Last Updated March 2020

Multiple Endocrine Neoplasia Type 1 (MEN1): *MEN1* Mutation

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary tumor syndrome associated with an increased risk for several endocrine neoplasms, primarily of the parathyroid, pancreas and pituitary gland.

MEN1 Cancer Risks and Features

- **Parathyroid Tumors:** Parathyroid tumors manifest as primary hyperparathyroidism due to overproduction of parathyroid hormone. Primary hyperparathyroidism is the main *MEN1*-associated endocrinopathy and is the first clinical manifestation of MEN1 in the majority of individuals. Onset in 90% of individuals is between ages 20 and 25 years and can be multiglandular. Nearly 100% of individuals with MEN1 will have hyperparathyroidism by age 50 years. [1,2]
- **Anterior Pituitary Tumors:** Pituitary tumors occur in approximately 30-40% of individuals with MEN1.[1,2] The most common pituitary tumors are prolactinomas followed by growth hormone-secreting tumors.[1-4]
- **Pancreatic Neuroendocrine Tumors**: Pancreatic tumors occur in 30-80% of patients with MEN1. The most common functional tumors are gastrinomas (40-50%) and insulinomas (10-30%). However, 20-55% of pancreatic tumors are non-functional and clinically silent.[1,4]
- **Carcinoids**: Individuals with MEN1 are at risk for foregut carcinoids, particularly of the bronchus and thymus. Carcinoid tumors exhibit an unequal male to female ratio with thymic carcinoids being more prevalent in males and bronchial carcinoids being more prevalent in females with MEN1. These tumors are generally non-functional and most patients are asymptomatic; however, they can occasionally cause Carcinoid syndrome.[1,5,6]
- **Adrenalcortical Tumors**: The incidence of adrenal cortical tumors in MEN1 is 20-73% and can be unilateral or bilateral. The majority of these tumors are non-functional; however, when functional, these tumors can cause Cushing's syndrome.[1,4]
- **Skin findings:** Cutaneous manifestations are found in the majority of patients with MEN1 and can include angiofibromas, collagenomas and lipomas.[4,7,8]

MEN1 Management Recommendations

<u>Recommended Minimal Surveillance Program[4,9]</u>

- Individuals with *MEN1* mutations who have no clinical manifestations of MEN1 should undergo annual biochemical screening and baseline pituitary and abdominal imaging (e.g. MRI or CT), which should then be repeated at 1 to 3-year intervals.
    - Biochemical screening should minimally include serum calcium, PTH, gastrointestinal hormones (e.g. gastrin, insulin with a fasting glucose, glucagon, VIP, and pancreatic polypeptide), chromogranin A, prolactin, and IGF-I.
    - Radiological screening should include an MRI (or CT scanning) of the pancreas, adrenal glands, and pituitary initially as a baseline and then every 1 to 3 years. Consider imaging for thymic and bronchial carcinoids using CT or MRI every 1 -3 years.
    - Additional surveillance may be indicated pending symptoms.

Cancer/Tumor Type	Age to Initiate Surveillance (yr)[4]	Screening/Management Recommendations[4,9]
Parathyroid	8	*Surveillance* • Annual primary hyperparathyroidism screening including assessment of plasma calcium and PTH concentrations • Neck ultrasound, parathyroid sestamibi with SPECT scan and 4-D CT can be considered as appropriate • For prolonged surveillance, studies without radiation are preferred *Surgery* • Subtotal parathyroidectomy ± cryopreservation of parathyroid ± thymectomy • Total parathyroidectomy with autotransplantation ± cryopreservation of parathyroids ± thymectomy

Pancreatic	Gastrinoma: 20
	Insulinoma: 5
	Other pancreatic NET: <10
		Surveillance
		• Consider annual biochemical evaluation:
		  ○ Serum pancreatic polypeptide (category 3), Chromogranin A (category 3).
		  ○ Insulinoma: serum insulin, pro-insulin and C-peptide levels during concurrent hypoglycemia
		  ○ VIPoma: serum VIP, electrolytes
		  ○ Glucogonoma: serum glucagon
		  ○ Gastrinoma: serum gastrin (basal, stimulated as indicated)
		• Consider abdominal/pelvic multiphasic CT or MRI with contrast every 1-3 years
		
		Surgery[10]
		• Surgical management is similar to those with sporadic tumors
		• The role of surgery is controversial in patients with multifocal tumors
		• Surgical resection should be considered if:
		  ○ Symptomatic functional tumors refractory to medical management
		  ○ Tumor larger than 1-2 cm in size
		  ○ Tumor with relatively rapid growth over 6-12 months
		• Endoscopy with EUS is recommended prior to pancreatic surgery in order to assess and

		localize tumors
Anterior Pituitary	5	*Surveillance* • Biochemical evaluation as clinically indicated (serum concentration of prolactin, and IGF1, and other previously abnormal pituitary hormones) every 3-5 years • Pituitary MRI with contrast every 3-5 years *Treatment* • Appropriate medical therapy depending on tumor type or selective transsphenoidal adenomectomy • Radiotherapy is reserved for residual unresectable tumor tissue
Carcinoids	15	*Surveillance* • CT or MRI of the chest every 1-3 years • Biochemical workup should be considered as appropriate • Consider somatostatin receptor-based imaging (i.e. 68Ga-dotatate PET/CT or somatostatin receptor scintigraphy)
Adrenal cortical	<10	*Surveillance* • Consider CT or MRI annually • Biochemical evaluation of adrenal lesions should be restricted to those with symptoms or signs of functional adrenal tumor or tumors more than 1 cm in size *Surgery* • Surgery is indicated for tumors size greater than 4 cm, tumors size 1-4 cm with atypical features, or rapid growth over a 6 month interval

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *MEN1* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

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