Surgical Management of MEN-1 and -2: State of the Art

Göran Åkerström, MD, PhD*, Peter Stålberg, MD, PhD

KEYWORDS

- Multiple endocrine neoplasia type 1
- Multiple endocrine neoplasia type 2
- Surgical treatment • Genetic diagnosis
- Surveillance

MEN TYPE 1

MEN-1 is an autosomal-dominant syndrome comprising endocrine tumors of the parathyroid, the endocrine pancreas-duodenum, and the anterior pituitary. In addition to these classical lesions there is increased incidence of foregut carcinoids (in the thymus, bronchial tree, and the stomach); adrenocortical hyperplasia; and nonendocrine tumors, such as meningioma, ependymoma, leiomyoma, lipoma, facial angiofibroma, and collagenoma.

MEN-1 occurs as a result of inactivating mutations of the *MEN-1* tumor suppressor gene on chromosome 11q13 encoding for menin.[1] Menin has a role for DNA replication and repair, and is involved in transcriptional regulation and histone modification. MEN-1 is relatively rare, with a prevalence of 2 to 3 per 100 000, and is equally common in males and females. The MEN-1 gene is a complex gene, with more than 1000 mutations identified in different families, without strong genotype-phenotype correlations.[2] The disease expression is variable even within families. Complete *MEN-1* gene sequencing is the best method of diagnosis, and can reveal mutations in 70% to 90% of typical MEN-1 cases. A multiplex ligation-dependent probe amplification (MLPA) assay is recently used for detection of large deletions occurring in 4% of MEN-1 cases.[3] Because genetic diagnosis is difficult negative genetic testing cannot exclude the syndrome, unless mutation is known in the family. In absence of genetic diagnosis MEN-1 can be diagnosed if a patient has tumors in two of the three classical endocrine organs (parathyroid, pancreas-duodenum, or pituitary) or has family history of MEN-1 and one such tumor.[4]

Surveillance and screening for MEN-1 endocrine tumors is recommended in presymptomatic gene carriers, because biochemical abnormalities can be detected decades before clinical symptoms become overt.[4,5] Delaying screening until

Department of Surgery, University Hospital, Uppsala, 751 85 Sweden
* Corresponding author.
E-mail address: goran.akerstrom@surgsci.uu.se (G. Åkerström).

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clinical symptoms develop can be associated with morbidity and mortality from MEN-1–related neuroendocrine pancreatic and thymic tumors.[4–6] Screening is done by a combination of biochemical tests and imaging studies aimed to reveal presence of any of the three classical endocrinopathies (**Table 1**), and is initiated in children during the first decade of life.[7]

Primary HPT

Primary HPT (pHPT) is the most common and generally first detected endocrinopathy in MEN-1, often possible to diagnose at approximately 20 years of age, and affecting more than 95% of patients by the age of 40 years.[4–7] MEN-1 pHPT accounts for 2% to 4% of all pHPT cases, and affects approximately 10% of patients with hyperplasia and multiglandular parathyroid disease. MEN-1 has been the most common of the familial pHPT syndromes, and the most important to exclude, and should be suspected in all cases with multiglandular involvement, or recurrent HPT. Younger patients may frequently (approximately 10%) be index cases for MEN-1 kindreds.[4–9] Screening with serum calcium may reveal MEN-1 in patients with pancreatic or pituitary tumors, or foregut carcinoids.

Symptoms are similar as in sporadic pHPT, with decrease in bone mineral density, nephrolithiasis in some patients, common fatigue, muscle weakness, asthenia, mild depression, and typical concentration difficulty. Bone mineral density decrease may be detected already at around 40 years of age.[10] Because hypercalcemia stimulates gastrin, early parathyroid surgery has been recommended in patients with MEN-1–associated Zollinger-Ellison syndrome (ZES), although similar effect is obtained by proton pump inhibitors.[11,12]

The diagnosis of pHPT is made by demonstration of raised ionized or total-albumin corrected serum calcium together with inappropriately raised serum parathyroid hormone (PTH).

Surgical Management

MEN-1 cases have markedly asymmetric nodular hyperplasia, where multiple monoclonal tumors develop from polyclonal hyperplasia (**Fig. 1**).[11,13] Lesions may occur asynchronously, and normal glands can especially in younger patients coexist with enlarged ones. Some patients initially have single gland enlargement, easily misinterpreted as adenoma, when associated glands have normal size and histology.

MEN-1 patients have aggressive HPT, with high recurrence rate. The authors routinely use surgeon-performed preoperative ultrasound to have glandular localization depicted before surgery, although bilateral neck exploration is required for primary explorations.[11,14] Surgery is regarded as palliative, and aims to map the location of four parathyroid glands, also for forthcoming reoperations. To ensure removal of the largest, most severely diseased glands it is crucial to refrain from glandular excision until both sides of the neck have been explored.[11] The surgeon should then remove the largest glands in radical parathyroidectomy, and explore common ectopic sites, possibly harboring supernumerary glands, occurring normally in up to 15%.[14–16] Cervical thymectomy and clearance of perithyroid fat is performed to remove supernumerary glands and parathyroid cell clusters, which may grow as a result of the genetic stimulation.[15]

Resections less than subtotal parathyroidectomy are associated with high frequency of persistent or recurrent HPT in MEN-1.[14,16–20] Subtotal parathyroidectomy implying 3 to 3.5 gland resection (combined with cervical thymectomy) is now the commonly recommended operation.[14] The smallest, most normal gland is