Mini Review

Multiple endocrine neoplasia type 1

R. V. Thakker

Nuffield Department of Medicine, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Headington, Oxford, OX3 7LJ, UK

ABSTRACT

Multiple endocrine neoplasia type 1 (MEN1) is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumors. Some patients may also develop carcinoid tumors, adrenocortical tumors, facial angiofibromas, collagenomas, and lipomas. MEN1 is an autosomal-dominant disorder, due to mutations in the tumor suppressor gene *MEN1,* which encodes a 610 amino acid protein, menin. Thus, the finding of MEN1 in a patient has important implications for family members because first-degree relatives have a 50% risk of developing the disease and can often be identified by *MEN1* mutational analysis. Patients with MEN1 have a decreased life-expectancy and the outcomes of current treatments, which are generally similar to that for the respective tumors occurring in non-MEN1 patients, are not as successful because of multiple tumors, which may be larger, more aggressive, and resistant to treatment, and the concurrence of metastases. The prognosis for MEN1 patients might be improved by pre-symptomatic tumor detection and undertaking treatment specific for MEN1-tumors. Thus, it is recommended that MEN1 patients and their families should be cared for by multi-disciplinary teams comprising relevant specialists with experience in the diagnosis and treatment of patients with endocrine tumors.

Key words: MEN1, parathyroid tumour, pancreatic islet cell tumour, pituitary tumour

Clinical features of MEN1

Multiple endocrine neoplasia type 1 (MEN1) is characterized by the combined occurrence of tumors of the parathyroids, pancreatic islets, and anterior pituitary. In addition to these tumors, adrenal cortical, carcinoid, facial angiofibromas, collagenomas, and lipomatous tumors may also occur in some patients.[1] MEN1 is inherited as an autosomal-dominant disorder with a high degree of penetrance, such that > 95% of patients develop clinical manifestations of the disorder by the fifth decade.[2] The earliest age at which manifestations of MEN1 may occur has been reported to be five years.[3] Parathyroid tumors, which lead to hypercalcemia, are the most common feature of MEN1 and occur in about 95% of patients. Pancreatic islet cell tumors, which consist of gastrinomas, insulinomas, pancreatic polypeptidomas (PPomas), glucagonomas and vasoactive intestinal polypeptidomas (VIPomas) occur in about 40% of patients; and anterior pituitary tumors, which consist of prolactinomas, somatotrophinomas, corticotrophinomas or non-functioning adenomas, occur in about 30% of patients. The clinical manifestations of MEN1 are generally related to their products of secretion and less frequently to their primary sites or metastasis. In the absence of treatment, MEN1 tumors result in an earlier mortality in patients.[4]

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Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.104058

Genetics

The gene causing MEN1 was localized to chromosome 11q13 by genetic mapping studies that investigated MEN1-associated tumors for loss of heterozygosity (LOH) and by segregation studies in MEN1 families. The results of these studies, which were consistent with Knudson's model for tumor development, indicated that the *MEN1* gene

Corresponding Author: Prof. R.V. Thakker, Nuffield Department of Medicine, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Headington, Oxford, OX3 7LJ, UK. E-mail: rajesh.thakker@ndm.ox.ac.uk

represented a putative tumor suppressor gene. Further genetic mapping studies defined a less than 300-Kb region as the minimal critical segment that contained the *MEN1* gene, and characterization of genes from this region led to the identification, in 1997, of the *MEN1* gene, which consists of 10 exons with a 1830-bp coding region that encodes a novel 610-amino acid protein, referred to as menin. Over 1100 germline and over 200 somatic mutations of the *MEN1* gene have been identified, and the majority (> 70%) of these are inactivating and are consistent with its role as a tumor suppressor gene.[5] These mutations are diverse in their types, and approximately 25% are nonsense mutations, approximately 40% are frameshift deletions or insertions, approximately 5% are in-frame deletions or insertions, approximately 10% are splice site mutations, approximately 20% are missense mutations, and less than 1% are whole or partial gene deletions. More than 10% of the *MEN1* mutations arise *de novo* and may be transmitted to subsequent generations. It is also important to note that between 5% and 10% of MEN1 patients may not harbor mutations in the coding region of the *MEN1* gene, and that these individuals may have mutations in the promoter or untranslated regions, which remain to be investigated. The mutations are not only diverse in their types but are also scattered throughout the 1830-bp coding region of the *MEN1* gene with no evidence for clustering. Correlations between the *MEN1* mutations and the clinical manifestations of the disorder appear to be absent. Tumors from MEN1 patients and non-MEN1 patients have been observed to harbor the germ line mutation together with a somatic LOH involving chromosome 11q13, as expected from Knudson's model and the proposed role of the *MEN1* gene as a tumor suppressor.

MEN1 MUTATIONAL ANALYSIS IN CLINICAL PRACTICE

MEN1 mutational analysis is helpful in clinical practice in several ways that include: 1) confirmation of the clinical diagnosis; 2) identification of family members who harbor the *MEN1* mutation and require screening for tumor detection and early/appropriate treatment; and 3) identification of the 50% of family members who do not harbor the familial germline *MEN1* mutation and can, therefore, be re-assured and alleviated of the anxiety burden of developing future tumors. This latter aspect cannot be over-emphasized as it helps to reduce the cost to the individuals and their children and also to the health services in not having to undertake unnecessary biochemical and radiological investigations. Thus, *MEN1* mutational analysis can be useful in clinical practice.[6-8]

MEN1 mutational analysis should be undertaken in: 1) an index case with two or more MEN1-associated endocrine tumors (i.e. parathyroid, pancreatic, or pituitary tumors); 2) asymptomatic first-degree relatives of a known *MEN1* mutation carrier; 3) a first-degree relative of an *MEN1* mutation carrier expressing familial MEN1 (i.e. having symptoms, signs, biochemical or radiological evidence for one or more MEN1-associated tumors); or 4) in patients with suspicious or atypical MEN1, which includes individuals with parathyroid adenomas occurring before the age of 30 years or multigland parathyroid disease, gastrinoma, or multiple pancreatic NETs at any age, or individuals who have two or more MEN1-associated tumors that are not part of the classical triad of parathyroid, pancreatic islet, and anterior pituitary tumors (e.g. parathyroid tumor plus adrenal tumor).[9,10]

Such mutational analysis may be undertaken in children within the first decade because children with MEN1-tumors have been reported by the age of 10 years, and appropriate intervention in the form of biochemical testing or treatment or both has been considered.[11] For example, the earliest reported age of onset for a MEN1-associated pituitary tumor, parathyroid tumor, insulinoma and non-functioning pancreatic NET > 2 cm in size, are 5, 8, 8 and 12 years, respectively.[12] Further, one study of 12 children under the age of 20 years from MEN1 families has reported that > 40% of children will have developed one or more MEN1-associated tumors. These studies suggest that that early identification of at risk individuals through mutation testing may be beneficial. Thus, a DNA test identifying an individual, who may be an asymptomatic relative of a patient with MEN1, as a mutant gene carrier, is likely to lead to earlier and more frequent biochemical and radiologic screening rather than to immediate medical or surgical treatment. In contrast, those relatives who do not harbor the *MEN1* mutation have their risk of developing MEN1-associated endocrine tumors markedly decreased from 1 in 2 for an autosomal-dominant disorder, to that of the general population, thereby freeing these relatives without the *MEN1* mutation from the requirement for further repeated clinical investigations. Thus, identification of *MEN1* mutations may be of help in the clinical management of patients and their families with this disorder. Finally, *MEN1* mutational analysis in a symptomatic family member (i.e. an individual already showing a clinical manifestation of MEN1), from a family with a known *MEN1* mutation, has been challenged as being unnecessary to establish the diagnosis of MEN1. However, two studies have reported that 5-10% of MEN1 kindreds have the occurrence of phenocopies (see above), which may confound the diagnosis, and, therefore, MEN1 family members with one MEN1-associated tumor should

be offered MEN1 mutation analysis.[13]

MEN1 germline mutational analysis should be considered in those presenting at an early age with a single, apparently sporadic MEN1-associated tumor. However, the occurrence of germline *MEN1* mutations in all patients with sporadic, non-familial parathyroid adenomas is 1%, in gastrinomas is 5%, in prolactinoma is 1%, and in foregut carcinoids is 2%. Investigations by two studies for germline *MEN1* mutations in patients developing non-familial (i.e. sporadic) parathyroid tumors below the age of 40 years has found the occurrence of such mutations in only 3 of 36 patients. All 3 of these patients had multi-gland parathyroid disease, whereas the majority (~95%) of the patients without *MEN1* mutations had solitary parathyroid adenomas. *MEN1* mutational testing, should therefore, be offered to patients who are below 40 years of age and have primary hyperparathyroidism due to multi-gland disease. The occurrence rates of germline *MEN1* mutations in individuals presenting with a single apparent non-familial (i.e. sporadic) pancreatic NET at similarly younger age has not been established, and at present, *MEN1* mutational analysis should also be considered in those with gastrinoma or multiple pancreatic NETs.[14,15]

Acknowledgements

I am grateful to the Medical Research Council (MRC), UK, for support and to Mrs Tracey Walker for typing the manuscript. Material previously published in: Thakker RV *et al* (2012), *Journal of Clinical Endocrinology and Metabolism* 97: 2990-3011; Thakker RV (2011) *Translational Endocrinology and Metabolism* 2: 13-14; Lemos M and Thakker RV (2008) *Human Mutation* 29: 22-32; and Newey PJ and Thakker RV (2011) *Endocrine Practice* 17 Suppl 3: 8-17.

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Cite this article as: Thakker RV. Multiple endocrine neoplasia type 1. Indian J Endocr Metab 2012;16:S272-4.

Source of Support: Nil, **Conflict of Interest:** None declared