Overview of the Updated Evidence of Multiple Endocrinal Neoplasia (MEN) in Children and Adolescents

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Authors’ contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

ABSTRACT

MEN syndromes are a collection of autosomal dominant disease including MEN 1 and MEN 2. Multiple endocrine neoplasia (MEN) syndromes are infrequent inherited disorders in which more than one endocrine glands develop noncancerous (benign) or cancerous (malignant) tumors or grow excessively without forming tumors. There are 3 famous and well-known forms of MEN syndromes (MEN 1, MEN 2A, and MEN 2B) and a newly documented one (MEN4). These syndromes are infrequent and occurred in all ages and both men and women. MEN1 is the most often happening form of MENs. The information of MEN’s genetic alterations and the connection among genotype and phenotype could be beneficial for MEN disease management. (MEN1) implicated IN primarily by tumors of the parathyroid glands, endocrine gastroenteropancreatic (GEP) tract and anterior pituitary. Before MEN-1 can be diagnosed it must be suspected, genetic screening for MEN-1 is recommended when an individual has 2 or more MEN-1 related tumors, MEN2 associates with medullary thyroid carcinoma, pheochromocytoma, and primaryhype-
rparathyroidism. MEN2A and MEN2B should be suspected in any patient diagnosed with MTC or pheochromocytoma, particularly when the age of presentation is very young (younger than 35), the genetic testing for RET proto-oncogene is employed to diagnose and identify a specific type of mutation present. Treatment is mainly surgical in most cases of multiple endocrine neoplasia syndrome.

Keywords: Multiple endocrine neoplasia (MEN); evidences; children; adolescents.

1. INTRODUCTION

First described in the early 1900s, multiple endocrine neoplasm type 1 (MEN 1) is a rare endocrine syndrome characterized by a combination of pituitary, parathyroid, and pancreatic tumors [1].

Multiple endocrine neoplasia (MEN) syndromes are infrequent inherited disorders in which more than one endocrine glands develop noncancerous (benign) or cancerous (malignant) tumors or grow excessively without forming tumors [2]. There are 3 famous and well-known forms of MEN syndromes (MEN 1, MEN 2A, and MEN 2B) and a newly documented one (MEN4). These syndromes are infrequent and occurred in all ages and both men and women [3]. Usually, germline mutations that can be resulted in neoplastic transformation of anterior pituitary, parathyroid glands, and pancreatic islets in addition to gastrointestinal tract can be an indicator for MEN1. The medullary thyroid cancer (MTC) in association with pheochromocytoma and/or multiple lesions of parathyroid glands with hyperparathyroidism can be indicative of MEN2 which can be subgrouped into the MEN 2A, MEN 2B, and familial MTC syndromes [4]. Other endocrine tumors noted with increased frequency in MEN1 include foregut carcinoid tumors, such as thymic and bronchial carcinoid, and gastric enterochromaffin-like tumors, which each have a penetrance of 2%, 2%, and 10%, respectively by 40 years of age [5].

There are no distinct biochemical markers that allow identification of familial versus nonfamilial forms of the tumors, but familial MTC usually happens at a younger age than sporadic MTC. The MEN1 gene (menin protein) is implicated in MEN 1 disease, CDNK1B for MEN 4, and RET proto-oncogene for MEN 2. The clinical features arising in each condition relate to the location of tumour development and/or hormonal hypersecretion, while treatment approaches aim to minimize morbidity and mortality, and preserve quality of life [6].

The focus over the molecular targets can bring some hope for both diagnosis and management of MEN syndromes. In the current review, we look at this disease and responsible genes and their cell signaling pathway involved [7].

Fig. 1. MEN syndromes in body
**Epidemiology:** The two main types of MEN syndromes are MEN1, which is the most often happening form of MENs, and MEN2. Multiple endocrine neoplasia type 1 affects about 2–3 per 100,000 and is reported to be present in 0.22–0.25% of autopsies, MEN-2 is a rare syndrome with an incidence of 1 in 200,000 live births [8]. Among the subtypes of type 2, MEN2A syndrome affects 60% to 90% of MEN2 families while MEN2B affects only 5% of MEN2 families. The prevalence of multiple endocrine neoplasia type 4 is unknown, although the condition appears to be rare. Parathyroid tumors are the main MEN1-associated endocrinopathy; onset in 90% of individuals is between ages 20 and 25 years with hypercalcemia evident by age 50 years. Multiple endocrine neoplasia type 2 (MEN2) is associated mostly with medullary thyroid cancer MTC [9].

**Etiology:** MEN-1 is inherited as an autosomal dominant disorder. The gene causing MEN-1 is located on the long arm of chromosome 11 (11q13) and is composed of 10 exons (9 coding) [10]. The MEN-1 gene is a tumor suppressor gene. It encodes a 610 amino acid nuclear protein called menin. Abnormalities of this gene result in mutations, deletions, and/or truncations of the menin protein [11]. The exact mechanism by which alterations of menin result in endocrine tumors is still unclear. Menin interacts with a large number of proteins many of which have important roles in transcriptional regulation, genomic stability, cell division and cell cycle control. The crystal structure of menin supports its role as a key scaffolding protein that regulates gene transcription [12].

MEN2 syndrome is caused by a mutation in a gene called RET. The rearranged during transfection (RET) protein is a receptor tyrosine kinase that is localized to chromosome 10q11.2. It appears to transduce growth and differentiae signals in several tissues, particularly those arising from neural crest cells. Some cytogenetic mutations have been reported; these may involve intracellular and extracellular domains of the RET protein signaling pathway. The germline RET mutations in MEN2 result in gain of function of this tyrosine kinase receptor. This is different from many other inherited predispositions to neoplasia that are due to heritable "loss-of-function" mutations that inactivate tumor suppressor proteins [13].

2. **DIAGNOSIS AND CLINICAL MANIFESTATION**

**Multiple endocrine neoplasia type 1 (MEN-1):** Before MEN-1 can be diagnosed it must be suspected. Suspicions should be raised in any patient with a family history of endocrine tumors of the pancreas, family members with pituitary or parathyroid disease or a family history of endocrinopathy, in patients with renal colic with neuroendocrine tumors NETs, in any patient with Zollinger-Ellison syndrome ZES (20–25% have it as part of the MEN-1 syndrome), with a young age onset of a functional pancreatic neuroendocrine tumors pNET, with multiple pNETs, with hyperparathyroidism with multiple gland involvement or with hyperplasia or with a pNET associated with hypercalcemia or another endocrinopathy [14]. In most patients (83%) MEN1 clinically presents after age 21. In the 17% of patients with MEN1 presenting before 21 years, which should lead to suspicion of the diagnosis, the most frequent abnormalities were hyperparathyroidism (75%), pituitary adenoma (34%), insulinoma (12%), nonfunction pNET (9%) and gastrinoma (2%) [15]. Genetic screening for MEN-1 is recommended when an individual has 2 or more MEN-1 related tumors, multiple abnormal parathyroid glands before age 30 years, recurrent HPT at a young age, gastrinoma and hyperparathyroidism (HPT) or multiple pNETs at any age, plus a family history of kidney stones or endocrine tumors that are part of the syndrome [16]. Genetic testing includes sequencing of the entire coding region of the MEN-1 gene (exons 2-10) and identifies mutations in about 80% of patients with familial MEN-1.

Primary hyperparathyroidism is the most common endocrine abnormality in MEN-1. HPT is usually the first manifestation of MEN-1 with a typical age of onset of 20–25 years. Decreased bone density and kidney stones are common. HPT often occurs at the same time as Zollinger-Ellison syndrome (ZES) and surgery to correct the HPT greatly ameliorates the clinical evidences of ZES [17]. As in sporadic cases, biochemical testing for HPT is critical to the diagnosis. Total or ionized serum level of calcium and intact serum parathyroid hormone levels are measured and both should be elevated [18].

The prevalence of pancreatic neuroendocrine tumors pNETs in MEN-1 is between 30–75% clinically [19]. The pathology of pNETs in MEN-1 is typically multicentric and multifocal with...
multiple endocrine tumors throughout the pancreas and the duodenum in patients with MEN-1. Gastrinomas (Zollinger-Ellison Syndrome, ZES) are the most common functional pNET in MEN1, insulinoma is the second most common functional one [20]. Although pNETs can secrete a number of peptides including chromogranin A, neuron specific enolase, pancreatic polypeptide, neurotensin or ghrelin, these don’t result in a distinct clinical syndrome. The only reliable method of establishing the presence of pNETs in MEN1 patients is to perform detailed imaging studies [21].

Anterior pituitary adenomas are the initial clinical manifestation of MEN-1 in 25% of cases. Its prevalence in MEN-1 is between 20% and 60% and in a recent study of all patients (N=144) with pituitary adenomas seen in one institution over a 6 year period, 7.7% had MEN-1 [22]. Most of these anterior pituitary tumors are microadenomas (<1 cm in diameter). Every type of anterior pituitary tumor has been reported to occur in MEN-1 with the most common being a prolactinoma. Screening for anterior pituitary tumors requires measuring serum levels of prolactin, IGF-1 and magnetic resonance imaging of the pituitary. Patients should be questioned for loss of peripheral vision. Visual fields are assessed formally, if any suspicion of change or there is evidence of a pituitary tumor [23].

Multiple endocrine neoplasia type2 (MEN-2): MEN2A and MEN2B should be suspected in any patient diagnosed with MTC or pheochromocytoma, particularly when the age of presentation is very young (younger than 35). MTC most commonly presents with a solitary thyroid nodule and/or cervical lymphadenopathy. Any patient with diagnosed MTC or family history of MTC should be tested for RET proto-oncogene mutations for both MEN2A and MEN2B. The patients who are diagnosed with pheochromocytoma at the age earlier than that of its sporadic forms should be tested for MEN2A and MEN2B. The classic symptoms of pheochromocytoma are the paroxysms of a headache, anxiety, diaphoresis, palpitations, and high blood pressure [24]. The presence of these symptoms in the third decade, particularly in between 25 and 32 years, should prompt to screen for MEN2.

A detailed history of the presence of associated conditions (described below) in the patient or the family members should be taken. Other possible physical examination findings include marfanoid habitus (decreased upper to lower body ratio), mucosal neuromas (red papules) over lips and tongues, and joint hyperlaxity associated with MEN2B [25]. The patients typically lack lens dislocation or aortic abnormalities, unlike Marfan syndrome. MEN2A also is suspected in patients with clinical features like purity, scaly, pigmented papules in the interscapular region as these are features of CLA that have an association with MEN2A [26].

Medullary thyroid cancer (MTC) is the most common manifestation of MEN2A and MEN2B with 100% penetrance and usually the first manifestation in MEN2 patients. MTC is a neuroendocrine tumor of the thyroid gland caused by the hyperplasia of calcitonin-producing parafollicular C-cells, the only cells in the thyroid gland derived from neural crest cells. Almost 100% of patients with MEN2A and MEN2B develop MTC, particularly early in life, with the highest incidence in the third decade, while 25% of MTC cases have RET proto-oncogene mutation. MTC most commonly presents with a solitary thyroid nodule and/or cervical lymphadenopathy [27].

Pheochromocytoma, a typically benign adrenal medullary tumor (usually bilateral and multicentric), occurs in 40% to 50% of patients with MEN2A or MEN2B; the frequency and penetration highly depend on the specific type of mutation [28]. The adrenal medulla is also a derivative of neural crest cells. Usually, it is identified as a part of the screening process in the patients with known or suspected MEN2. Although it is rare for pheochromocytoma to appear before MTC, it can be the initial manifestation of MEN2 with the classic symptoms of pheochromocytoma such as paroxysmal attacks of a headache, anxiety, diaphoresis, and palpitations. The mean age of presentation is 25 to 32 years, and it may appear as early as 8 to 12 years of age [29].

Primary hyperparathyroidism is present in 10% to 25% of patients with MEN 2A, while it is not associated with MEN 2B. The condition is usually mild and asymptomatic.

As the most common presentation of both MEN2A and MEN2B is MTC, any patient presenting with a cold, solitary nodule and cervical lymphadenopathy must be evaluated further for the possibility of MTC. The clinical
presentation of sporadic MTC is the same as genetic MTC except the latter appears early in life [30]. For this reason, the patient should be biopsied by fine-needle aspiration (FNA) to identify MTC and genotyping should be done for underlying potential RET mutations in the patient as well as first-degree family members [31]. The genetic testing for RET proto-oncogene is employed to diagnose and identify a specific type of mutation present in an index patient (the first affected member of the family) such as high-risk, moderate-risk or low-risk mutations. The type of mutations not only determine the expressivity and penetrance of the disease but also spares the effort to test for all the possible mutations in all the family members and determine when to start the screening process for associated tumors and when to do the prophylactic surgery [32].

2.1 Management

In multiple endocrine neoplasia type 1 (MEN-1): Surgery is the definitive treatment for the control of hypercalcemia due to primary hyperparathyroidism. Subtotal (3–5 glands) or total parathyroidectomy with forearm autotransplantation is performed with an open bilateral neck exploration. The recommended timing and type of surgery is controversial. Recurrent hypercalcemia is common. Reimplantation after total parathyroidectomy has a high incidence of graft failure and subsequent permanent hypoparathyroidism [33]. Parathyroid ethanol ablation (PEA) treatment has been shown to safely and effectively control hyperparathyroidism with a low rate of hypocalcemia and permanent complications, when performed by an experienced radiologist, but it cannot replace primary surgical therapy. Calcimimetics can be used to reduce parathyroid hormone release by parathyroid cells and to control cell growth [34]. Cinacalcet normalizes serum calcium in 70–80% of patients with primary hyperparathyroidism and can maintain the effect over 5 years. Gastrinomas located in the pancreas can be surgically excised, surgical cure of multiple duodenal gastrinomas is difficult and is not associated with a high disease-free state [34]. More extensive gastrointestinal surgery, such as Whipple pancreatoduodenectomy, can be associated with a higher cure rate at the expense of a higher operative mortality risk. Other novel approaches, such as chemotherapeutic agents or hormonal therapy with somatostatin analogs, can be considered for treatment of disseminated gastrinomas. For insulinomas, no curative long-term medical treatment exists. Surgical removal of the tumor is the treatment of choice [34]. Unresectable tumors can be treated with diazoxide or octreotide. Chemotherapeutic agents or hepatic artery embolization has been used to treat metastatic disease. In case of pituitary tumor, treatment is similar to non-MEN1–associated pituitary tumors. Prolactinomas are treated with dopamine agonists (bromocriptine or cabergoline); trans-sphenoidal surgery and radiotherapy are usually reserved for drug-resistant tumors and for macroadenomas that are compressing adjacent structures.

In multiple endocrine neoplasia type 2 (MEN-2): treatment is with surgery, preoperative medical treatment may consist of prostaglandin inhibitors to alleviate diarrhea that may be associated with medullary thyroid cancer. Evaluation for pheochromocytomas is important because these should be removed before other surgical interventions. This evaluation can be performed before parathyroidectomy or thyroidectomy under a single general anesthetic if the patient is stable [34]. For the patients with a predisposition to MEN2B, total prophylactic thyroidectomy with lymph node dissection is indicated at 1 year of age as the metastatic disease have been reported in such patients soon after the first year of life. The lymph nodes are removed even when there is no evidence of involvement [34]. For the patients with high-risk mutations of MEN2A, total thyroidectomy with lymph node dissection is indicated at age of five. The patients with unilateral pheochromocytoma and normal-appearing contralateral glands, unilateral adrenalectomy is recommended because in patients who have undergone unilateral adrenalectomy and developed a contralateral tumor, later on, the chances of metastatic pheochromocytoma were found minimal and no death has even been reported due to catecholamine crisis in patients with MEN2, prior to unilateral or bilateral adrenalectomy, patients should be treated with alpha-blockade preoperatively; the patient should receive glucocorticoid stress coverage while awaiting transfer to the surgery [34].

3. CONCLUSION

Multiple endocrine neoplasia (MEN) syndromes are rare inherited diseases in which more than one endocrine gland develops benign (benign) or cancerous (malignant) tumors or grows excessively without tumor formation. MEN1 must be suspected before MEN1 can be diagnosed,
MEN1 genetic screening is recommended if a person has 2 or more MEN1-related tumors, MEN2 associated with medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. MEN2A and MEN2B should be suspected in any patient diagnosed with CMT or pheochromocytoma, especially if the age of presentation is very young (less than 35 years). Treatment in most cases of multiple endocrine neoplasia syndrome is primarily surgical.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


