Multiple Endocrine Neoplasia Types 1 and 2 (MEN1 & MEN2) are hereditary endocrinopathy syndromes which predispose individuals to develop tumors of the endocrine glands. While MEN1 and MEN2 share a similar name, it is important to know that they are distinct syndromes with different features and genetic etiology.

**Multiple Endocrine Neoplasia Type 2**

One of the important things to know about medullary thyroid carcinoma (MTC) is that *RET* genetic testing is standard of care for all individuals with MTC, regardless of their family history. MEN2 is inherited as an autosomal dominant condition. When a mutation is identified all first-degree relatives should undergo *RET* genetic testing as prophylactic thyroidectomy is recommended to avoid the development of cancer.

MEN2 is characterized by medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. MEN2 is divided into three subtypes: MEN2A, MEN2B and Familial Medullary Thyroid Carcinoma (FMTC). In all subtypes, there is nearly 100% risk of developing MTC. MEN2A is the most common form of MEN2 and is associated with MTC typically occurring in young adulthood. Pheochromocytoma occurs in about 50% of MEN2A, while 25% develop hyperparathyroidism. MEN2B is the most aggressive form of MEN2 with MTC developing in early childhood. Approximately 50% of people with MEN2B will develop a pheochromocytoma, however hyperparathyroidism is rare. Additional features of MEN2B include mucosal neuromas, ganglioneuromatosis of the gastrointestinal tract, and a Marfanoid body habitus. MEN2 is classified as FMTC when there are multiple family members who have MTC and no other features of MEN2. To avoid missing a diagnosis of MEN2A with its risk of pheochromocytoma, FMTC should be diagnosed only from rigorous criteria.

MEN2 is caused by mutations in the *RET* gene on chromosome 10. MTC is generally the first clinical manifestation MEN2 and is typically multifocal. Approximately 25% of all medullary thyroid carcinoma is due to *RET* germline mutations. Importantly, 7% of apparently sporadic MTC will have *RET* mutation. Genotype-phenotype correlations exist such that *RET* mutations can be classified into 3 levels based on the risk for aggressive early onset MTC. This classification helps guide the age at which to perform prophylactic thyroidectomy. De novo mutations occur in 50% of MEN2B so oftentimes there is no family history.

Pheochromocytomas in MEN2 are typically benign and are bilateral in 50% of cases. Prior to any surgery, the presence of a functioning pheochromocytoma should be excluded by biochemical analysis in all patients with MEN2. Females with *RET* mutations should also be screened before or early in pregnancy.
Multiple Endocrine Neoplasia Type 1
MEN1 causes a variety of endocrine and non-endocrine tumors. One way to remember the main features of MEN1 are to think of the 3 P’s; Parathyroid, Pancreatic, and Pituitary tumors. A practical definition of MEN1 is an individual with 2 of the 3 main MEN1-related endocrine tumors. The most common tumor to develop in MEN1 are those involving the parathyroid glands. Nearly 100% of people with MEN1 will develop parathyroid hyperplasia in some or all parathyroid glands by the age of 50. The resulting hyperparathyroidism can cause osteoporosis, kidney stones, and lethargy. Individuals with MEN1 can also develop tumors in the islet cells of the pancreas. Approximately 40% of individuals with MEN1 develop gastrinomas, which manifests as Zollinger-Ellison syndrome with ulcers, reflux, and diarrhea. Gastrinomas can also occur in the duodenum and usually are malignant. Insulinoma occurs in approximately 10% of patients with MEN1 causing hypoglycemia. Approximately 10-60% of patients with MEN1 will develop an anterior pituitary tumor, most commonly a prolactinoma.

Individuals with MEN1 will develop carcinoid tumors about 10% of the time, which are typically bronchial or thymic in origin. Thymectomy is recommended at the time of parathyroidectomy given the risk of malignant carcinoid. Adrenocortical tumors occur in 20-40% of patients and are typically benign. Non-endocrine, benign tumors may also develop, such as facial angiofibromas, collagenomas, and lipomas.

MEN1 is caused by mutations in the MEN1 gene on chromosome 11. MEN1 is inherited in an autosomal dominant fashion; therefore offspring of an affected individual have a 50% chance of developing MEN1.

In summary, MEN1 tumors cause important morbidity through hormone excess and through malignancies. The greatest risk of malignancy is in the tumors of the pancreas, duodenum and carcinoids. It is important that at-risk individuals undergo screening at a young age to identify and treat tumors at early stages.

Please feel free to call our office at (214) 645-HOPE with questions regarding the MEN syndromes or if you have other questions regarding hereditary cancer risk assessment for your patients.

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