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Men Syndromes: Modern Clinical and Molecular Aspects of Diagnosis and Treatment

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Annotation: Multiple endocrine neoplasia (MEN) syndrome is a group of hereditary diseases characterized by the development of hormonally active and inactive neoplasms in two or more endocrine organs. The article presents a generalized analysis of modern concepts of the pathogenesis, clinical course, diagnostic algorithms and principles of treatment of various forms of MEN (types 1, 2A, 2B and 4). Particular attention is paid to the molecular genetic aspects of the disease, including mutations in the MEN1, RET and CDKN1B genes that underlie the development of these syndromes. The possibilities of personalized (precision) medicine, including preventive surgery in carriers of high-risk mutations, are highlighted. A comparative analysis of current international and domestic clinical guidelines is provided. The importance of early genetic screening and the introduction of an interdisciplinary approach to the system of monitoring and managing patients with suspected MEN syndromes is emphasized.

Keywords: MEN-1, MEN-2A, MEN-2B, RET, menin, pheochromocytoma, hyperparathyroidism, medullary thyroid cancer.

Introduction

Multiple Endocrine Neoplasia Syndrome (MEN)is a heterogeneous group of hereditary diseases in which the development of hyperplasia, benign adenomas and malignant neoplasms in various endocrine glands is observed [1,6]. According to the traditional classification, there are three main types of the syndrome: MEN-1, MEN-2A and MEN-2B, each of which is characterized by a unique molecular genetic nature and clinical and phenotypic features [8]. The prevalence of MEN is estimated at between 1:30,000 and 1:50,000 cases, which emphasizes the need for timely diagnosis due to the high risk of tumor malignancy and the development of life-threatening complications [1,2].

Genetics and pathogenesis. The pathogenesis of MEN-1 is based on a mutation in the MEN1 gene, which encodes the menin protein, a regulator of transcription and cell proliferation. MEN1 mutations are autosomal dominant with high penetrance, reaching almost 100% by the age of 50. In turn, MEN-2A and MEN-2B are caused by point mutations in the RET proto-oncogene, leading to constitutive activation of tyrosine kinase receptors and promoting tumor transformation of thyroid C-cells [3,4,9]. These mutations determine not only the likelihood of developing medullary thyroid cancer, but also its clinical course, as well as the risk of pheochromocytoma [4,5].

Clinical characteristics

Type MEN	Main manifestations
MEN-1 (Wermer's syndrome)	Hyperparathyroidism (>90%), pancreatic tumors (insulinoma, gastrinoma), prolactinoma
MEN-2A (Sipple syndrome)	Medullary thyroid cancer, pheochromocytoma, primary hyperparathyroidism
MEN-2B (Gorlin syndrome)	Medullary thyroid cancer (aggressive), pheochromocytoma, neuromas, marfanoid phenotype

Given the polymorphism of the clinical picture and varying degrees of penetrance in different types of multiple endocrine neoplasia (MEN) syndrome, timely detection of the disease plays a key role in preventing severe and sometimes fatal complications - primarily pheochromocytoma and medullary thyroid cancer.

Diagnostic algorithmIf MEN is suspected, it should include a comprehensive examination based on international and domestic clinical guidelines: biochemical and hormonal studies: determination of levels of total calcium, ionized calcium, parathyroid hormone (PTH), calcitonin, catecholamines and their metabolites (metanephrines and normetanephrines in plasma and/or urine); instrumental visualization: thyroid ultrasound, CT or MRI of the adrenal glands and parathyroid glands, scintigraphy with 99mTc-sestamibi (if hyperparathyroidism is suspected); molecular genetic testing: direct sequencing of exons of the MEN1, RET, CDKN1B genes, as well as prenatal or family screening in close relatives.

Particular attention should be paid to carriers of mutations in the RET gene, in whom clinical observation should be started from an early age. In cases of detection of mutations associated with high oncogenic activity (for example, RET M918T), preventive thyroidectomy is indicated in pediatric age, before clinical manifestation of the disease.

Therapeutic tactics

Treatment of patients with MEN should be individualized and based on the type of syndrome, localization and degree of aggressiveness of neoplasms. Surgery remains the leading method of treatment and includes thyroidectomy, adrenalectomy, parathyroidectomy and gastrin/insulin resection in MEN-1. Pharmacotherapy is indicated in cases of inoperable tumors or relapses. Somatostatin analogues (eg, octreotide) are used for neuroendocrine tumors, tyrosine kinase inhibitors (vandetanib, cabozantinib) for progressive MTC. Radiation and radioiodine therapy are usually of limited effectiveness in MEN, but can be considered in the metastatic process in the context of a multidisciplinary solution. The effectiveness of treatment is significantly increased by an interdisciplinary approach, which involves close interaction between an endocrinologist, oncologist, geneticist, surgeon and other specialized specialists.

The role of genetic counseling

Given the genetically determined nature of MEN syndromes, genetic counseling is considered an integral element of modern clinical practice. It is aimed at: identifying family members at risk of inheriting mutations; early diagnosis and implementation of preventive strategies; psychological support for patients and their relatives.

Planned consultation with subsequent dynamic observation allows not only to reduce the incidence of cancer, but also to significantly improve the prognosis and quality of life of patients with MEN syndromes.

MEN-1 syndrome (Wermer). The most common tumors are those of the parathyroid glands (hyperparathyroidism), pancreas (gastrinoma, insulinoma), and pituitary gland (prolactinoma, somatotropinoma). Tumors of the adrenal glands, thymus, lungs, and skin (e.g., lipomas, angiofibromas) may also develop. MEN-1 is caused by mutations in the MEN1 gene, which encodes the menin protein, which plays a role in regulating cell growth and apoptosis; Inheritance is autosomal dominant with high penetrance. Diagnostics includes determination of hormone levels (calcium, PTH, prolactin, gastrin), imaging methods (MRI, CT, ultrasound), and molecular genetic testing for mutations in the MEN1 gene [4]. The main method is surgical removal of tumors; Drug therapy may include hormone secretion inhibitors (eg, octreotide for gastrinomas) [1,5].

MEN-2 syndrome (Sipple syndrome)is a hereditary disease that includes a complex of tumor lesions of the endocrine system. The key clinical manifestations of MEN-2 are medullary thyroid cancer (MTC), pheochromocytoma and primary hyperparathyroidism. Depending on the phenotypic features, the syndrome is divided into two subtypes: MEN-2A: the classic triad - MTC, pheochromocytoma and

hyperparathyroidism; MEN-2B: characterized by an aggressive form of MTC, pheochromocytoma, mucosal neuromas and marfanoid phenotype. The pathogenesis of the syndrome is based on mutations in the RET proto-oncogene, leading to constitutive activation of the tyrosine kinase receptor, which contributes to tumor transformation of cells. Inheritance of the disease is carried out according to the autosomal dominant type with high penetrance.

Diagnostics. The diagnosis of RET syndrome includes molecular genetic testing for RET gene mutations, as well as determination of levels of specific biomarkers (calcitonin, metanephrines, catecholamines) and visualization (ultrasound and CT/MRI of the adrenal glands, thyroid scintigraphy). Early detection of RET mutants is of fundamental importance for timely intervention. Treatment tactics are based on the principles of preventive oncology. Carriers of high-risk RET mutations (for example, C634 or M918T) are indicated for , especially in pediatric age, before the manifestation of the disease. In the presence of clinically significant pheochromocytomas or hyperparathyroidism, appropriate surgical intervention is performed. An integrated approach involving an endocrinologist, oncologist, geneticist and surgeon is the key to successful management of this category of patients.

MEN-4 syndrome. Clinical manifestations withSymptoms of MEN-1 include: tumors of the parathyroid glands, pituitary gland, and pancreas. Tumors of the adrenal glands and sex glands may also occur [9]. Genetics are due to mutations in the CDKN1B gene, encoding the p27 protein, which regulates the cell cycle. Inheritance is autosomal dominant. Diagnosis and treatment are similar to those for MEN-1. They include regular screening and surgical intervention if necessary [3,4]

Conclusion

Multiple endocrine neoplasia (MEN) syndromes are rare but clinically significant hereditary diseases associated with a high risk of developing malignant tumors. Despite their low prevalence, these syndromes are of significant importance in the practice of an endocrinologist, oncologist and geneticist due to their multiorgan involvement, aggressive course and frequent manifestation at a young age. Modern advances in molecular genetics and the expansion of early screening capabilities have significantly improved the diagnosis and management of patients with MEN. Genetic testing allows not only to confirm the diagnosis, but also to identify asymptomatic carriers of mutations among relatives, thereby ensuring timely preventive measures. In particular, preventive thyroidectomy in children with high-risk RET mutations (for example, M918T) has proven its effectiveness in preventing the development of medullary thyroid cancer.

The most effective strategy for preventing severe consequences of MEN syndromes remains a multidisciplinary approach, including clinical observation, dynamic laboratory and instrumental diagnostics, planned surgery, as well as drug and targeted therapy when indicated. Early diagnostics of hormonally active tumors, regular monitoring of mutation carriers and clear routing of patients to specialized centers contribute to a significant reduction in cancer and endocrine morbidity, an increase in life expectancy and quality of life. Thus, the integration of molecular diagnostics and the principles of personalized medicine into clinical practice for MEN syndromes is one of the promising areas of modern endocrinology and oncogenetics.

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