cys618Arg being most common in FMTC, and Met918Thr being most common in MEN 2B (Tables 400-1 and 400-4). Between 5 and 10% of patients with MTC or MEN 2A– associated tumors have de novo RET germline mutations, and ~50% of patients with MEN 2B have de novo RET germline mutations. These de novo RET germline mutations always occur on the paternal

allele. Approximately 5% of patients with sporadic pheochromocytoma have a germline RET mutation, but such germline RET mutations do not appear to be associated with sporadic primary hyperparathyroidism. Thus, RET mutational analysis should be performed in (1) all patients with MTC who have a family history of tumors associated with MEN 2, FMTC, or MEN 3, such that the diagnosis can be confirmed and genetic testing offered to asymptomatic relatives; (2) all patients with MTC and pheochromocytoma without a known family history of MEN 2 or MEN 3; (3) all patients with MTC, but without a family history of MEN 2, FMTC, or MEN 3, because these patients may have a de novo germline RET mutations; (4) all patients with bilateral pheochromocy toma; and (5) patients with unilateral pheochromocytoma, particularly if this occurs with increased calcitonin levels. Screening for MEN 2/MEN 3–associated tumors in patients with RET germline mutations should be undertaken annually and include serum calcitonin measurements, a neck ultrasound for MTC, plasma (or 24-h urinary) fractionated metanephrines for pheochromocytoma, and albumin-corrected serum calcium or ionized calcium with PTH for primary hyperparathyroidism. In patients with MEN 2–associated RET mutations, screening for MTC should begin by 1–5 years, for pheochromocytoma by 11–16 years, and for primary hyperparathy roidism by 11–16 years of age (Table 400-4). ■ ■MULTIPLE ENDOCRINE NEOPLASIA TYPE 4 Clinical Manifestations Patients with MEN 1–associated tumors, such as parathyroid adenomas, pituitary adenomas, and pancreatic NETs, occurring in association with gonadal, adrenal, renal, and thy roid tumors have been reported to have mutations of the gene encod ing the 196–amino acid cyclin-dependent kinase inhibitor (CK1) p27 kip1 (CDKN1B). Such families with MEN 1–associated tumors and CDKN1B mutations are designated to have MEN 4 (Table 400-1). The investigations and treatments for the MEN 4–associated tumors are similar to those for MEN 1 and non–MEN 1 tumors. Genetics and Screening To date, 50 MEN patients (from <20 kindreds) with mutations of CDKN1B, which is located on chromo some 12p13, have been reported, and all of these are predicted to result in a loss of function. These MEN 4 patients may represent ~3% of the 5–10% of patients with MEN 1 who do not have mutations of the MEN1 gene. Germline CDKN1B mutations may rarely be found in patients with sporadic (i.e., nonfamilial) forms of primary hyperparathyroidism. ■ ■MULTIPLE ENDOCRINE NEOPLASIA TYPE 5 Clinical Manifestations Two kindreds in whom multiple endo crine tumors were associated with heterozygous germline MAX mutations have been reported. Although MAX mutations have been described in rare cases of hereditary pheochromocytoma and para ganglioma, the occurrence of these tumors in these kindreds was also

associated with pituitary adenomas, parathyroid adenomas, and non endocrine tumors including chondrosarcoma, lung adenocarcinoma, ganglioneuroma, and neuroblastoma. Additional tumors reported in patients with germline MAX mutations include pancreatic NETs, renal oncocytomas, and renal carcinoma. Genetics and Screening The MAX gene is located on chromo some 14q23.3 and

encodes the ubiquitously expressed MYC-associated factor X transcription factor, which is presumed to act as a tumor suppressor. The spectrum of clinical manifestations associated with germline MAX mutations and MEN 5 remains to be fully defined, although most patients appear to have development of early-onset pheochromocytoma. ■ ■HYPERPARATHYROIDISM-JAW TUMOR SYNDROME (SEE ALSO CHAP. 422) Clinical Manifestations Hyperparathyroidism-jaw tumor (HPTJT) syndrome is an autosomal dominant disorder characterized by the development of parathyroid tumors (15% are carcinomas) and fibroosseous jaw tumors. In addition, some patients may also develop Wilms' tumors, renal cysts, renal hamartomas, renal cortical adenomas, renal cell carcinoma (RCC), pancreatic adenocarcinomas, uterine tumors, testicular mixed germ cell tumors with a major seminoma component, and Hürthle cell thyroid adenomas. The parathyroid tumors may occur in isolation and without any evidence of jaw tumors, and this may cause confusion with other hereditary hypercalcemic disorders, such as MEN 1. However, genetic testing to identify the causative mutation will help to establish the correct diagnosis. The investigation and treatment for HPT-JT–associated tumors are similar to those in non-HPT-JT patients, except that early parathyroidectomy is advisable because of the increased frequency of parathyroid carcinoma. Genetics and Screening The gene that causes HPT-JT is located on chromosome 1q31.2 and encodes a 531–amino acid protein, parafibromin (Table 400-2). Parafibromin is also referred to as cell division cycle protein 73 (CDC73) and has a role in transcrip tion. Genetic testing in families helps to identify mutation carriers who should be periodically screened for the development of tumors (Table 400-5). ■ ■VON HIPPEL–LINDAU DISEASE (SEE ALSO CHAP. 399) Clinical Manifestations von Hippel–Lindau (VHL) disease is an autosomal dominant disorder characterized by hemangioblasto mas of the retina and CNS; cysts involving the kidneys, pancreas, and epididymis; RCC; pheochromocytomas; and pancreatic islet cell tumors. The retinal and CNS hemangioblastomas are benign vascular tumors that may be multiple; those in the CNS may cause symptoms TABLE 400-5 HPT-JT Screening Guidelines TUMORa TEST FREQUENCYb Parathyroid Serum Ca, PTH 6–12 months Ossifying jaw fibroma Panoramic jaw x-ray with neck shieldingc 5 years Renal Abdominal MRIc,d 5 years Uterine Ultrasound (transvaginal or transabdominal) and additional imaging ± D&C if indicatede Annual aScreening for most common HPT-JT–associated tumors is considered. Assessment for other reported tumor types may be indicated (e.g., pancreatic, thyroid, testicular tumors). bFrequency of repeating test after baseline tests performed. cX-rays and imaging involving ionizing radiation should ideally be avoided to minimize risk of generating subsequent mutations. dUltrasound scan recommended if MRI unavailable. eSuch selective pelvic imaging should be considered after obtaining a detailed menstrual history. Abbreviations: Ca, calcium; D&C, dilation and curettage; HPT-JT, hyperparathyroidism-jaw tumor syndrome; MRI, magnetic resonance imaging; PTH, parathyroid hormone. Source: Reproduced with permission from PJ Newey, MR Bowl, T Cranston et al: Cell division cycle protein 73 homolog (CDC73) mutations in the hyperparathyroidism-jaw tumor syndrome (HPT-JT) and parathyroid tumors. Hum Mutat 31:295, 2010.

by compressing adjacent structures and/or increasing intracranial pressure. In the CNS, the cerebellum and spinal cord are the most fre quently involved sites. The renal abnormalities consist of cysts and car cinomas, and the lifetime risk of RCC in VHL is 70%. The endocrine tumors in VHL consist of pheochromocytomas and pancreatic islet cell tumors. The clinical presentation of pheochromocytoma in VHL disease is similar to that in sporadic cases, except that there is a higher frequency of bilateral or multiple tumors, which may involve extraadrenal sites in VHL disease. The most frequent pancreatic lesions in VHL are multiple cyst-adenomas, which rarely cause clinical

disease. However, nonsecreting pancreatic islet cell tumors occur in <10% of VHL patients, who are usually asymptomatic. The pancreatic tumors in these patients are often detected by regular screening using abdominal imaging. Pheochromocytomas should be investigated and treated as described earlier for MEN 2. The pancreatic islet cell tumors frequently become malignant, and early surgery is recommended.

Multiple Endocrine Neoplasia Syndromes CHAPTER 400 Genetics and Screening The VHL gene, which is located on chromosome 3p26-p25, is widely expressed in human tissues and encodes a 213–amino acid protein (pVHL) (Table 400-2). A wide variety of germline VHL mutations have been identified. VHL acts as a tumor-suppressor gene. A correlation between the type of mutation and the clinical phenotype has been reported; large deletions and proteintruncating mutations are associated with a low incidence of pheochro mocytomas, whereas some missense mutations in VHL patients are associated with pheochromocytoma (referred to as VHL type 2C). Other missense mutations may be associated with hemangioblastomas and RCC but not pheochromocytoma (referred to as VHL type 1), whereas distinct missense mutations are associated with hemangioblastomas, RCC, and pheochromocytoma (VHL type 2B). VHL type 2A, which refers to the occurrence of hemangioblastomas and pheochromocytoma without RCC, is associated with rare missense mutations. The basis for these complex genotype-phenotype relationships remains to be eluci dated. One major function of pVHL, which is also referred to as elongin, is to downregulate the expression of vascular endothelial growth factor (VEGF) and other hypoxia-inducible mRNAs. Thus, pVHL, in complex with other proteins, regulates the expression of hypoxia-inducible factors (HIF-1 and HIF-2) such that loss of functional pVHL leads to a stabiliza tion of the HIF protein complexes, resulting in VEGF overexpression and tumor angiogenesis. Screening for the development of pheochromo cytomas and pancreatic islet cell tumors is as described earlier for MEN 2 and MEN 1, respectively (Tables 400-3 and 400-4). ■ ■NEUROFIBROMATOSIS Clinical Manifestations Neurofibromatosis type 1 (NF1), which is also referred to as von Recklinghausen’s disease, is an autosomal dominant disorder characterized by the following manifestations: neurologic (e.g., peripheral and spinal neurofibromas); ophthalmo logic (e.g., optic gliomas and iris hamartomas such as Lisch nodules); dermatologic (e.g., café au lait macules); skeletal (e.g., scoliosis, mac rocephaly, short stature, pseudoarthrosis); vascular (e.g., stenoses of renal and intracranial arteries); and endocrine (e.g., pheochromocy toma, carcinoid tumors, precocious puberty). Neurofibromatosis type 2 (NF2) is also an autosomal dominant disorder but is characterized by the development of bilateral vestibular schwannomas (acoustic neuromas) that lead to deafness, tinnitus, or vertigo. Some patients with NF2 also develop meningiomas, spinal schwannomas, peripheral nerve neurofibromas, and café au lait macules. Endocrine abnormali ties are not found in NF2 and are associated solely with NF1. Pheo chromocytomas, carcinoid tumors, and precocious puberty occur in ~1% of patients with NF1, and growth hormone deficiency has also been reported. The features of pheochromocytomas in NF1 are simi lar to those in non-NF1 patients, with 90% of tumors being located within the adrenal medulla and the remaining 10% at an extra-adrenal location, which often involves the para-aortic region. Primary carci noid tumors are often periampullary and may also occur in the ileum but rarely in the pancreas, thyroid, or lungs. Hepatic metastases are associated with symptoms of the carcinoid syndrome, which include flushing, diarrhea, bronchoconstriction, and tricuspid valve disease.

Precocious puberty is usually associated with the extension of an optic glioma into the hypothalamus with resultant early activation of gonad otropin-releasing hormone secretion. Growth

hormone deficiency has also been observed in some NF1 patients, who may or may not have optic chiasmal gliomas, but it is important to note that short stature is frequent in the absence of growth hormone deficiency in patients with NF1. The investigation and treatment for tumors are similar to those undertaken for each respective tumor type in non-NF1 patients. Genetics and Screening The NF1 gene, which is located on chro mosome 17q11.2 and acts as a tumor suppressor, consists of 60 exons that span >350 kb of genomic DNA (Table 400-2). Mutations in NF1 are of diverse types and are scattered throughout the exons. The NF1 gene product is the protein neurofibromin, which has homologies to the p120GAP (GTPase activating protein) and acts on p21ras by converting the active GTP bound form to its inactive GDP form. Mutations of NF1 impair this downregulation of the p21ras signaling pathways, which in turn results in abnormal cell proliferation. Screening for the develop ment of pheochromocytomas and carcinoid tumors is as described earlier for MEN 2 and MEN 1, respectively (Tables 400-3 and 400-4).

PART 12 Endocrinology and Metabolism ■ ■CARNEY COMPLEX Clinical Manifestations Carney complex (CNC) is an autosomal dominant disorder characterized by spotty skin pigmentation (usually of the face, labia, and conjunctiva), myxomas (usually of the eyelids and heart, but also the tongue, palate, breast, and skin), psammoma tous melanotic schwannomas (usually of the sympathetic nerve chain and upper gastrointestinal tract), and endocrine tumors that involve the adrenals, Sertoli cells, somatotropes, thyroid, and ovary. Cushing's syndrome, the result of primary pigmented nodular adrenal disease (PPNAD), is the most common endocrine manifestation of CNC and may occur in one-third of patients. Patients with CNC and Cushing's syndrome often have an atypical appearance by being thin (as opposed to having truncal obesity). In addition, they may have short stature, muscle and skin wasting, and osteoporosis. These patients often have levels of urinary free cortisol that are normal or increased only margin ally. Cortisol production may fluctuate periodically with days or weeks of hypercortisolism; this pattern is referred to as "periodic Cushing's syndrome." Patients with Cushing's syndrome usually have loss of the circadian rhythm of cortisol production. Acromegaly, the result of a somatotrope tumor, affects ~10% of patients with CNC. Testicular tumors may also occur in one-third of patients with CNC. These may either be large-cell calcifying Sertoli cell tumors, adrenocortical rests, or Leydig cell tumors. The Sertoli cell tumors occasionally may be estrogen-secreting and lead to precocious puberty or gynecomastia. Some patients with CNC have been reported to develop thyroid fol licular tumors, ovarian cysts, or breast duct adenomas. Genetics and Screening CNC type 1 (CNC1) is due to mutations of the protein kinase A (PKA) regulatory subunit 1 α (R1α) (PRAKAR1A), a tumor suppressor, whose gene is located on chromosome 17q.24.2 (Table 400-2). The gene causing CNC type 2 (CNC2) is located on chromosome 2p16 and has not yet been identi fied. It is interesting to note, however, that some tumors do not show LOH of 2p16 but instead show genomic instability, suggesting that this CNC gene may not be a tumor suppressor. Screening and treatment of these endocrine tumors are similar to those described earlier for patients with MEN 1 and MEN 2 (Tables 400-3 and 400-4). ■ ■COWDEN'S SYNDROME Clinical Manifestations Multiple hamartomatous lesions, espe cially of the skin, mucous membranes (e.g., buccal, intestinal, colonic), breast, and thyroid, are characteristic of Cowden's syndrome (CWS), which is an autosomal dominant disorder. Thyroid abnormalities occur in two-thirds of patients with CWS, and these usually consist of multinodular goiters or benign adenomas, although <10% of patients may have a follicular thyroid carcinoma. Breast abnormalities occur in

> 75% of patients and consist of either fibrocystic disease or adenocar cinomas. The investigation and treatment for CWS tumors are similar to those undertaken for non-CWS patients.

Genetics and Screening CWS is genetically heterogenous, and seven types (CWS1–7) are recognized (Table 400-2). CWS1 is due to mutations of the phosphate and tensin homologue deleted on chromosome 10 (PTEN) gene, located on chromosome 10q23.31. CWS2 is caused by mutations of the succinate dehydrogenase subunit B (SDHB) gene, located on chromosome 1p36.13; and CWS3 is caused by mutations of the SDHD gene, located on chromosome 11q13.1. SDHB and SDHD mutations are also associated with pheochromocy toma. CWS4 is caused by hypermethylation of the Killin (KLLN) gene, the promoter of which shares the same transcription site as PTEN on chromosome 10q23.31. CWS5 is caused by mutations of the phospha tidylinositol 3-kinase catalytic alpha (PIK3CA) gene on chromosome 3q26.32. CWS6 is caused by mutations of the V-Akt murine thymoma viral oncogene homolog 1 (AKT1) gene on chromosome 14q32.33, and CWS7 is caused by mutations of the saccharomyces cerevisiae homol ogy of B (SEC23B) gene on chromosome 20p11.23. Screening for thy roid abnormalities entails neck ultrasonography and fine-needle aspiration with analysis of cell cytology. ■ ■MCCUNE-ALBRIGHT SYNDROME (SEE ALSO CHAP. 424) Clinical Manifestations McCune-Albright syndrome (MAS) is characterized by the triad of polyostotic fibrous dysplasia, which may be associated with hypophosphatemic rickets; café au lait skin pigmentation; and peripheral precocious puberty. Other endocrine abnormalities include thyrotoxicosis, which may be associated with a multinodular goiter, somatotrope tumors, and Cushing’s syndrome (due to adrenal tumors). Investigation and treatment for each endocri nopathy are similar to those used in patients without MAS. Genetics and Screening MAS is a disorder of mosaicism that results from postzygotic somatic cell mutations of the G protein α-stimulating subunit (Gsα), encoded by the GNAS1 gene, located on chromosome 20q13.32 (Table 400-2). The Gsα mutations, which include Arg201Cys, Arg201His, Glu227Arg, or Glu227His, are activating and are found only in cells of the abnormal tissues. Screening for hyper function of relevant endocrine glands and development of hypophospha temia, which may be associated with elevated serum fibroblast growth factor 23 (FGF23) concentrations, is undertaken in MAS patients.

Acknowledgment The author is grateful to the National Institute of Health Research (NIHR) Oxford Biomedical Research Centre Programme for support and to Mrs. Tracey Walker for typing the manuscript. ■ ■FURTHER READING Binderup MLM et al: von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance. Eur J Med Genet 65:104538, 2022. Bouys L, Bertherat J: Management of endocrine disease: Carney complex: Clinical and genetic update 20 years after the identification of the CNC1 (PRKAR1A) gene. Eur J Endocrinol 184:R99, 2021. Brandi ML et al: Multiple endocrine neoplasia type 1: Latest insights. Endocr Rev 42:133, 2021. Legius E et al: Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: An international consensus recommendation. Genet Med 23:1506, 2021. Hadoux J et al: Phase 3 trial of selpercatinib in advanced RET-mutant medullary thyroid cancer. N Engl J Med 389:1851, 2023. Minisola S et al: Epidemiology, pathophysiology, and genetics of pri mary hyperparathyroidism. J Bone Miner Res 37:2315, 2022. Ruggeri RM et al: Multiple endocrine neoplasia type 4 (MEN4): A thorough update on the latest and least known MEN syndrome. Endocrine 82:480, 2023. Seabrook AJ et al: Multiple endocrine tumors associated with germ line MAX mutations: Multiple endocrine neoplasia type 5? J Clin Endocrinol Metab 106:1163, 2021. Thakker RV et al: Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 97:2990, 2012.

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