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Review

Multiple Endocrine Neoplasia in Childhood: An Update on Diagnosis, Screening, Management and Treatment

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Abstract: Multiple endocrine neoplasia (MEN) is a group of heterogenous syndromes characterized by the occurrence of two or more endocrine gland tumors in a patient or related individuals in the same family. They are inherited in an autosomal dominant fashion and are highly penetrant. There are three types of MEN syndromes: MEN type 1 (MEN1), MEN type 2 (MEN2), and MEN type 4 (MEN4). MEN2 is further divided into MEN2A, MEN2B (formerly known MEN3), and familial medullary thyroid carcinoma (FMTC). Although MEN syndromes are rare, it is crucial to identify individuals at risk for potentially life-threatening neoplasias. This review article provides an update on each MEN syndrome, its genetics, diagnosis, and management in children.

Keywords: multiple endocrine neoplasia; MEN1; MEN2A; MEN2B; MEN4; familial medullary thyroid carcinoma

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1. Introduction

Multiple endocrine neoplasia (MEN) is a rare group of inherited disorders with the occurrence of two or more endocrine gland tumors in an individual or related individuals in the same family [1]. These disorders are inherited in an autosomal dominant fashion and are highly penetrant. They can appear at any age, and symptoms vary depending on which endocrine and non-endocrine organs are affected. There are three types of MEN syndromes: MEN type 1 (MEN1), MEN type 2 (MEN2), and MEN type 4 (MEN4). MEN1 (Wermer's syndrome) mainly affects the parathyroid, pituitary, and pancreas [2]. MEN1 is caused by germline heterozygous loss-of-function mutations in the tumor suppressor gene *MEN1* [1]. MEN2 is further divided into MEN2A, MEN2B (formerly known MEN3), and familial medullary thyroid carcinoma (FMTC). Thyroid, parathyroid, and adrenal glands are the principal glands involved in MEN2 syndromes. According to the latest American Thyroid Association (ATA) 2015 guidelines, FMTC is recognized as a variant of MEN2A with decreasing penetrance of hyperparathyroidism and pheochromocytoma [3]. MEN2 occurs due to mutations in the tyrosine kinase receptor encoded by the REarranged during Transfection (*RET*) proto-oncogene on 10q11.2 [4].

MEN4 is the most recent member of the MEN syndromes caused by mutations in the putative tumor suppressor gene, a cyclin-dependent kinase inhibitor (*CDNK1B)* [5]. Similar to MEN1, affected patients have primary hyperparathyroidism and pituitary adenoma (the most common phenotype), pancreatic neuroendocrine tumors in association with gonadal, adrenal, renal, and thyroid tumors [6].

In this review, we provided an update on MEN syndromes and their genetics as well as guidelines for screening and management considerations in children. Identifying at-risk individuals is crucial in preventing and treating potentially life-threatening endocrine and non-endocrine neoplasias, thereby improving and prolonging life.

2. Multiple Endocrine Neoplasia Type 1 (MEN1)

2.1. Clinical Presentation

MEN1, also known as Wermer's syndrome, is characterized by tumors of the parathyroid glands, anterior pituitary, and gastro-entero-pancreatic system. The worldwide prevalence is 3–20 in 100,000 individuals; this variation in prevalence is theorized to be due to founder effects (Table 1) [7–10]. The syndrome is autosomal dominant with an extremely high penetrance—50% of cases will manifest characteristic tumors by age 20 and 95% by age 40 [8]. Both hereditary (familial) and non-hereditary (sporadic) forms exist [7,9].

Table 1. MEN syndrome types and associated clinical and genetic characteristics in children.

	Prevalence	Clinical Features	Youngest Age of Presentation (Years)	Genes and Common Variants
MEN 1				*MEN1*
	3–20:100,000	Parathyroid adenoma (most common)	10	
		Pancreatic neuroendocrine tumors		
		- Gastrinoma - Insulinoma - Glucagonoma - VIPoma	Rare; insulinoma reported in a 5 year old child	
		Pituitary adenomas		
		- Prolactinoma (most common) - Somatotrophinoma - Corticotrophinoma	5	
		Associated tumors (less common): Endocrine:		
		- Adrenocortical - Thymic and bronchial carcinoid	Rare	
		Non-endocrine:		
		- Angiofibroma - Collagenoma - Lipoma		
MEN 2				*RET*
Type 2A	1:36,000–1:200,000	MTC	2	Exons 10 (codon 634) and 11
		Pheochromocytoma	8	
		Parathyroid adenoma	2	
Type 2B	1:600,000–1:4,000,000	MTC	Infancy	Exon 16 (codon 918)
		Pheochromocytoma	12	
		Intestinal ganglioneuroma Mucosal neuroma Marfanoid habitus	Infancy	
MEN 4	Unknown	Parathyroid hyperplasia and adenoma	Third decade of life	*CDKN1B*

RET = REarranged during Transfection; MTC = medullary thyroid carcinoma.

The most common manifestation of MEN1 in children is primary hyperparathyroidism (PHPT) due to parathyroid gland hyperplasia; up to 75% of affected children will develop PHPT, most commonly after age 10 [11]. By age 50, 95% of MEN1 patients will have developed PHPT; onset is typically at 20 to 25 years of age [2,12,13]. Prevalence is similar in both males and females [14,15]. MEN1-associated PHPT occurs about 30 years earlier than sporadic forms of PHPT. Moreover, MEN1-associated PHPT presents with diffuse parathyroid hyperplasia versus the single adenomas characteristic of sporadic PHPT. PHPT

is typically asymptomatic, even if hypercalcemia is present. If hypercalcemia does become symptomatic, an affected child can present with malaise, polyuria, polydipsia, or constipation. The degree of hypercalcemia is rarely severe enough to lead to crisis [10,14].

Pancreatic islet cell tumors, also referred to as pancreatic neuroendocrine tumors (NETs), are the second most frequent manifestation of MEN1 [14]. These tumors occur in 70–80% of patients with onset most often after the age of 40 [10]. In order of decreasing penetrance, NETs include gastrinomas (40%), non-functioning pancreatic polypeptide-secreting tumors (PPomas), insulinoma, glucagonomas, and vasoactive intestinal polypeptidomas (VIPomas) [14]. Pancreatic tumors have significant potential for malignancy and are therefore important to screen for during evaluation in patients with MEN1.

Gastrinomas are gastrin-secreting tumors that are characterized by excessive gastric acid production and recurrent peptic ulcers that occur in individuals older than 30 years of age [14]. They are rare in children but are typically aggressive if present [11,16]. Gastrinomas occur three times more commonly in the duodenum than in the pancreas [17]. However, those found in the pancreas have a 50% incidence of liver metastasis [18]. The extent of the liver involvement due to a gastrinoma is the most important predictor of survival [19]. Zollinger-Ellison Syndrome (ZES) is a syndrome of gastric acid hypersecretion caused by gastrinomas and occurs in approximately 50% of patients with MEN1. Diagnosis may be delayed up to 3 to 5 years [20]. Individuals may present with signs and symptoms of peptic ulcer disease, gastroesophageal reflux, and secretory diarrhea. Severe ulcers resulting from gastric acid hypersecretion are one of the most common causes of MEN1-related premature death [12]. Hypercalcemia from parathyroid adenomas can further increase serum gastrin levels and thus worsen symptoms [21]. The onset of ZES is more likely to occur after PHPT is diagnosed [20]. Diagnosis is established by identifying serum gastrin levels greater than 10 times the upper limit of normal in the setting of increased basal gastric acid secretion [14].

Insulinomas are insulin-secreting tumors of the pancreatic beta-cells and are the second most common NET to occur in those with MEN1 (incidence of approximately 10%) [14]. They are most often the first manifestation of MEN1 in individuals less than 20 years old [2,11]. Insulin hypersecretion leads to hypoglycemia, which at times can be severe, and is often pronounced during times of fasting or exertion [14]. Individuals will clinically present with symptoms such as weakness, blurry vision, or even seizures. Biochemical studies reveal inappropriately elevated insulin and c-peptide levels in the setting of hypoglycemia.

Several MEN1-associated neuroendocrine tumors, which have been noted to occur in adults, have not been well-described in children. Glucagon-secreting pancreatic tumors, also known as glucagonomas, arise from alpha-cells of the pancreas. They occur in less than 3% of adults with MEN1 [14]. Interestingly, *MEN1* mutations are discovered in 60% of sporadic glucagonomas [17]. Clinically, patients may present with a rash (necrotizing migratory erythema), weight loss, or hyperglycemia. Individuals with glucagonoma also have an increased risk of venous thromboembolism [22]. Glucagonomas may be found incidentally on routine imaging. Another rare MEN1-associated tumor is VIPoma, which presents in less than 1% of patients and is characterized by profuse secretory diarrhea, hypokalemia, and achlorhydria [14]. Diagnosis may be established by noting fasting stool volumes of 0.5 to 1.0 L per day in addition to a markedly elevated plasma VIP concentration. Aside from alpha and beta islet cell tumors, delta cells (somatostatin-producing cells) may also participate in hormone hypersecretion. However, hypersecretion of somatostatin is rare.

Non-functioning NETs are tumors that are not associated with a particular syndrome and do not present clinically, except in the case of significant mass effect. They have a frequency of 55% in those with MEN1 and are most often located within the pancreas [9,23]. Non-functioning NETs have been discovered in patients less than 15 years of age and as young as age 10 [24,25].

Pituitary adenomas are the third-most common tumors in adults with MEN1 and occur in approximately 30 to 50% of individuals, with prolactinomas being the most common (60%) [9,11,14,16]. In children, pituitary adenomas occur second in frequency (34%) of MEN1 tumors and occur as young as 5 years of age [11,16,26]. In sporadic pediatric prolactinoma cases, up to 6.5% are associated with previously undiagnosed MEN-1 [27]. Pituitary adenomas are more frequent in females with a 3.2:1 female to male ratio during childhood [14]. However, in both children and adults, males present with more macroadenomas, which are also more aggressive than those found in females [11,28]. Other anterior pituitary tumors include somatotrophinomas (growth hormone-secreting; 25%) and corticotrophinomas (adrenocorticotropic hormone-secreting; 5%) with the remainder being non-functioning adenomas [14,29]. Clinical symptoms depend on the hormones secreted in addition to tumor size, which can cause compressive effects leading to vision loss; malignancy is highly unusual [9].

Affected individuals may also develop other endocrine tumors, including adrenocortical tumors, bronchial and thymic carcinoid tumors, as well as non-endocrine tumors such as collagenomas, facial angiofibromas, and lipomas.

2.2. Diagnosis

Diagnosis of MEN1 can be made on clinical, familial, or genetic grounds [14]. A clinical diagnosis is suspected if there are two or more MEN1-associated tumors. However, expression of the MEN1 phenotype is age-dependent. As such, clinical manifestations may not be noted prior to age 5, as clinical features are rare before this age [14]. For familial diagnosis, the patient must have a MEN1-associated tumor and a first-degree relative with MEN1. Identification of a germline *MEN1* mutation secures a genetic diagnosis and is the primary means by which children and adolescents are diagnosed [16]. In relatives of MEN1-affected patients, genetic testing should be completed before age 5 since children are often clinically asymptomatic [14]. In approximately 5–25% of individuals with a clinical diagnosis of MEN1, a genetic mutation cannot be found [30,31]. This is described as a phenocopy. MEN1 phenocopies are common and can be a confounder for genetic testing. Those with a mutation-negative MEN1 phenotype tend to develop MEN1 characteristics, such as PHPT and pituitary adenoma, at more advanced ages [31,32]. Given that MEN1 mutation-positive and mutation-negative individuals have differing clinical courses, those who are mutation-negative are sometimes considered to have a separate MEN1-like syndrome [32]. Population analysis indicates that the life expectancy of an individual with mutation-negative MEN1 is not altered by their diagnosis [31]. However, in patients with a confirmed *MEN1* mutation, they present with a reduced life expectancy averaging 63 years of age, often due to death from gastroenteropancreatic malignancy [12].

2.3. Genetics

MEN1 is caused by a germline mutation in the *MEN1* gene, which is found at locus 11q13 [16]. The gene consists of 10 exons that encode a 2.8 kB mRNA segment, which is then translated into a 610 amino acid protein called menin [12,17]. There are more than 1200 reported mutations that result in MEN1, 75% of which result in the loss of function of menin [8]. Mutations in both the coding and noncoding regions of *MEN1* have been implicated in MEN1 pathogenesis [12]. Identification of MEN1 index cases is generally through the discovery of MEN1-related tumors, followed by confirmation of *MEN1* mutation via genetic testing [9]. Although such a wide variety of *MEN1* mutations exist, MEN1 does not have any known genotype-phenotype correlation. Lack of a strong genotype-phenotype correlation, even within one family, is likely due to the structure of menin itself, as all regions of this protein are essential for proper function [17].

Though a genotype-phenotype correlation is not well-recognized in MEN1, studies have explored potential epigenetic changes in menin that may be responsible for MEN1 phenocopies, especially in mutation-negative individuals. MicroRNAs (miRNAs) regulate gene expression and several have been found to downregulate the expression of menin

such as miR-24, miR-29b and miR-762 [33]. Specific miRNAs have been found to be key in the development of insulinomas and parathyroid adenomas [34,35]. In evaluating both MEN1-related and sporadic NETs, hypermethylation of CpG regions on DNA has also been frequently noted [36]. As epigenetic changes are reversible, further study may ultimately help discover potential therapeutic options.

2.4. Screening

In individuals with MEN1, mortality rates associated with manifestations of the syndrome are as high as 50%; the most common causes of death are sequelae of pancreatic endocrine tumors [37–40]; therefore, early screening is crucial. Children as young as age 5 can present with manifestations of MEN1, such as insulinomas [11,14,41]. *MEN1* germline mutation testing should be offered to relatives of MEN1 patients, especially children and adolescents, even if relatives are asymptomatic. Individuals found to have a *MEN1* germline mutation are recommended to undergo annual screening for MEN1-related tumors (Table 2). Annual screening for PHPT with plasma calcium and parathyroid hormone (PTH) is recommended. Screening for NETs, such as insulinomas and gastrinomas, should start at 5 years and 20 years of age, respectively. Imaging with MRI, CT, or endoscopic ultrasound are recommended, but recent advances have shown benefit in utilizing 68Ga dotatate PET/CT [42]. Pituitary adenomas are screened with annual serum prolactin and insulin-like growth factor-1 (IGF-1) and MRI every three years. Even after pituitary adenoma resection, it is suggested that screening continue as tumors may recur from residual tumor cells [43].

Table 2. Screening recommendations for MEN1 and MEN2.

	Tumor	Age to Begin (Years)	Laboratory and Imaging
MEN 1	Parathyroid adenoma	8	Calcium, PTH
	Gastrinoma	20	Gastrin
	Insulinoma	5	Fasting glucose and insulin
	Pituitary adenoma	5	Prolactin, IGF-1, MRI
MEN 2			Genetic testing for RET
Type 2A	MTC	3–5	Calcitonin
	Pheochromocytoma	16	Plasma/urine metanephrines and normetanephrines, CT or MRI
	Parathyroid adenoma	16	Calcium, PTH
Type 2B	MTC	0.5	Calcitonin
	Pheochromocytoma	11	Plasma/urine metanephrines and normetanephrines, CT or MRI

PTH = parathyroid hormone; IGF-1 = insulin-like growth factor 1; MRI = magnetic resonance imaging; RET = RE-arranged during Transfection; MTC = medullary thyroid carcinoma; CT = computed tomography.

2.5. Treatment

The treatment of choice for parathyroid tumors is surgical resection [9,14]. The preferred timing and surgical approach of tumor resection is still debated in children and adolescents. In adults, surgical options include partial parathyroidectomy, subtotal parathyroidectomy (removal of 3.5 glands), or total parathyroidectomy with or without autotransplantation (transplantation of the remaining normal parathyroid tissue into the forearm) [44,45]. Post-surgical complications, such as permanent hypoparathyroidism and laryngeal nerve damage, can occur and are important to consider with respect to age and timing of surgery. Studies of MEN1-related PHPT are limited. However, studies have shown that children with non-MEN1 PHPT can be successfully treated by partial parathyroidectomy in the same manner as adults [46]. Persistent PHPT can affect the development of peak bone mass and can lead to osteoporosis and fragility fractures in adulthood [47,48]. Therefore, it has been suggested that adults have surgical intervention prior to the onset of symptoms or hypercalcemia in order to reduce the effects of unopposed parathyroid hormone hypersecretion [49]. Ultimately, providers must take into account the various considerations in pursuing parathyroid surgery, such as the presentation of

symptomatic hypercalcemia, prevention of long-term consequences of unopposed PHPT, and the presence of gastrinoma. If concomitant endocrinopathies are present, parathyroidectomy is recommended to be completed first. However, if an active insulinoma is present, hypoglycemia must first be cured and parathyroidectomy must therefore be postponed [50,51].

Medical therapy is the preferred treatment for gastrinomas. H^+-K^+-adenosine triphosphatase inhibitors (i.e., omeprazole or lansoprazole) have been proven to be most effective for medical therapy [14]. Surgical therapy is ideally reserved for non-metastatic gastrinomas that are located within the pancreas and are larger than 2 cm as disease-related survival is reported to improve after surgery [52]. Other treatment modalities, such as chemotherapy, may be indicated in certain specific cases [53]. Tumors smaller than 2 cm have been found to have an excellent prognosis with medical management [54]. Overall, tumor size and the presence of hepatic metastases best determine the prognosis of MEN1 patients with gastrinomas. In 50% of patients, tumors can recur within 5 years after resection [55]. Therefore, long-term pediatric gastrinoma follow up is essential.

Surgical therapy is the treatment of choice for insulinomas, glucagonomas, and VIPomas [2,14]. Insulinomas require removal of a single tumor enucleation or partial pancreatectomy, and these surgical procedures have been quite successful, leading to minimal morbidity in children [56,57]. Preoperative and intraoperative localization, using preferred modalities of MRI and endoscopic ultrasound, is crucial in pediatric insulinoma management. Glucagonomas are most frequently found at the tail of the pancreas. Since 50 to 80% of glucagonomas have metastasized at time of diagnosis, surgical treatment may be unsuitable and patients may require treatment with somatostatin analogs or chemotherapy [58]. VIPomas are also primarily located at the tail of the pancreas and surgical resection is curative [2,14].

Non-functioning NETs do not present with symptoms despite elevated hormone levels that are present biochemically. Nonetheless, they are considered potentially malignant. Surgery is not definitively recommended. However, tumor size can direct treatment decisions. In adults, tumors less than 2 cm are not recommended to undergo surgical resection [59]. A retrospective analysis found that there was no difference in overall survival when small tumors were observed versus surgically resected [60].

Pituitary tumors are treated both medically and surgically. In the case of prolactinomas, the most commonly presenting pituitary adenoma in MEN1 patients, first-line medical management includes the use of dopamine agonists. Dopamine agonists, such as cabergoline or bromocriptine, work to reduce tumor size and, in turn, normalize prolactin levels [61]. Resistance to medical therapy is defined as persistent hyperprolactinemia after three months of maximal treatment dosing and less than 50% tumor shrinkage. In these resistant cases, the prolactinoma can be considered more aggressive [62]. Surgical intervention is thus indicated. Surgery is also reserved for neuro-ophthalmologic emergencies. Transsphenoidal surgery is considered first-line treatment [14,63]. Endonasal transsphenoidal endoscopic surgery (ETES) is also emerging as a surgical treatment option, especially in recurrent lesions [64]. Radiotherapy is reserved for unresectable tumors [14,65].

3. Multiple Endocrine Neoplasia Type 2 (MEN2)

MEN 2 is divided into two clinical subtypes: MEN2A and MEN2B. Familial medullary thyroid carcinoma (FMTC) is recognized as a variant of MEN2A. All types of MEN2 are due to a mutation in the *RET* gene. The estimated prevalence of MEN2—including MEN2A, MEN2B, FMTC, and other subtypes—is 1 in 30,000 [10]. It is important to note that genetic screening for MEN2 is highly disparate in different regions of the world; this heavily influences prevalence estimation by region [66]. While MEN2A and MEN2B are both characterized by medullary thyroid carcinoma (MTC) and pheochromocytoma (PHEO), clinical features and age of onset differ between the two forms. MTC is typically the first manifestation and is most aggressive. In all variants of MEN2, the lifetime risk of developing MTC is nearly 100% [67]. 25% of all identified MTC cases have been shown to

be due to genetic causes, including MEN2 [10,68]. For this reason, guidelines recommend that all patients in whom MTC is identified receive routine genetic screening for *RET* mutations [69].

3.1. MEN2A

3.1.1. Clinical Presentation

MEN2A, also known as Sipple syndrome, has an estimated prevalence of 1 in 36,000 to 1 in 200,000 live births (Table 1) [70] with some countries, such as Denmark, noted to have a higher incidence of MEN2 due to founder effects within the population [71]. A diagnosis of MEN2A is made when a child has two or more of the following endocrine manifestations: MTC, PHEO, and/or PHPT [72].

MTC is typically the first manifestation of MEN2A and occurs in more than 90% of individuals [14]. The peak incidence of MTC in MEN2A patients is in the third decade of life [73]. In children, MTC may present before the age of 6, with some cases identified in children as young as 2 years of age [74]. MTC is a neuroendocrine tumor of the thyroid gland that presents as a proliferation of parafollicular C-cells, which secrete calcitonin. Unlike adults, children may not present with a neck mass at diagnosis, as diagnosis is frequently determined earlier than their clinical presentation by way of genetic testing. Nevertheless, signs and symptoms may include an anterior neck lump or symptoms related to an enlarged tumor, such as difficulty with breathing or swallowing, pain, or hoarseness. Elevated calcitonin levels on routine screening are also noted prior to the development of clinical symptoms [72]. However, calcitonin levels should be carefully interpreted. Clinicians should be aware that calcitonin levels are generally quite a bit higher in children under 3 years of age, especially in children under 6 months of age. Calcitonin levels are also higher in males as compared to females [75].

PHEO and PHPT more commonly present in adulthood. The development of the two tumors is significantly affected by the specific underlying *RET* gene mutation and mutation penetrance [75–77]. In adults, up to 50% of individuals with MEN2A present with PHEO in the second to third decade of life [78]. However, children as young as 8 years of age have presented with PHEO as well [79]. Symptoms may include headaches, flushing, diaphoresis, palpitations, tremors, nausea, and anxiety. PHEOs are generally non-malignant. MEN2A-associated PHEOs are typically bilateral and isolated to the adrenal gland, rarely metastasizing [75]. The tumors can be diagnosed with elevated plasma or urinary metanephrine and normetanephrine levels [75].

PHPT occurs in 10–30% of MEN2A patients and is generally mild, presenting as a benign adenoma or parathyroid hyperplasia [78,80]. The mean age of diagnosis is approximately 34 years, ranging from 12 to 70 years. However, children as young as 2 years have been diagnosed [81]. Often, individuals do not present with clinical symptoms. If symptomatic, an individual may clinically present with fatigue, polyuria, nausea, decreased appetite, or constipation due to hypercalcemia. Rarely has nephrolithiasis or osteitis fibrosa cystica been reported [81]. A laboratory evaluation may reveal a high or normal parathyroid hormone level in the setting of hypercalcemia.

Cutaneous lichen amyloidosis (CLA) is a rare dermatologic manifestation of MEN2A that presents as an intense pruritic rash that is classically found in the interscapular region. The rash improves with sun exposure and worsens with stress. The lesion may present at a young age prior to any clinically evident MTC [82,83]. The dermatologic condition has almost invariably been found in patients with a *RET* codon 634 mutation [84].

Hirschsprung disease is another condition that co-occurs with MEN2A [85]. The condition presents in infancy and newborns can present with constipation. Patients with Hirschsprung disease and an exon 10 *RET* mutation warrant further evaluation for MEN2A [75].

3.1.2. Genetics

MEN2 is due to a germline mutation of the *RET* proto-oncogene on chromosome 10q11.2 [67,86]. The *RET* gene contains 21 exons and is 60 kB in length [73]. This gene codes for a transmembrane tyrosine kinase, which was shown to be mutated in cases of both MEN2A and FMTC in 1993 [87]. The inciting mutation causes a gain of function within the translated protein, leading to a dysregulated cell cycle and oncogenesis [3]. In contrast with the *MEN1* gene involved in MEN1, *RET* has a "hot spot" locus where mutations are more prevalent [12]. Unlike MEN1, MEN2 has a strong genotype-phenotype correlation, allowing for the main classifications of MEN2A and MEN2B, as well as their subtypes [88]. Genotype-phenotype correlation has been specifically noted in the case of PHEO risk, with specific codons of *RET* (634 and 918) being more frequently implicated [89]. Codon 634 has also been associated with an increased risk of CLA and PHPT in patients with MEN2A [76,81,90]. In patients with identifiable codon 634 mutations, the incidence of CLA is similar to the incidence of pheochromocytoma [83]. A cross-sectional genetic analysis of families with known MEN2A has shown that *RET* exons 10 and 11 are the most commonly implicated in syndromic pathogenesis [4]. More recent studies have furthered this analysis, showing that the most prevalent MEN2A-causative mutation lies in codon 634 within exon 11 [91]. FMTC is associated with germline mutations, which are found in 95% of families [10]. Many variations of *RET* mutations resulting in FMTC have been documented.

3.2. Familial Medullary Thyroid Carcinoma (FMTC)

Although FMTC was historically considered to be a distinct syndrome in which only increased risk for MTC occurred, the current concept of FMTC involves a MEN2A-FMTC spectrum, consisting of a phenotypic continuum involving progressively decreasing penetrance of PHEO and PHPT [3,75]. Using the information available due to the widespread increase in *RET* genetic screening, it has been suggested that up to 25% of all diagnosed MTC can be considered FMTC-related [10,73]. Diagnosis of FMTC typically occurs in the third to fourth decade of life, with a mean age of diagnosis of 34 [92,93]. There are strict clinical criteria that describe those with familial MTC: more than 10 family members with MTC, multiple carriers or affected members over 50 years of age, and an adequate medical history to exclude the presence of PHEO and PHPT [13]. Alternative diagnostic criteria describing the presence of at least four family members with MTC but without other manifestations of MEN2A has also been suggested [88,94]. Diagnosis may also occur via genetic testing that reveals a known FMTC-associated *RET* mutation [95]. The age of onset of MTC is typically late, appearing in the second or third decade of life. MTC associated with FMTC has a better prognosis than MTC associated with either MEN2A or MEN2B, and is also associated with better outcomes than sporadic MTC [3,92]. Distinguishing FMTC from MEN2A is challenging, especially since premature categorization of individuals in having FMTC can fail to identify individuals who may, in fact, later present with PHEO or PHPT. This concern further underscores the importance of correctly diagnosing familial MTC.

3.3. MEN2B

3.3.1. Clinical Presentation

MEN2B has a much lower prevalence than MEN2A, between 1 in 600,000 and 1 in 4,000,000 depending on location (Table 1) [96,97]. Unlike MEN2A, children with MEN2B may present with additional clinical features apart from thyroid nodules. Features include marfanoid body habitus, mucosal neuromas (lips, tongue), eyelid eversion, prominent corneal nerves, and scoliosis. However, some of these features may not be clinically evident until several years of age [98,99]. In infancy, there may be earlier signs, such as alacrima and constipation, which can offer clues for early diagnosis [75]. Other clinical signs include decreased muscle tone, talipes equinovarus, and a failure to thrive with feeding difficulties [100].

Virtually all patients develop MTC, often before 1 year of age, much earlier than in individuals with MEN2A [101,102]. MTC is the leading cause of death in MEN2B.

Unfortunately, phenotypic features often go unrecognized until late childhood because many patients carry de novo mutations. As such, individuals may present as adults when MTC is discovered. Therefore, tumor detection lag time rather than its invasive characteristics is suggested to be a reason for increased mortality in MEN2B [3,100,103].

RET germline mutations in exon 16 codon M918T are the most common pathogenic variants associated with MTC, occurring in approximately 95% of patients [96]. The variant has an aggressive clinical presentation of MTC during childhood and can present in infancy [75,104]. As 25% of patients have hereditary MEN2B, the remaining 75% typically have de novo *RET* mutations and can present as phenotypically normal. As such, those with de novo mutations are more difficult to identify. Children with a de novo *RET* codon M918T mutation are more commonly diagnosed after detection of a thyroid nodule [105]. Individuals with MEN2B have a 50% risk of developing PHEOs, which are benign tumors [100]. In children, PHEOs may develop as early as age 12 years with a mean age of about 15 years [106,107]. The tumors generally present earlier in MEN2B than in MEN2A and are more frequently bilateral in nature [108]. PHPT is not associated with MEN2B [101].

Ganglioneuromas of the gastrointestinal tract are rare tumors that present in up to 40% of individuals with MEN2B [105]. Patients may report symptoms of constipation, diarrhea, and bloating, and symptoms can begin as early as infancy or early childhood [105,109].

3.3.2. Genetics

Like MEN2A, MEN2B is caused by a germline mutation within the *RET* gene that codes for a transmembrane tyrosine kinase [87]. However, while the most common mutation causing MEN2A is within codon 634, MEN2B is most often due to a mutation of codon 918 [91,97]. 95% of identified cases worldwide have been most frequently due to a M to T substitution; 75% of these mutations occur de novo with the rest being inherited [96]. Most newly identified mutations are inherited paternally due to involvement of the *RET* protein in the renewal of spermatogonia [3]. Pathogenesis of MEN2B is similar to MEN2A, with dysfunctional protein leading to an unregulated cell cycle, causing an inborn predisposition to oncogenesis via constitutive intracellular kinase activation [110].

3.4. MEN2 Screening

Given that all children with MEN2B will develop MTC and particular *RET* codons may present with more aggressive MTC in children with MEN2A, screening and diagnosis is imperative in the prevention of metastatic MTC at an early age [99,105,111]. In their most recent MTC guidelines [75], the American Thyroid Association (ATA) stratified all known *RET* mutations into one of four risk levels to allow for better screening and treatment management: "highest risk" (HST), "high risk" (H), and "moderate risk" (MOD).

Children born to parents with MEN2B should obtain genetic testing for *RET* mutations. In cases where there is resistance to parental disclosure and child testing, legal intervention may be necessary as the child is at great risk for inheriting a malignant tumor [75]. Certain guidelines recommend that annual serum calcitonin screening should begin at age 6 months in children with MEN2B and age 3 to 5 years in those with MEN2A or history of FMTC [95]. Due to the early age of MTC onset, total thyroidectomy by 6 months of age is recommended in cases with confirmed MEN2B [97].

Individuals diagnosed with MEN2 are recommended to be screened annually for the presence of PHEO and PHPT even if asymptomatic (Table 2). Tumor screening should begin at age 11 for those with MEN2B and age 16 for those with MEN2A [75]. Although, the development of PHEO has been noted to develop at earlier ages [100]. Free plasma or 24-h metanephrines and normetanephrines are recommended for PHEO screening. If there is biochemical evidence of tumor, imaging with CT or MRI is then considered [75]. PHPT should be screened in those with MEN2A at the time of screening for PHEO, that is, by age 11 in those in the ATA "high risk" (ATA-H) category and by age 16 in those in the ATA "moderate risk" (ATA-MOD) ATA-high risk category [75].

Patients with MEN2A have a high risk of developing Hirschsprung's disease. As such, genetic screening in children with family history of Hirschsprung's disease is also recommended [112].

3.5. MEN2 Treatment

As DNA analysis has improved in recent decades, strong genotype-phenotype correlations have been established and have helped to facilitate guidelines for pediatric MEN2 treatment. Previously, calcitonin levels alone were used to determine candidacy for thyroidectomy. However, this led to some children being subjected to thyroidectomy when no *RET* mutation was identified by DNA analysis [113]. With DNA analysis, certain mutations have been determined to be more aggressive, especially in regards to MTC, and, therefore, specific treatment strategies have been recommended accordingly.

MTC is treated surgically. The goal is for the patient to undergo thyroidectomy before metastasis occurs, as MTC, at that point, is considered incurable and the most common cause of tumor death in individuals with MEN2A. Prophylactic thyroidectomy is defined as thyroid gland removal in children who have an inherited *RET* mutation. Those who do not undergo prophylactic thyroidectomy at an early age are more likely to develop metastatic MTC. The average survival expectancy in MEN2B carriers was approximately 21 years prior to the current, more standardized, recommendations for prophylactic thyroidectomy [99].

In children with MEN2A with a *RET* codon 634 mutation (ATA-H category), MTC develops in the first few years of life. Children are recommended to have annual physical examinations, thyroid ultrasounds, and serum calcitonin measurements starting at age 3 [75,111]. Children with mutations in the ATA-MOD category have similar screening recommendations but begin later at age 5; thyroidectomy in these patients is expected to occur in childhood or young adulthood depending on the serum calcitonin level. Despite prophylactic thyroidectomy, it is important to note that certain *RET* mutations appear to be associated with persistent or recurrent disease (i.e., codons 620 and 634) [102,114]. There are no generally accepted guidelines for basal or stimulated calcitonin levels in the development of C-cell hyperplasia. Levels are very high in the first months of life and decline to adult levels after 3 years of age [115]. Due to this phenomenon, it is recommended that providers become familiar with their own institution's calcitonin reference ranges [75].

With regards to MEN2B, MTC is usually highly aggressive and thus prophylactic thyroidectomy occurs much earlier in life. Those with known hereditary MEN2B are recommended to have a thyroidectomy in the first year of life, especially if they have a *RET* codon M918T mutation [97]. Thyroidectomy should be performed by an experienced surgeon in children, especially since the risk of hypoparathyroidism and subsequent hypocalcemia is higher [45,75]. If an experienced surgeon is not available, some suggest that thyroidectomy should be delayed to 2 years of age [116,117]. As surgical management can be challenging, parents known to be carriers for MEN2B mutations are encouraged to consider in vitro fertilization and preimplantation genetic diagnosis technologies [75].

If both MTC and PHEO are identified in a patient, the PHEO should be resected first given the significant morbidity and risk of stress-induced cardiovascular mortality [75,97]. To note, since PHEOs primarily occur later in adolescence, obtaining plasma or urine metanephrines and normetanephrines before prophylactic thyroidectomy is not indicated [75,95].

The decision for bilateral or unilateral adrenalectomy depends upon the presence of bilateral or unilateral PHEOs, respectively, but also the risk for adrenal insufficiency. Individuals with solitary PHEO are recommended to have a unilateral adrenalectomy even though many will ultimately develop a contralateral PHEO [118]. The reason for this decision is based on the high risk for adrenal insufficiency after bilateral adrenalectomy. Laparoscopic adrenalectomy or retroperitoneoscopic adrenalectomy are the procedures of choice with no apparent difference in outcomes [119]. Adrenal-sparing surgery in bilateral PHEOs has also been shown to be successful and preferred if feasible and safe [89,120].

If total bilateral adrenalectomy is determined, it is imperative that individuals are given corticosteroid stress dosing perioperatively and postoperatively, as they will develop primary adrenal insufficiency [75,89]. Another consideration prior to adrenalectomy is the initiation of anti-hypertensive treatment with alpha and beta-adrenergic receptor blockade even if there is no evidence of biochemical abnormalities [13].

Surgical treatment for PHPT is similar to treatment in those with MEN1 as discussed earlier.

4. Multiple Endocrine Neoplasia Type 4 (MEN4)

MEN4 was first described in 2006 as an autosomal dominant disorder caused by germline loss of function in the cyclin-dependent kinase inhibitor 1B (CDKN1B) gene [5]. Despite its name, MEN4 is considered a variant of MEN1 [10]. It is an estimated 3% of MEN1 cases and only 29 cases of MEN4 had been documented as of 2019, with 16 different underlying mutations [121,122]. Patients with MEN4 develop MEN1-associated tumors, although at a higher average age than in MEN1 [121]. The most common manifestation is parathyroid hyperplasia, which occurs in approximately 80% of patients (Table 1) [6]. Pituitary adenomas also occur but are typically smaller and less aggressive than MEN1-related pituitary adenomas. The incidence of pancreatic neuroendocrine tumors is lower in MEN4 than in MEN1, with a penetrance of 20.6% [31].

5. Conclusions

Multiple endocrine neoplasia (MEN) is a group of rare, heterogenous genetic disorders where two or more endocrine gland tumors occur in an individual or related individuals in the same family. The presentation of each disorder is variable and unique, and one must have a high index of suspicion to make the diagnosis, particularly in children. Our understanding of the clinical phenotypes and genetics of these conditions has grown significantly over the last several years, and guidelines have been developed for diagnosis and treatment of patients with MEN. Children diagnosed with one of the MEN syndromes require complex management and surveillance throughout their lifetime and should be referred to a tertiary care center with a multidisciplinary team of specialists.

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