Multiple Endocrine Neoplasia Syndromes

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Key Points

- While children with MEN1 most commonly manifest clinical disease after reaching 10 years of age, there are multiple reports of the syndrome affecting children as young as 5 years.
- The most common initial presenting feature of MEN1 is primary hyperparathyroidism with hypercalcemia, followed by pituitary prolactinoma, and insulinoma with hypoglycemia.
- Medullary thyroid carcinoma and its management dominate the landscape in the management of children with MEN2A and MEN2B, with the specific RET mutation determining level of risk and subsequently the timing of prophylactic thyroidectomy. Surgery is indicated before 1 year of age in the highest-risk group.
- Children with a family history indicating a risk of MEN1 or MEN2 should undergo *MEN1* or *RET* sequencing, respectively, as such testing allows for the targeted use of biochemical and radiographic screening in MEN1, while crucially determining the optimal age for thyroidectomy in MEN2.

35.1 Overview

The multiple endocrine neoplasia (MEN) syndromes constitute an assorted group of familial disorders that include neoplasias (hyperplasia, adenomas, and carcinomas) of endocrine glands. The MEN syndromes include MEN type 1, MEN type 2A and the related familial medullary thyroid carcinoma (FMTC), MEN type 2B, and the rare MEN type 4. The MEN syndromes share similar modes of pathogenesis consisting of germline mutations in discrete genetic loci, propagated via autosomal dominant inheritance. Clinical manifestations vary widely within and between their respective patterns of tumorigenesis. Prior to the identification of the responsible gene mutations, all offspring of affected individuals were considered at risk and were thus subjected to regular biochemical and radiographic best-practice screening. Today, mutation carrier status assessment eliminates the need for prospective screening in any child not harboring the specific familial mutation.

Other syndromes featuring endocrine gland neoplasia, such as von Hippel-Lindau disease, Carney complex, the PTEN hamartoma tumor syndromes, and the rare MEN4 [1], are beyond the scope of this chapter, which is limited to discussion of MEN syndrome types 1 and 2 as they pertain to children and adolescents.

35.2 Multiple Endocrine Neoplasia Type 1

35.2.1 Introduction and Background

Approximately 20 individuals affected by multiple adenomas of various endocrine glands had been described in Europe and the United States when, in 1954, Paul Wermer's paper entitled *Genetic Aspects of Adenomatosis of Endocrine Glands* appeared in the American Journal of Medicine [2]. The presentations of tumors variably affecting the adenohypophysis, the pancreatic islets, and parathyroid glands in a man and four of his nine adult offspring were described, and while the possibility had previously been suggested that a familial disorder may account for the syndrome, Dr. Wermer was the first to propose a single genetic defect with autosomal dominant transmission and high penetrance. Over the 40 years which followed, Wermer syndrome, subsequently renamed multiple endocrine neoplasia (MEN) type 1 [3], proved to fulfill perfectly the assertions made by Dr. Wermer in 1954.

The estimated prevalence of MEN1 ranges from one in 10,000 to one in 50,000 of the general population [4, 5] with an estimated incidence of up to 0.25% from random postmortem studies [6]. MEN1 is a familial syndrome of neoplastic transformation of combinations of endocrine glands, featuring the principle triad of parathyroid hyperplasia, pancreatic neuroendocrine tumors, and pituitary adenomas, recalled by the mnemonic "the 3 Ps" [2, 7]. Nonsecreting carcinoid tumors and adrenocortical tumors, including carcinomas, and non-endocrine tumors, such as lipomas, facial angiofibromas, meningiomas, and skin collagenomas, are occasionally present [8–11]. Any of the three chief components may be

the initially presenting manifestation, and the syndrome may be diagnosed in the presence of any two of the three types of endocrine tumors. The specific constellation of tissue involvement is variable between kindreds, between individuals in an affected family, and even between identical twins [12].

35.3 Primary Hyperparathyroidism

35.3.1 Overview

Primary hyperparathyroidism (pHPT) manifests in approximately 95% of individuals with MEN1 by the fifth decade of life, thus exhibiting the highest penetrance of the MEN1 tumors [4, 13–15]. MEN1-related pHPT is the result of a process of multiglandular, asymmetric, and asynchronous hyperplasia [16], differentiating it from the usually solitary adenoma found in sporadic pHPT.

35.3.2 Clinical Presentation

Primary hyperparathyroidism is usually the initial manifestation of MEN1. It was detected in 75% (120/160) of patients less than 21 years of age in a large, multicenter French study of MEN1 subjects published by the Groupe d'étude des Tumeurs Endocrines (GTE) [11]. Ninety percent of these (110 of 120) were at least 10 years of age, with a mean age at diagnosis of 16 years. Similarly, pHPT was detected at a mean age of 19 years during prospective biochemical screening of adolescents at risk for MEN1 in a Swedish cohort [17]. In the GTE, three children with asymptomatic pHPT were detected before 6 years of age [11], recalling a previous report of MEN1-associated pHPT in a 5-year-old child [18].

The degree of hypercalcemia may be relatively mild [19], and classic symptoms (polyuria, constipation, myalgias, abdominal pain, etc.) may be absent. In adults, loss of bone mineral density tends to be more severe, and onset of renal manifestations such as urolithiasis tends to occur earlier in MEN1-related pHPT in comparison with sporadic pHPT [20–22]. Clinical symptoms, including urolithiasis, fatigue, or bone pain, were present in 17% of the GTE cohort, with a mean age of symptom onset of 15 years [11].

35.3.3 Diagnosis

Primary hyperparathyroidism is diagnosed by the combination of elevated albumin-corrected total serum calcium and an elevated plasma parathyroid hormone (PTH) measured by either an intact PTH assay or a PTH 1–84 assay [23]. Secondary hyperparathyroidism (e.g., PTH elevation subsequent to vitamin D deficiency) and tertiary hyperparathyroidism in the setting of chronic renal failure must be excluded. In cases of hypercalcemia with an inappropriately normal PTH level, familial hypocalciuric hypercalcemia (FHH) must also be considered. When pHPT is confirmed biochemically, parathyroid scintigraphy and/or an ultrasound of the parathyroid glands should be performed but may be relatively insensitive for the detection of multigland hyperplasia [24].

35.3.4 Therapy

As with sporadic pHPT, MEN1-related pHPT is treated surgically, the indications for which, in adults, include symptomatic hypercalcemia or serum calcium more than 1.0 mg/dL above the upper limit of normal, nephrolithiasis or marked hypercalciuria (>400 mg/day), impaired renal function (GFR < 60 ml/min), osteoporosis, or young age (less than 50 years) [25]. Reflecting the characteristic four-gland parathyroid hyperplasia and the predisposition for thymoma in MEN1, the surgical approach consists of bilateral neck exploration with total or subtotal parathyroidectomy and transcervical thymectomy. Two surgical strategies are described [26, 27], consisting of (a) total parathyroidectomy with autograft, in which all identified parathyroid glands are removed, with implantation of a parathyroid autograft to the nondominant forearm and (b) subtotal parathyroidectomy, in which all but one-half gland is removed, leaving a small residual in the neck with its native vasculature. Postoperative hypocalcemia resulting from hypoparathyroidism may complicate either approach but is generally avoided in subtotal parathyroidectomy when as little as 50 mg of parathyroid tissue is left intact [27]. In total parathyroidectomy with autograft, permanent hypoparathyroidism due to autograft failure results in approximately one-third of patients [28]. Regardless of surgical strategy, rates of recurrent hypercalcemia are high – greater

than 50% by 10 years in long-term follow-up series [26, 29], a reflection of the inexorable parathyroid hyperplasia of MEN1.

35.4 Pancreatic Neuroendocrine Tumors

35.4.1 Overview

Neoplastic transformation of pancreatic ductal pluripotent stem cells is reported to occur in 30–80% of adult patients with MEN1. Because of the risk of malignant transformation and metastasis, pancreatic neuroendocrine tumors (PNTs) represent the most important threat to survival in individuals with MEN1 [15]. PNTs are classified according to the primary hormone secreted, if any, and the resulting clinical syndrome. "Nonsecreting" pancreatic tumors (NSPT), which may secrete chromogranin A or pancreatic polypeptide (PP), are otherwise clinically silent and present with mass effects or with metastatic disease, unless detected early via radiographic screening. Among functional PNTs in adults, gastrinoma with Zollinger-Ellison syndrome (ZES) is usually reported as the most common, followed by insulinoma; however in the GTE cohort of patients under 21 years of age, this trend was unambiguously reversed, with 20 out of 160 diagnosed with insulinoma and only 3 presenting with a gastrinoma [11]. NSPTs have been reported in a child as young 12 years of age [30]. Tumors secreting somatostatin, vasoactive intestinal polypeptide, glucagon, and adrenocorticotropic hormone (ACTH) are far less common [31].

35.4.2 Clinical Presentation

Pancreatic neuroendocrine tumors occasionally present as the initial manifestation of MEN1 in children [11, 18]. The mean age at diagnosis of PNT in the Swedish series was 25 years, with a youngest presentation at 16 years [17]; however in the larger GTE cohort, the youngest was a 5-year-old with an insulinoma, who presented with signs of neuroglycopenia [11, 31]. As noted above, insulinoma was diagnosed in 12.5% of subjects (20 of 160) under 21 years of age in the GTE cohort and was the initial manifestation of MEN1 in 10% of all subjects [11], suggesting a greater relative prevalence of this tumor in children and adolescents with MEN1, as compared with adults.

The symptoms and signs of MEN1-related insulinoma are identical to those of sporadic cases, with recurrent and often severe postabsorptive and fasting hypoglycemia, fulfilling Whipple's triad. None of the insulinomas reported in the GTE cohort were malignant; however metastatic insulinoma in an adolescent male has been reported [32] (see below).

Gastrinoma with ZES develops in about one-third of adults with MEN1 and presents roughly 10 years earlier than sporadic ZES [33, 34]. In a large NIH series of ZES, the average age of diagnosis was 33 years, and the youngest patient was 12 years old [35]. Three of the 160 MEN1 subjects in the GTE cohort developed ZES, the youngest of whom was a 6-year-old girl presenting with diarrhea and esophagitis, followed by duodenal and antral ulcers leading to the diagnosis at age 7 [11]. As in adults, in whom gastrinomas as small as 1–2 mm often arise within the duodenal wall and tend to metastasize to local nodes [36], the child in the GTE study had a 2 mm prepyloric gastrinoma with a retropancreatic metastatic node and required reoperation in her adolescent years for hepatic metastases [11].

35.4.3 Diagnosis

Insulinoma should be suspected in a child at risk for MEN1 with symptoms of hypoglycemia such as weakness and adrenergic activation or with symptoms of neuroglycopenia, including confusion, disorientation, loss of consciousness, or seizure. During a carefully monitored fast, the finding of a plasma insulin concentration above 3 μU/mL (18 pmol/L) and C-peptide above 0.60 ng/mL (200 pmol/L), concurrent with plasma glucose less than 45 mg/dL (2.5 mmol/L), confirms hyperinsulinism [37].

Classic symptoms of a gastrinoma include diarrhea, epigastric pain, and peptic ulcer disease or hyperplastic gastric folds on endoscopy. A fasting plasma gastrin level above 200 pg/mL (114 pmol/L) with fasting gastric pH below 5.0 is diagnostic of hypergastrinemia. When the fasting gastrin is under 200 pg/mL, the secretin stimulation test may provide confirmation (increase in serum gastrin of >200 pg/ml above baseline after administration of

1–2 μg/kg of secretin IV) [34]. Gastric carcinoid tumors are common in adults with MEN1-related hypergastrinemia, while enterochromaffin-like cell hyperplasia was reported as essentially universal in such patients [38].

PNTs may secrete multiple hormones; the presence of a NSPT or preclinical tumor formation may be detected by the analysis of plasma PP and gastrin response to ingestion of a mixed meal [39]; however measurement of unstimulated levels of the neuroendocrine hormones glucagon, chromogranin A, and PP has low diagnostic utility [40].

35.4.4 Therapy

As reliable pharmacologic suppression of insulinoma secretory activity is not currently available, localization and surgical excision are the only effective treatment [41, 42], while adjuvant somatostatin analog therapy may be useful in controlling secretory activity of unresectable disease [43]. All of the 20 insulinoma cases reported from the GTE cohort were operated; 17 (85%) were immediately successful, while 3 cases required reoperation [11].

Following imaging for tumor localization, surgery is indicated in patients with PTNs because of the risk for malignant transformation and metastasis. Imaging studies include a combination of T1-weighted magnetic resonance imaging (MRI) and endoscopic ultrasonography [44], somatostatin-receptor imaging [45], or Gallium 68-DOTATATE PET/CT [46]. Surgery may include a combination of duodenotomy and subtotal pancreatectomy or, with the aid of intraoperative ultrasonography, focused enucleation of any identifiable PNTs [31, 33, 47]. Long-term risks of subtotal pancreatectomy include insulin-dependent diabetes mellitus and exocrine pancreas dysfunction.

Because very small, 1–2 mm gastrinomas are commonly hidden within the duodenal wall or within the pancreas, surgical attempts at cure of MEN1-related ZES have historically failed. Medical management of ZES however, irrespective of the potential necessity for surgical resection of bulky or metastatic disease, is extremely effective. The commonest cause of death related to MEN1 classically – duodenal or gastric ulceration and perforation, with massive bleeding – has been virtually eliminated by the mitigation of gastric acid hypersecretion with proton pump inhibitors (PPI) such as omeprazole and lansoprazole.

35.5 Tumors of the Anterior Pituitary

35.5.1 Overview

MEN1-associated anterior pituitary adenomas occur with a general order of incidence comparable to sporadic pituitary tumors: prolactin (PRL)-secreting adenomas are most common, followed by nonsecreting, co-secreting, growth hormone (GH)-secreting, and adrenocorticotropic hormone (ACTH)-secreting adenomas [48]. A pituitary adenoma was the second most frequent tumor in the GTE cohort of young persons, diagnosed in 55 of 160 subjects (34%), and accounting for the initial clinical manifestation of MEN1 in 21% of patients [11]. There were 38 PRL-secreting adenomas (of which 4 co-secreted either GH or ACTH), 14 nonsecreting, 1 GH-secreting, and 1 ACTH-secreting, while one tumor could not be further characterized [11].

35.5.2 Clinical Presentation

Similar to PNTs, the clinical features of pituitary adenomas depend upon hormone hypersecretion, if any, and upon the presence of mass effects. They are very rare before 10 years of age; however an aggressive PRL/GH co-secreting macroadenoma in a 5-year-old child with MEN1 has been reported [49]. As in sporadic cases, pituitary adenomas in adults with MEN1 demonstrate a 2–3:1 female/male ratio [48, 50]. Three-fourths of cases diagnosed before 21 years of age in the GTE cohort occurred in females [11]. Clinical symptoms were present in 55% of GTE cases and included amenorrhea/galactorrhea (44%), headache (13%), visual impairment (9%), Cushing's disease (4%), and acromegaly (2%) [11]. Delayed puberty or hypogonadism, hypopituitarism, and central diabetes insipidus are other possible presentations [51]. GH-secreting adenomas produce acromegalic changes (such as coarsened facial features, hyperhidrosis, interphalangeal synovitis, and headaches) and, if epiphyseal growth plates are open, accelerated linear growth with gigantism. Features of ACTH-secreting adenoma, Cushing's

disease, in children include growth failure and weight gain [51, 52] in addition to classic Cushingoid changes. In the GTE cohort, larger, more locally aggressive pituitary tumors tended to occur in adolescent males [11]. MEN1-associated pituitary tumors in adults are frequently multicentric, large, and may be locally invasive [48].

35.5.3 Diagnosis

A small pituitary adenoma may be seen on MRI as a hypointense lesion on post-gadolinium images [53]. Biochemical screening for a pituitary adenoma in a child or adolescent at risk should include investigation for PRL and GH excess. A plasma PRL concentration of greater than 200 ng/mL (8696 pmol/L) strongly suggests the presence of a prolactinoma, although lower PRL levels in the absence of drugs which raise PRL should also raise concerns for a prolactinoma [51]. A GH-secreting tumor should be suspected when the plasma insulin-like growth factor I (IGF-I) level is above the age- and sex-matched reference range, while confirmation is defined by a failure of plasma GH to suppress to less than 1 mcg/L after an oral glucose challenge [54]. In suspected cases of Cushing's disease, the diagnosis requires unambiguously abnormal results on at least two different first-line tests, which include late-night salivary cortisol, urinary excretion of free cortisol in a 24-h collection, and the overnight low-dose (1 mg) dexamethasone suppression test [55], with a non-suppressed ACTH level.

35.5.4 Therapy

Because dopamine agonist (DA) therapy is usually effective in suppressing PRL hypersecretion and can lead to markedly reduced tumor volume, it is the first line of treatment for a prolactinoma. Tumor resistance to DA therapy in adolescents is not uncommon and may require relatively high dosing [56, 57]. Cabergoline is preferred over bromocriptine due to better tolerability, greater effectiveness at normalizing PRL and at reducing tumor volume, and more convenient twice-weekly administration. It is dosed variably at 0.25–3.5 mg per week [58]. Transsphenoidal or occasionally transcranial surgery at a high-volume center is indicated for the treatment of acromegaly/pituitary gigantism and Cushing's disease and for large non-secreting adenomas [52, 53]. Macroprolactinomas which impinge upon the optic chiasm and/or are unresponsive to dopamine agonist therapy and those causing hydrocephalus may also require operative management.

35.6 Genetics of MEN1

MEN1 is caused by a heritable germline loss-of-function mutation of the *MEN1* gene, located on chromosome 11q13. *MEN1* encodes a 610 amino acid nuclear protein, menin, which acts as an anti-oncogene by regulating several cell-cycle functions including DNA replication, repair, and transcription [16, 59–61]. The syndrome is expressed via loss of heterozygosity, in which a somatic mutation, "a second hit," affects the wild-type normal allele inherited from the non-affected parent. More than 80% of probands with a family history of MEN1 are identified as harboring a germline mutation, whereas in individuals with simplex MEN1 syndrome (i.e., a single occurrence in a family), a mutation of *MEN1* is identified in about 65% [16]. With possible rare exceptions [62], genotype-phenotype correlation is not observed [16, 48, 63].

MEN1 gene mutation analysis should be obtained in any child suspected of having MEN1 on clinical grounds and in all children with a family history of the syndrome [64]. By virtue of autosomal dominant transmission, every child of a parent affected by MEN1 has a 50% chance of inheriting the mutation. The risk of MEN1 in relatives of a proband with no family history will depend upon the genetic status of the proband's parents. DNA analysis and genetic counseling should be offered to all patients and closely related family members at risk for MEN1. Gene analysis should further be obtained in any child or adolescent with pHPT or with a PNT and should be considered in any with a pituitary adenoma.

35.7 Screening of Children and Adolescents at Risk of Developing MEN1

As noted above, the genetic status of any child with a family history of MEN1 must be determined in order to identify those at risk and in need of prospective biochemical and radiographic

Table 35.1 Recommended MEN1 screening outline

	Biochemical (age)	Radiographic (age)
Parathyroid	Total calcium, intact PTH (5–8 yrs)	–
Pancreas	Fasting glucose (5 yrs)	EUS or MRI every other year (10 yrs)
	Fasting gastrin (10 yrs)	
Pituitary	PRL, IGF-I (5–8 yrs)	MRI every other year (5–8 yrs)

All biochemical screening is recommended yearly
EUS endoscopic ultrasound, *IGF-I* insulin-like growth factor I, *MRI* magnetic resonance imaging, *PTH* parathyroid hormone, *PRL* prolactin
Adapted from Goudet et al. [11]

screening. Such screening is unnecessary in any child whose *MEN1* analysis is negative for the mutation identified in affected relatives. Several groups have published recommendations for MEN1 screening in children [5, 11, 16, 63]. Screening should be carried out in any child with a known *MEN1* mutation, as well as in any child of a parent with clinical MEN1 without an identified mutation (Table 35.1).

The recommended age for initiating annual biochemical screening has decreased as numerous reports of children as young as 5 years of age, affected by various MEN1-related tumors, have accumulated [11, 18, 31, 49]. The relatively low risk of tumorigenesis before the second decade, however, suggests that delay of screening until 5–10 years of age and of proceeding with a stepwise approach is reasonable. Screening for insulinoma is recommended to begin at 5 years of age with the annual measurement of fasting plasma glucose; the fasting insulin is not a useful screening test. Clinicians must watch for indications of hypoglycemia, while parents and young patients should also be familiarized with the classic symptoms [11]. Annual screening for hyperparathyroidism should begin at 5–8 years of age with measurement of plasma total calcium with intact PTH. Pituitary tumor screening should also begin at 5–8 years with measurement of plasma IGF-I and prolactin, as well as pituitary MRI every third year. Screening for non-insulinoma PNTs should begin by age 10 years [11], with the annual measurement of fasting plasma gastrin, and with T1-weighted contrast-enhanced pancreatic MRI or endoscopic ultrasound, every other year. The reader is referred to Table 6 in Goudet et al. [11] for a direct comparison of various screening recommendations.

35.8 Multiple Endocrine Neoplasia Type 2

35.8.1 Introduction

In 1959, 5 years after the publication of Dr. Wermer's paper and while a resident in internal medicine at the State University of New York, Syracuse, John Sipple was consulted on a hypertensive man who had been operated for a hemorrhagic cerebral arteriovenous malformation [65]. The patient died in a matter of days, and on autopsy, Dr. Sipple was impressed by the striking finding of bilateral pheochromocytomas, bilateral thyroid carcinomas, and a parathyroid adenoma. He commenced a meticulous review of published cases of pheochromocytoma in search of other patients with associated thyroid carcinoma. Among 537 cases of pheochromocytoma, five also had thyroid cancer [65]. He published *The association of pheochromocytoma with carcinoma of the thyroid gland*, in the American Journal of Medicine in 1961 [66]. Sipple syndrome, as the entity has been known, was named MEN type 2 in 1968 [3].

Progressive advances in our understanding of MEN2 have revolutionized clinical care of patients with the syndrome. Recognition of its clinical components and autosomal dominant pattern of inheritance was followed by the development of improved biochemical methods of preclinical screening [67]. The characterization of activating point mutations of the *RET* proto-oncogene as the initiating molecular defect for MEN2 and for the familial medullary thyroid carcinoma variant [68, 69] allowed for recognition of the strong genotype-phenotype correlation with specific *RET* codon involvement [70]. This enabled prediction of medullary thyroid carcinoma (MTC) tumor

aggressiveness and risk for early tumorigenesis, which transformed clinical practice. Genetic testing in members of families affected by MEN2 is therefore a tool not merely for recognition and screening but also as an important guide to disease management of MTC in particular, surpassing the utility of calcitonin-based stimulation testing.

MEN2 includes two distinct syndromes – MEN2A with its three subtypes and MEN2B [71]. Classic MEN2A, the most common of the MEN2 syndromes, consists of MTC, pheochromocytoma, and parathyroid hyperplasia [72]. The MEN2A subtypes include:

- MEN2A with cutaneous lichen amyloidosis (MEN2A-CLA), characterized by a pruritic rash caused by deposition of keratin-like peptide in the dermal-epidermal junction [73, 74] and accounting for about 5% of MEN2A cases
- MEN2A with Hirschsprung disease (MEN2A-HD), heralded in infancy with underweight, abdominal distension, and constipation or obstipation [75] and accounting for about 8% of MEN2A cases [76]
- Familial medullary thyroid carcinoma (FMTC), a distinct entity involving only MTC without other associated endocrinopathies [77] and accounting for 10–20% of cases of MEN2 [75]

MEN2B, which accounts for about 5% of all MEN2 cases, includes MTC associated with pheochromocytoma; parathyroid hyperplasia is almost universally absent. MEN2B is further defined by peculiar phenotypic features including a Marfanoid habitus (without cardiac, palate, or lens anomalies), mucosal and conjunctival neuromas [78–80], and diffuse transmural intestinal ganglioneuromas [81]. The often unsubtle presence of oral mucosal neuromas may be present in infancy, allowing for the possibility of early diagnosis of the syndrome [82]. The incidences of the various clinical manifestations of MEN2 are summarized in Table 35.2.

Table 35.2 Incidence of clinical manifestations associated with MEN2A, 2B, and FMTC

	MEN2A (%)	MEN2B (%)	FMTC (%)
MTC	95	100	100
Parathyroid hyperplasia	10–25	<5	0
Pheochromocytoma	~50	~50	0
Mucosal ganglioneuromas	0	~100	0

35.9 Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) is a bilateral, multifocal cancer originating in the calcitonin-secreting parafollicular C cells, distributed primarily in the upper third of the thyroid lobes. MTC develops in more than 90% of individuals with MEN2, often as the initial manifestation of disease [83, 84]. The MEN2 syndromes account for about 25% of all MTC cases. Metastatic MTC is the most common cause of death in the MEN2 syndromes [85] and represents the end result of a process which begins with C cell hyperplasia progressing to microscopic carcinoma, macroscopic carcinoma, locoregional lymph node metastases, and finally distant metastatic disease over a time course of months to years [83–86]. The specific *RET* codon mutation determines the risk of early tumorigenesis, which can be extremely early: MTC has been diagnosed in a 9-week-old infant with MEN2B [87]. Similarly, in MEN2A, C cell hyperplasia has been demonstrated in a child as early as 20 months of age [88], MTC as early as 3 years of age [89], and metastatic disease as early as 6 years of age [90]. MTC associated with MEN2B is more aggressive than both sporadic MTC and MEN2A-associated MTC [91].

Total thyroidectomy offers the only possibility of cure for MTC and is recommended for all children with MEN2. Surgery performed before disease that is clinically apparent has been termed "prophylactic" thyroidectomy; however in most cases C cell hyperplasia or MTC is identified in surgical pathology [71]. The appropriate age for thyroidectomy is determined based upon the particular *RET* mutation involved and upon clinical data including the basal or stimulated calcitonin level [71]. Although consensus is lacking in regard to timing of surgery, guidelines updated by the American Thyroid Association in 2015 offer a

thorough discussion of the problem with expert recommendations [71]. The guidelines take into consideration the *RET* mutation risk divided into highest-, high-, and moderate-risk categories, informed further by serum calcitonin and carcinoembryonic antigen levels. Surgery is recommended before 1 year of age in the highest-risk group, by 5 years in the high-risk group, and before age 10 in the moderate-risk group [71]. The adequacy of the initial operation determines clinical success [5, 71]. In light of the rarity of MEN2, its complicated diagnostic considerations, clinical and surgical demands, postoperative decision-making, and the need for ongoing outcome data, it is recommended that early thyroidectomy for children occur in experienced tertiary care settings [71].

35.10 Pheochromocytoma

Pheochromocytoma occurs in about one-half of patients with MEN2, with a mean age at presentation of 25–32 years [92, 93]. It has been reported, however, in a child with MEN2A as young as 8 years of age [94], and hypertensive encephalopathy secondary to pheochromocytoma has been described in a 13-year-old child with MEN2A [95]. It is infrequently detected before the onset of MTC [85, 92, 93]. Similar to MTC, pheochromocytoma in MEN2 is usually multicentric and is found in the context of diffuse adrenomedullary hyperplasia [72]. About half of MEN2-related pheochromocytomas are bilateral [96], and while extra-adrenal tumors occur, they are rare. Malignant pheochromocytoma is also relatively rare in MEN2, with an incidence in the range of 0–8% [96, 97].

The classic history of facial pallor, paroxysmal hypertension, and headache is not reliably present in MEN2-related pheochromocytoma. Clinical manifestations may be subtle, and more than one-half of individuals are asymptomatic and normotensive [98]. Symptoms may include paroxysms of anxiety, palpitations or tachycardia, headaches, and diaphoresis. Most children with pheochromocytoma who are hypertensive have sustained rather than paroxysmal hypertension [99]. Initial biochemical findings include elevated plasma levels of the epinephrine metabolite metanephrine, with an increase in urinary excretion of metanephrines and catecholamines.

35.11 Primary Hyperparathyroidism

Approximately 20% of persons affected by MEN2A eventually develop hyperparathyroidism [5], as a result of parathyroid adenomatous formation within a background of hyperplasia involving multiple glands [100]. The diagnosis of pHPT in MEN2 is as noted in the discussion of MEN1 above, hinging on hypercalcemia with a concurrently elevated (or high normal) intact PTH level. Pheochromocytoma is a rare cause of hypercalcemia but should be considered and excluded as well in patients with MEN2 [86].

35.12 Diagnostic Guidelines: Screening for the Presence of MEN2

35.12.1 Genetics of MEN2 Syndromes

Discussion of screening paradigms for the presence of MEN2 must be prefaced by an understanding of the molecular genetics of the disorder, since current standards of care are based on the outcome of DNA testing. The MEN2 syndromes are either inherited as an autosomal dominant disorder, or they occur as new germline mutations in the absence of a family history. The gene locus for MEN2 was linked in 1987 to the centromeric region of chromosome 10 [101, 102]. Single activating point mutations within the *RET* proto-oncogene were found to associate with the range of clinical phenotypes of the MEN2 syndromes [70]. The *RET* gene, at chromosome 10q11.2, encodes RET, a transmembrane receptor tyrosine kinase which transduces growth and differentiation signals in several developing tissues, and plays a critical role in neural crest development and in neural crest-derived tumors [80, 103]. MEN2 is caused by gain-of-function missense mutations in the RET extracellular cysteine-rich region involved in receptor dimerization and in the intracellular tyrosine kinase domain [70]. Codon 634 mutations are present in about 80% of individuals affected with the classic MEN2A syndrome, although a small percentage of families harboring this mutation have FMTC only. MEN2B is most commonly associated with a germline

mutation of codon 918 and less commonly with a mutation of codon 883 [104]. The specific *RET* codon mutation present correlates with the phenotypic expression of MEN2 [70, 105].

35.12.2 Screening for the Presence of MEN2

Prior to the era of molecular genetic screening, provocative testing of calcitonin release using pentagastrin stimulation was the preferred procedure for MTC screening [86]. The test is administered by giving pentagastrin 0.5 mcg/kg as an intravenous bolus over 5–10 s, followed by plasma calcitonin measurement at 2 and 5 min. Widely available DNA testing has surpassed calcitonin stimulation in importance, though biochemical screening does retain utility in the assessment for C cell hyperplasia and MTC [71].

The use of DNA testing in at-risk family members allows detection of the MEN2 syndrome before development of C cell abnormalities, allowing for potentially curative or truly prophylactic thyroidectomy. DNA testing also eliminates the need for repeated biochemical testing in those that do not harbor a *RET* mutation. And finally, DNA testing eliminates the false-positive rate of the pentagastrin test, which is estimated at 3–5% and which may have resulted in unnecessary thyroidectomy [104]. Screening for *RET* germline mutations can be performed at any age from birth onward, since only a small blood sample is required. Genotyping should thus ideally be performed before the age at which thyroidectomy would be recommended if a mutation were discovered [106]. Multiple centers now offer genomic DNA analysis for *RET* mutations (see endnote). Perhaps the greatest difficulty occurs in the rare situation where germline transmission of MTC is proven, but no *RET* mutation is identified, in which case it may be necessary to identify a research laboratory that will analyze regions of the *RET* gene outside the most commonly mutated regions [107].

35.12.3 Screening: Pheochromocytoma and Hyperparathyroidism

Annual screenings for pheochromocytoma consisting of blood pressure measurement and biochemical testing should be initiated in all children with a known RET mutation beginning at 5 years of age [108]. Measurement of plasma-fractionated metanephrines offers the highest sensitivity and is generally easier to obtain in children than 24-h urine collection. However the relatively low specificity of plasma metanephrines necessitates measuring fractionated metanephrines and catecholamines in a 24-h urine collection, for confirmation [109]. When the diagnosis is confirmed biochemically, imaging with adrenal computed tomography (CT) or MRI is indicated for localization. The presence of pheochromocytoma must be ruled out prior to any operative procedure to avoid a hypertensive crisis in the perioperative period. When both MTC and pheochromocytoma are present, the adrenal tumor should be resected before thyroidectomy is undertaken.

Screening for hyperparathyroidism in patients with MEN2A includes measurement of serum calcium yearly, beginning at 11–16 years, depending upon the RET mutation present [71]. An elevated serum albumin-corrected total calcium should be repeated for confirmation, with an intact PTH. Treatment is as discussed above for MEN 1-related primary hyperparathyroidism.

35.13 Management of MEN2 Kindreds: Incorporating Genetic Data

The availability of the highly sensitive and specific DNA-based screening for identification of the MEN2 syndromes spares half of patients at risk – those without a demonstrable genetic mutation – from further specialized medical follow-up. Because pheochromocytoma is rarely malignant in the MEN2 syndromes, genetic identification of a *RET* mutation does not dictate prophylactic adrenalectomy. Hyperparathyroidism occurs in a minority of patients and also does not have malignant potential. Recommendations for screening for these components of the syndrome therefore remain unchanged by the genetic advances, with the exception that only those with mutations demonstrated by DNA-based testing need to undergo recurrent screening.

Most influenced by the advent of DNA-based diagnostic testing is the management of MTC. The opportunity to improve the outcome for those with MTC lies in the performance of a safe and comprehensive initial surgical procedure [71, 88, 89].

Multiple studies have demonstrated that stage of disease at diagnosis most accurately predicts the length of patient survival [71, 88]. For those with MEN2B, due to the more aggressive form of disease, prophylactic thyroidectomy is recommended as early as possible [88]. Genetic diagnosis of the MEN2 syndromes is readily available commercially.

35.14 Conclusion

The multiple endocrine neoplasia syndromes in their various forms are capable of producing significant morbidity in children and adolescents. Molecular genetic analysis allows conclusive identification of children at risk, making possible the elimination of needless and costly surveillance for half of offspring of affected parents. Extensive experience with affected and at-risk children, as accumulated and published by the GTE and other groups, has yielded fuller awareness of the early natural history of the MEN syndromes while allowing for improved biochemical and radiographic screening protocols. The goal of early disease detection before the onset of morbidity has become increasingly possible. The treatment of MEN-related tumors should be undertaken in centers with experience in the management of these challenging syndromes.

MEN1 Case Study

A previously well 16-year-old male was referred for evaluation of a 4-month history of episodic tremors, sweats, and palpitations. Episodes tended to occur in the morning hours, were sometimes accompanied by disorientation, and were relieved with eating. He had gained 15 pounds in the 2 months prior to presentation. He was taking no medications, and no family members were taking oral hypoglycemic drugs. A paternal uncle had been diagnosed with a prolactinoma at 30 years of age; there was no family history of further tumors nor of hypercalcemia. On examination he was moderately overweight and had stage IV sexual maturity.

Laboratory testing revealed:

- Fasting blood glucose 41 mg/dL, 2.3 mmol/L (60–99 mg/dL, 3.4–5.6 mmol/L)
- Plasma insulin 38 mIU/L, 264 pmol/L (0–17 mIU/L, 0–118 pmol/L)
- C-peptide 5.0 ng/mL, 1655 pmol/L (0.9–4.3 ng/mL, 298–1423 pmol/L)
- Albumin-corrected serum total calcium 10.9 mg/dL, 2.73 mmol/L (8.6–10.4 mg/dL, 2.15–2.60 mmol/L)
- Intact PTH 72.1 pg/mL, 7.6 pmol/L (11.0–67.0 pg/mL, 1.2–7.1 pmol/L)
- Serum prolactin 19.5 ng/mL, 415 mU/L (3.0–15.0 ng/mL, 63–319 mU/L)
- Serum testosterone 216 ng/dL, 7.5 nmol/L (100–1200 ng/dL, 3.5–41.7 nmol/L)

Serum gastrin was not measured preoperatively.

Abdominal MRI revealed a macrolobulated distal pancreatic neoplasm measuring 10 x 8 x 7 cm, with heterogeneous T1 hypointensity and intermediate to hyperintense T2 signal. Several hepatic lesions ranging from 2 to 11 mm were also noted; the larger lesions demonstrated T2 hyperintensity and rim enhancement. Brain MRI demonstrated a 5 mm anterior pituitary T1-hyperintense microadenoma. Ultrasonography of the neck revealed a subcentimeter left parathyroid mass, a suspected adenoma. Genetic analysis of *MEN1* was recommended but was declined.

Distal pancreatectomy and splenectomy with wedge biopsy of the left lateral liver were performed, confirming a pancreatic neuroendocrine tumor with liver metastases, staining positive for insulin, with minor positive staining for gastrin (TNM tumor classification T2 N0 M1). Immediately following surgery, episodes of hypoglycemia and of dyspepsia ceased.

Indium In-111 pentetreotide (OctreoScan®) revealed minimal uptake of octreotide within hepatic metastases. Monthly Sandostatin® LAR (octreotide acetate) injections were started after a short initial course of subcutaneous octreotide injections.

No further episodes of hypoglycemia occurred over the 24 months following surgery, while the liver metastases remained stable on Sandostatin® LAR. Mild hypercalcemia and hyperprolactinemia remained stable, and the pituitary microadenoma also remained stable in size. After 2 years of treatment, the patient elected to discontinue octreotide because of abdominal discomfort and lightheadedness which were attributed to somatostatin analog treatment. Within several months however, new growth of the liver metastatic disease was noted. Treatment was restarted with lanreotide (Somatuline® Depot), and the patient remains under close follow-up.

For information on genetic screening for MEN types 1 and 2, see ► www.genetests.com.

Review Questions

1. Which of the three tumor types forming the classic triad of MEN1 is most commonly the initial presentation in the pediatric age group?
2. What is the second most commonly encountered category of tumors in children and adolescents, and what is the most common subtype?
3. What PNT tumor subtype, relatively rare in adults with MEN1, was the most common PNT tumor among the GTE cohort of patients? What was the second most commonly diagnosed PNT in this study?
4. C cell hyperplasia or MTC occurs in virtually all children with MEN type 2A and type 2B and has been reported extremely early in both types, necessitating prophylactic thyroidectomy. In which type, MEN 2A or 2B, does MTC most characteristically exhibit aggressive behavior?
5. Which MEN2A and 2B tumor occurs in about one-half of patients and is uncommonly diagnosed prior to adulthood?
6. What physical characteristic of MEN2B may appear early in life and allows for ready differentiation from MEN2A?
7. A child with no family history of endocrine tumors presents with hypercalcemia and an intact PTH level in the upper one-third of the normal range. What gene should be sequenced?

Answers

1. pHPT was detected in 75% of the GTE cohort of patients under 21 years of age, presenting at a mean age of 16 years. It was the most common initially diagnosed tumor of MEN1 in the study; however it was the initially presenting tumor in only 56% of cases. Three children with asymptomatic pHPT presented under age 6, indicating how early parathyroid hyperplasia may develop in MEN1.
2. Pituitary adenoma is the second most common tumor type diagnosed in children with MEN1, led by prolactinoma. Prolactinoma is the second most commonly diagnosed discrete MEN1 tumor in the pediatric age group, after pHPT.
3. Insulinoma was the most common PNT diagnosed in the GTE cohort, representing the initial manifestation of MEN1 in 10% of cases. NSPT was the second most common PNT in the GTE cohort.
4. MTC tends to be more aggressive, metastasizing early in MEN2B, as compared with sporadic MTC and MEN2A-associated MTC.
5. Pheochromocytoma occurs in MEN2A and 2B with roughly equal incidence, about 50%.
6. Mucosal ganglioneuromas are distinct in appearance and may be seen in very young children affected with MEN2B. They do not occur in MEN2A.
7. A child presenting with pHPT without a family history may likely represent a proband case of MEN1 and should be screened for a mutation in *MEN1*, the menin gene.

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