MEN1 Clinical Background

Peter Igaz*

Abstract

Multiple endocrine neoplasia Type 1 (MEN1) is a rare hereditary tumor syndrome predisposing to tumor development in several endocrine organs. Its major manifestations include hyperparathyroidism, tumors of endocrine pancreas and pituitary. Beside these three, several other endocrine (adrenocortical, foregut carcinoid) and nonendocrine (lipoma, angiofibroma, collagenoma, ependymoma, meningioma) tumors have been described to be associated with this syndrome. Both familial and sporadic forms of the disease are known. The diagnosis of MEN1 can be established if two of the three major manifestations are found in the same patient, whereas the diagnosis of familial MEN1 requires one MEN1 patient and a first degree relative with at least one MEN1 manifestation. MEN1 is transmitted as an autosomal dominant trait with high penetrance, approaching 95-100% by the age of 60. Both benign (parathyroid, anterior pituitary) and malignant (gastrinoma, glucagonoma) lesions may develop in MEN1 patients. Regular surveillance of MEN1 gene mutation carriers is necessary to reveal disease manifestations. Several diagnostic modalities can be used to screen for and to examine MEN1-related tumors. The therapy of MEN1-associated tumors requires specific approach in some cases, as multiple tumors and recurrence is frequently observed.

Introduction

Multiple endocrine neoplasia syndrome Type 1 (MEN1, OMIM 131100) has been first described by Wermer in 1954 as an association of tumors of several endocrine organs.1 The main organs affected include the parathyroids, the endocrine pancreas and pituitary. Apart from these three major organs, many other, including some nonendocrine tumors may develop in the affected patients.2,7

MEN1 is a hereditary disorder with autosomal dominant transmission, therefore a child of a MEN1 affected parent has 50% chance of inheriting the disease. The development of multiple endocrine tumors in the same patient is of great significance also from a scientific point of view, that may indicate common points in the tumorigenesis of different endocrine organs. The genetic background of MEN1 was elucidated in 1997 by the identification of a putative tumor suppressor gene (MEN1 gene, on chromosome 11q13), whose inactivating mutations have already been found in the majority of MEN1 patients.8 Unfortunately, no mutation hotspots (i.e., gene regions, where mutations are frequently found) have been revealed in the MEN1 gene and efforts at establishing genotype-phenotype correlations have also been largely unsuccessful to date. The MEN1 gene codes for a protein termed menin that is involved in numerous molecular biological pathways which are discussed in other chapters in detail.9 Besides its inherited form, MEN1 is also observed in a sporadic setting, mostly due to de novo mutations. The likelihood of finding an MEN1 gene mutation is about 70-80% in familial cases, whereas only 45-50% of sporadic cases were found to harbor

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**Table 1. Comparison of MEN1 and MEN2 syndromes**

<table>
<thead>
<tr>
<th></th>
<th>MEN1</th>
<th>MEN2</th>
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</thead>
<tbody>
<tr>
<td>Function of responsible gene</td>
<td>Tumor suppressor</td>
<td>Protooncogene</td>
</tr>
<tr>
<td>Type of mutations</td>
<td>Inactivating</td>
<td>Gain of function</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AD</td>
<td>AD</td>
</tr>
<tr>
<td>Mutation hotspots</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Penetrance</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Genotype-Phenotype correlations</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Likelihood of finding germline mutations in familial cases</td>
<td>70-80%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Indication of prophylactic surgery</td>
<td>No*</td>
<td>Yes (MTC)</td>
</tr>
</tbody>
</table>

*As MEN1-related tumors arise in indispensable organs (pituitary, endocrine pancreas) or the disease can be efficiently diagnosed and cured (HPT), prophylactic surgery is not indicated, except for prophylactic thymectomy performed during parathyroid surgery to prevent the development of thymic carcinoids.

MEN1 mutations. The chance of finding an MEN1 gene mutation in an individual increases with the number of MEN1-related tumors present in the patient and with a positive family history.\(^\text{10}\)

There are several other monogenic tumor syndromes that include tumors of endocrine organs, as well. It is interesting to note that almost all such syndromes show an autosomal dominant inheritance pattern.

Manifestations of the other major multiple endocrine neoplasia syndrome (multiple endocrine neoplasia type 2, MEN2) include medullary thyroid cancer (MTC), pheochromocytoma and hyperparathyroidism (HPT). MEN2 is caused by gain-of-function mutations of the RET (Rearranged during Transfection) protooncogene. MEN2 has three forms: (i) MEN2A is an association of MTC, pheochromocytoma and HPT; (ii) in MEN2B a very aggressive MTC variant may associate with pheochromocytoma without HPT and patients show characteristic marfanoid appearance with mucocutaneous neurinomas; (iii) in familial MTC (FMTC) MTC is the only manifestation. Significant genotype-phenotype correlations have been established in MEN2 syndrome, i.e., it is possible to predict the expected phenotype in individuals with certain mutations. The likelihood of finding germline mutations in MEN2 patients is higher than in MEN1. In individuals carrying RET mutations, prophylactic thyroidectomy is indicated for the prevention of MTC development.\(^\text{1,6}\)

The major differences between MEN1 and MEN2 syndromes are summarized in Table 1.

Table 2 summarizes the major manifestations of some of the tumor syndromes with endocrine relevance.

In the following, the clinical features of MEN1 syndrome and questions related to its diagnostics, therapy and follow-up will be discussed.

**Clinical Features**

MEN1 is a rare syndrome with an overall prevalence of approximately 1:30,000.\(^\text{4,6}\) Its penetrance is high (i.e., the likelihood of overt disease in an individual carrying a MEN1 gene mutation), reaching 95% by the age of 55 years. MEN1 is rare in children and young adolescents, the typical age of its diagnosis is around 20-30 years.\(^\text{3}\)

The most common and most characteristic manifestation of MEN1 is hyperparathyroidism. In contrast with its sporadic counterpart, MEN1-associated HPT is mostly caused by the asymmetric hyperplasia of all parathyroid glands or multiple tumors. Ectopic, mainly mediastinal location is also common. HPT in MEN1 manifests itself decades earlier than sporadic forms, often at the age of 20-25 years, therefore HPT in a patient under 30 years should raise the suspicion of MEN1.