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Hereditary Endocrine Tumors: MEN1, MEN2, and Other Familial Syndromes

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Abstract

Hereditary endocrine tumors are a group of genetically inherited disorders characterized by the development of tumors in multiple endocrine organs. Among these, multiple endocrine neoplasia type 1 (MEN1) and multiple endocrine neoplasia type 2 (MEN2) are the most well-studied syndromes, each associated with specific genetic mutations and tumor profiles. MEN1 results from mutations in the MEN1 gene and primarily affects the parathyroid, pancreas, and pituitary glands. MEN2, caused by mutations in the RET proto-oncogene, is further classified into MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC), with medullary thyroid carcinoma as a hallmark feature. Other familial syndromes, such as von Hippel-Lindau (VHL) disease, pheochromocytoma-paraganglioma syndromes, and Carney complex, also contribute to hereditary endocrine tumor pathogenesis. Advances in genetic testing, early screening, and targeted therapies have significantly improved patient outcomes. This review provides an overview of the genetic basis, clinical presentation, diagnostic approaches, and treatment strategies for MEN1, MEN2, and related familial endocrine tumor syndromes.

Keywords: Hereditary endocrine tumors; Multiple endocrine neoplasia; MEN1; MEN2; Familial syndromes; RET gene; MEN1 gene

Introduction

Hereditary endocrine tumors are a diverse group of genetic disorders that predispose individuals to developing tumors in multiple endocrine glands. Among these, multiple endocrine neoplasia type 1 (MEN1) and multiple endocrine neoplasia type 2 (MEN2) are the most well-characterized syndromes, each associated with specific genetic mutations and distinct tumor patterns [1]. MEN1 is caused by mutations in the MEN1 gene, leading to tumors primarily in the parathyroid, pancreas, and pituitary glands. MEN2, on the other hand, results from mutations in the RET proto-oncogene and is subdivided into MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC), with medullary thyroid carcinoma (MTC) being a hallmark feature. In addition to MEN1 and MEN2, other familial syndromes contribute to hereditary endocrine tumor development, including von Hippel-Lindau (VHL) disease, pheochromocytoma-paraganglioma syndromes, and Carney complex. These syndromes exhibit variable penetrance, tumor progression rates, and organ involvement, necessitating tailored surveillance and management strategies [2].

Advancements in genetic testing and molecular diagnostics have significantly improved early detection and risk assessment in affected individuals and their families. Identifying pathogenic mutations enables targeted screening protocols and prophylactic interventions, particularly in conditions like MEN2, where early thyroidectomy can prevent the progression of medullary thyroid carcinoma [3]. Moreover, novel therapeutic approaches, including targeted kinase inhibitors, have expanded treatment options for aggressive or metastatic endocrine tumors associated with these syndromes. This review aims to provide an overview of the genetic basis, clinical manifestations, diagnostic strategies, and therapeutic approaches for MEN1, MEN2, and other familial endocrine tumor syndromes. Understanding the underlying genetic mechanisms and optimizing early detection strategies are crucial for improving patient outcomes and developing more personalized treatment approaches in hereditary endocrine oncology [4].

Discussion

Hereditary endocrine tumors, including multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2), and other familial syndromes, present complex clinical challenges due to their genetic basis, variable disease expression, and need for lifelong surveillance. MEN1, caused by mutations in the MEN1 gene, typically leads to tumors in the parathyroid, pancreas, and pituitary glands, with primary hyperparathyroidism often being the earliest manifestation [5]. The progression of MEN1-related tumors varies, making early genetic screening and biochemical monitoring crucial for timely intervention. In contrast, MEN2 is driven by mutations in the RET proto-oncogene and is subdivided into MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). Medullary thyroid carcinoma (MTC) is a hallmark feature of MEN2, often necessitating prophylactic thyroidectomy in genetically at-risk individuals to prevent malignancy. Other syndromes, such as von Hippel-Lindau (VHL) disease and pheochromocytoma-paraganglioma syndromes, involve mutations in tumor suppressor genes and can lead to aggressive endocrine and non-endocrine tumors [6]. Advancements in genetic testing have significantly improved the early detection and management of these hereditary conditions. Next-generation sequencing (NGS) allows for comprehensive screening of mutations in MEN1, RET, VHL, SDHx, PRKAR1A, and other genes associated with familial endocrine tumor syndromes. Identifying these mutations enables early intervention strategies, including prophylactic surgeries and targeted surveillance, reducing morbidity and mortality. Additionally, biochemical markers such as serum calcitonin and carcinoembryonic antigen (CEA) play a

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crucial role in detecting MTC in MEN2, while plasma metanephrines aid in diagnosing pheochromocytomas associated with MEN2 and VHL. Advanced imaging modalities, including MRI, PET-CT using tracers like 68Ga-DOTATATE, and functional imaging techniques, have further enhanced tumor localization, allowing for more precise treatment planning [7].

Surgical management remains the cornerstone of treatment for many hereditary endocrine tumors. In MEN2, prophylactic total thyroidectomy based on RET mutation status has proven highly effective in preventing MTC. Similarly, parathyroidectomy is the primary treatment for MEN1-associated hyperparathyroidism, although the recurrence risk and potential complications such as hypoparathyroidism must be carefully considered. For neuroendocrine tumors associated with MEN1, surgical resection is often required, particularly in insulinomas and gastrinomas, where tumor progression can lead to severe metabolic complications [8]. However, surgical approaches must be tailored to individual patient risk profiles, considering factors such as tumor burden, metastatic potential, and overall health status. Targeted therapies have revolutionized the treatment landscape for hereditary endocrine tumors, particularly for patients with advanced or metastatic disease. Tyrosine kinase inhibitors (TKIs) such as vandetanib and cabozantinib have been approved for treating progressive or inoperable MTC by targeting the RET and VEGF pathways, thereby inhibiting tumor growth. Additionally, somatostatin analogs like octreotide and lanreotide are commonly used to manage hormone-secreting neuroendocrine tumors, helping to control symptoms and slow disease progression. mTOR inhibitors such as everolimus have also shown promise in treating pancreatic neuroendocrine tumors associated with MEN1. The development of selective RET inhibitors, including selpercatinib and pralsetinib, represents a significant advancement, offering more targeted and effective treatment options with fewer off-target effects compared to older multi-kinase inhibitors [9].

Despite these advancements, several challenges remain in managing hereditary endocrine tumors. One of the primary difficulties is the variability in disease expression, where some individuals carrying pathogenic mutations develop aggressive tumors early in life, while others remain asymptomatic for years. This variability complicates risk assessment and decision-making regarding prophylactic interventions. Additionally, lifelong surveillance is required for individuals with hereditary endocrine tumor syndromes, necessitating multidisciplinary care involving endocrinologists, genetic counselors, surgeons, and oncologists. In resource-limited settings, access to genetic testing, specialized imaging, and targeted therapies remains a significant barrier, limiting early detection and optimal treatment. Future research aims to address these challenges by refining risk prediction models, improving molecular diagnostic techniques, and developing more effective gene-directed therapies. Advances in CRISPR-based gene editing and precision medicine approaches hold promise for selectively targeting pathogenic mutations, potentially preventing tumor development in high-risk individuals. Additionally, integrating artificial intelligence (AI) into predictive analytics could enhance early detection and personalized treatment planning, optimizing outcomes for patients with hereditary endocrine tumors. As the understanding of the genetic and molecular mechanisms underlying these syndromes continues to evolve, the development of novel therapies and improved surveillance strategies will further enhance disease management, ultimately improving the quality of life for affected individuals and their families [10].

Conclusion

Hereditary endocrine tumors, including MEN1, MEN2, and other familial syndromes, present significant diagnostic and management challenges due to their genetic basis, variable disease expression, and potential for life-threatening complications. Advances in genetic testing, biochemical markers, and imaging techniques have greatly improved early detection and risk stratification, allowing for timely interventions such as prophylactic surgeries and targeted therapies. Surgical management remains a key treatment strategy, particularly in MEN2-associated medullary thyroid carcinoma and MEN1-related pancreatic neuroendocrine tumors, though the emergence of targeted therapies, such as tyrosine kinase inhibitors and somatostatin analogs, has expanded treatment options for advanced disease. Despite these advancements, challenges remain, including the need for lifelong surveillance, variability in disease progression, and disparities in access to specialized care and genetic testing. Future research should focus on refining precision medicine approaches, enhancing predictive models, and exploring gene-directed therapies to further improve patient outcomes. Continued multidisciplinary collaboration and advancements in molecular research will play a crucial role in optimizing the prevention, diagnosis, and management of hereditary endocrine tumors, ultimately improving the quality of life for affected individuals and their families.

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