Familial hyperparathyroidism syndromes

Kai Duan
Ozgur Mete

Abstract

Primary hyperparathyroidism is a common endocrine disorder and the most prevalent cause of hypercalcemia worldwide. While most cases are sporadic, 5−10% of cases are inherited as part of a familial syndrome: multiple endocrine neoplasia (MEN-1, MEN-2A, MEN-4), hyperparathyroidism jaw-tumor syndrome (HPT-JT), familial hypocalciuric hypercalcemia (FHH), neonatal severe hyperparathyroidism (NSHPT), autosomal dominant moderate hyperparathyroidism (ADMH), or familial isolated hyperparathyroidism (FIHPT). Recent developments in molecular pathology identified specific germline mutations (*MEN1*, *RET*, *CDKIs*, *CDC73/HRPT2*, *CaSR*, *GNA11*, *AP2S1*) implicated in their pathogenesis. In contrast to sporadic primary hyperparathyroidism which is usually caused by a solitary parathyroid adenoma, hereditary hyperparathyroidism tend to present with multiglandular parathyroid disease, with variable penetrance according to the genetic syndrome. As a result, the clinical severity of each familial condition varies tremendously, resulting in distinct prognosis and treatment strategies. With the advent of molecular testing, genetic subtyping has become an integral part of treatment decision making, requiring correlation with clinical and pathologic findings. This review provides an update on the current knowledge of hereditary hyperparathyroidism and its associated genetic syndromes.

Keywords adenoma; carcinoma; familial; familial hypocalciuric hypercalcemia; hereditary; hyperparathyroidism; hyperplasia; multiple endocrine neoplasia; parathyroid

Introduction

Primary hyperparathyroidism (PHPT) is a common disorder of the parathyroid gland(s), characterized by autonomous oversecretion of parathyroid hormone (PTH).[1−8] It is currently the most prevalent cause of hypercalcemia worldwide, with an annual incidence ranging from 34 to 120 cases per 100,000.[1,5,8−12] Early detection of primary hyperparathyroidism is important to prevent potential complications on the renal and skeletal systems.[1,5,7,9,13−16] While most cases (90−95%) occur sporadically, 5−10% arise as part of a familial syndrome: multiple endocrine neoplasia (MEN-1, MEN-2A, MEN-4), hyperparathyroidism jaw-tumor syndrome (HPT-JT), familial hypocalciuric hypercalcemia (FHH), neonatal severe hyperparathyroidism (NSHPT), autosomal dominant moderate hyperparathyroidism (ADMH; also known as familial hypercalciuric hypercalcemia), or familial isolated hyperparathyroidism (FIHPT).[1,17−23]

As a general rule, sporadic primary hyperparathyroidism has a propensity to occur in postmenopausal women, whereas hereditary hyperparathyroidism tend to present at an earlier age, with equal frequency between both sexes.[1,18,19,24] A family history of hypercalcemia and/or other endocrinopathy, younger age of presentation (<45 years), history of failed parathyroidectomy and/or negative preoperative localization studies (using sestamibi scintigraphy) should prompt the clinician to exclude an underlying genetic condition.[1,5,8,18−20,24−29] It should be noted that family history may be absent in some patients with inherited disease due to the occurrence of de novo mutations in familial syndromes. As a result presentations in individuals older than 45 years with synchronous or asynchronous multiglandular parathyroid disease unassociated with secondary or tertiary hyperparathyroidism should prompt the attention of physicians for the possibility of genetic predisposition even in the absence of family history.[1,5,8,18−20,24−29]

The distinction between sporadic and familial disease is clinically relevant, given their distinct prognosis and treatment strategies.[1,18,19,24] On one hand, sporadic primary hyperparathyroidism is a relatively "homogeneous" disease, often caused by a uniglandular parathyroid disease (i.e. parathyroid adenoma) and curable by minimally invasive parathyroidectomy with intraoperative PTH measurement guidance.[1,18,19,24,30−33] On the other hand, familial hyperparathyroidism is a more "heterogeneous" disorder usually affecting multiple parathyroid glands (conventionally considered as parathyroid hyperplasia) with variable age- and mutation-dependent penetrance, thus requiring bilateral neck exploration and/or cervical thymectomy with intraoperative rapid parathyroid hormone (PTH) measurements.[1,18,19,24,30−35] Moreover, as a result of the genotype−phenotype correlations in familial disease, the management of inherited hyperparathyroidism can vary significantly from one condition to the other, ranging from more extensive parathyroid surgery (as in MEN-1, MEN-4, HPT-JT, NSHPT) to minimally invasive parathyroid surgery (as in most MEN-2A, ADMH, FIHPT) or no surgery at all (as in almost all patients with FHH).[1,17−19,21,22,24,34−36] In MEN-2A syndrome, a subset of patients initially cured with minimally invasive parathyroid surgery may still present with recurrent disease, even 10−11 years following the initial surgery, likely due to asynchronous parathyroid involvement;[37] thus, a closer biochemical monitoring is always required in those managed with selective surgery. Finally, while the prevalence of parathyroid carcinoma remains extremely low (<1%) in the general population, it increases to ~15% in patients with germline *CDC73/HRPT2* mutations (in HPT-JT and *CDC73/HRPT2*-related FIHPT), warranting more aggressive surveillance and genetic counseling.[17,38−41]

The role of the diagnostician has evolved tremendously over the past decade with the advent of molecular genetics leading to a

Kai Duan *MD Department of Pathology, University Health Network, Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada. Conflicts of interest: none declared.*

Ozgur Mete *MD FRCPC Associate Professor, Department of Pathology, University Health Network, Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada; Endocrine Oncology Site Group, Princess Margaret Cancer Centre, Toronto, Ontario, Canada. Conflicts of interest: none declared.*

better understanding of mutation-specific clinical presentations along with recognition of morphological and immunohistochemical features suggestive of subtypes of hereditary hyperparathyroidism.[1,18,19,21] As a consequence, the integrative approach combining clinical, biochemical, radiological, pathological, and molecular biological features has become an integral part of the management of patients with hereditary hyperparathyroidism. This review highlights the important clinical, pathological, and molecular features of familial hyperparathyroidism.

Multiple endocrine neoplasia (MEN) syndromes

Multiple endocrine neoplasia (MEN) encompasses several distinct genetic syndromes, which are inherited in an autosomal dominant manner and predispose to the formation of endocrine tumors.[1,18,19,29,42,43] Three subtypes (MEN-1, MEN-2A, MEN4 syndromes) are known to cause familial primary hyperparathyroidism, as a result of germline mutations in the *MEN1*, *RET* and *CDKN1B* genes respectively.[1,18,19,26,29,30,42,43] These syndromes will be discussed here.

MEN-1 syndrome

First described in 1954, MEN-1 is a rare familial syndrome with a propensity to develop multiple endocrine neoplasms in the parathyroid (95%), anterior pituitary (30–40%) and pancreatic (40–70%) locations, although tumors at other locations (gastrointestinal tract, adrenal, thymus, lung, breast, skin) have also been reported.[1,18,42–45] Of these, hyperparathyroidism is the earliest and most prevalent feature, with a penetrance of ~90% between ages 20–25, and nearly 100% by age 50.[1,18,19,29,42–46] As a result, MEN-1 also represents the most common familial cause of primary hyperparathyroidism, accounting for 2–4% of cases. It has a reported prevalence of 1–10 per 100 000, with equal distribution between both sexes.[1,18,19,29,42,43,45,46]

Clinically, MEN-1 patients may be asymptomatic or present with common symptoms of hyperparathyroidism (nephrolithiasis, osteoporosis), hypercalcemia (fatigue, weakness, neurocognitive changes), and characteristic skin lesions (lipomas, facial angiofibromas, truncal collagenomas).[1,18,19,29,45] Radiographically, parathyroid scintigraphy may show normal glands or multiglandular involvement.[45] Pathologically, multiglandular parathyroid disease is identified in almost all individuals (Figure 1), due to proliferation of parathyroid cells, responsible for PTH overproduction. This process can occur synchronously or metachronously, resulting in symmetrical or asymmetrical growth of the parathyroid gland(s), resulting in increase of their weight (>60 mg each) and size (>8 mm each).[1,18,19,26,30,32,42,43] Traditionally, the involvement of multiple parathyroid glands is referred to as 'parathyroid hyperplasia'; however, in patients with underlying genetic susceptibility, they likely represent a hyperplasia-neoplasia sequence leading to multiple multiglandular parathyroid adenomas.[1,30,32,43,47–50] As the distinction of hyperplasia from neoplasia is arbitrary in light of microscopic findings, most experts now consider using the term "multiglandular parathyroid disease" rather than "parathyroid hyperplasia" in the setting of genetic predisposition.[1,30,32,43,47–50]

Morphologically, MEN-1-related multiglandular parathyroid disease may contain regions of fibrosis simulating parathyroid carcinoma or atypical parathyroid neoplasm.[1,18,19,30,32,42,49,51] Proliferating chief cells may be trapped in fibrotic areas, representing pseudoinvasion. The morphological features of MEN-1-related multiglandular parathyroid disease are also identical to those associated with MEN-4 syndrome.[1,18,19,30,32,42,49] Previous manipulations, lithium- and chronic renal failure-related hyperparathyroidism may also display areas of fibrosis.[1,17,52] In extremely rare cases, parathyroid carcinoma has also been reported to arise in the setting of MEN-1 syndrome.[17,19,53,54] However, the diagnosis of parathyroid carcinoma is restricted only to parathyroid neoplasms showing invasive growth (angioinvasion, perineural invasion, and local gross malignant invasion) or metastasis.[1,17,30–32,51,55–57] Biomarkers of malignancy including loss of parafibromin expression (the gene product of *CDC73/HRPT2* gene) and molecular assays can be used to diagnose parathyroid carcinoma in the appropriate morphological context.[17,41,49,56,58–62]

From a molecular perspective, the disordered proliferation of parathyroid chief cells is thought to be caused by inactivating germline mutation in *MEN1* (11q13) and its gene product "menin", which serve important tumor suppressor functions by inhibiting the Wnt/β-catenin, a well-known tumorigenesis pathway.[1,26,30,43,63,64] Interestingly, recent evidence suggests that menin may also play a role in vitamin D receptor (VDR) regulation.[43,65] Finally, it should be noted that inactivation of the remaining copy (the wild-type allele) causing biallelic inactivation of *MEN1*, leads to the formation of multiple multiglandular parathyroid tumors in the setting of MEN-1 related parathyroid disease.[1,26,30,43,63,64]

While a diagnosis of MEN-1 can be inferred based on clinical or familial criteria, most patients are now identified through genetic testing.[18,19,45] The most recent international guidelines recommend *MEN1* mutation testing in all patients with primary

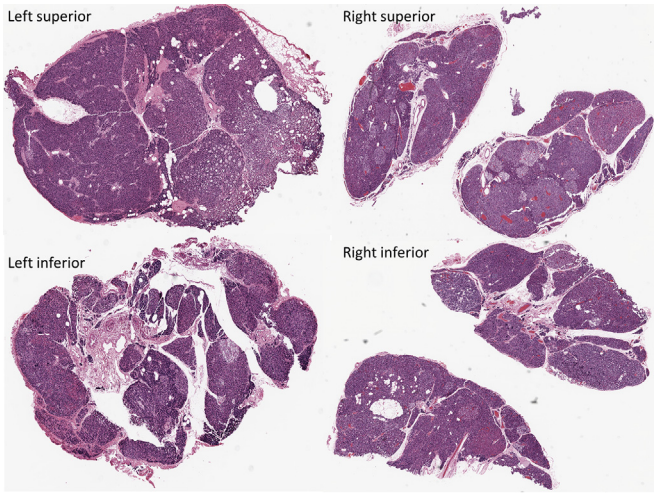

Figure 1 MEN-1 related hyperparathyroidism. MEN-1 related hyperparathyroidism almost always manifests with multiglandular parathyroid disease. This composite photomicrograph illustrated the four parathyroid glands that are enlarged and cellular. Although the identification of multiglandular parathyroid disease is often referred to as "parathyroid hyperplasia", in MEN1 such nodular proliferations represent clonal proliferations. Thus, the term "multiple adenomas" can also be used to reflect the underlying biology.