We briefly review the characteristics of pituitary tumors associated with multiple endocrine neoplasia type 1. Multiple endocrine neoplasia type 1 is an autosomal-dominant disorder most commonly characterized by tumors of the pituitary, parathyroid, endocrine-gastrointestinal tract, and pancreas. A MEDLINE search for all available publications regarding multiple endocrine neoplasia type 1 and pituitary adenomas was undertaken. The prevalence of pituitary tumors in multiple endocrine neoplasia type 1 may vary from 10% to 60% depending on the studied series, and such tumors may occur as the first clinical manifestation of multiple endocrine neoplasia type 1 in 25% of sporadic and 10% of familial cases. Patients were younger and the time between initial and subsequent multiple endocrine neoplasia type 1 endocrine lesions was significantly longer when pituitary disease was the initial manifestation of multiple endocrine neoplasia type 1. Tumors were larger and more invasive and clinical manifestations related to the size of the pituitary adenoma were significantly more frequent in patients with multiple endocrine neoplasia type 1 than in subjects with non-multiple endocrine neoplasia type 1. Normalization of pituitary hypersecretion was much less frequent in patients with multiple endocrine neoplasia type 1 than in subjects with non-multiple endocrine neoplasia type 1. Pituitary tumors in patients with multiple endocrine neoplasia type 1 syndrome tend to be larger, invasive and more symptomatic, and they tend to occur in younger patients when they are the initial presentation of multiple endocrine neoplasia type 1.

KEYWORDS: Pituitary Neoplasms; Multiple Endocrine Neoplasia Type 1; Review; Genetics.

Luis V. Syro,1 Bernd W. Scheithauer (in memoriam),2 Kalman Kovacs,3 Rodrigo A. Toledo,4 Francisco J. Londoño,5 Leon D. Ortiz,6 Fabio Rotondo,3 Eva Horvath,3 Humberto Uribe3

1Department of Neurosurgery, Hospital Pablo Tobon Uribe and Clinica Medellin, Medellin, Colombia. 2Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA. 3Department of Laboratory Medicine, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada. 4Endocrine Genetics Unit (LIM25), Endocrinology, Hospital das Clinicas, University of Sao Paulo School of Medicine, Sao Paulo/SP, Brazil. 5Department of Neurosurgery, Universidad de Antioquia, Hospital San Vicente de Paul, Medellin, Colombia. 6Division of Neuro-oncology, Instituto de Cancerologia, Clinica Las Americas, Medellin, Colombia. 7Department of Neurosurgery, Clinica SOMA, Medellin, Colombia.

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E-mail: lvsyro@une.net.co
Tel.: 57 4 231 9099

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1, OMIM #131100) is an autosomal-dominant disorder mostly characterized by tumors of the pituitary, parathyroid, endocrine-gastrointestinal tract, and pancreas (1). Adrenocortical and thyroid tumors, cutaneous lipomas, meningiomas, facial angiofibromas and gastric, thymic or bronchial carcinoid can also occur (2–5). The phenotype of MEN1 may vary widely, and this neoplasia should be suspected in patients with an endocrinopathy of two of the three main affected glands or with one endocrinopathy of one of these organs plus a first-degree relative who is affected by MEN1 syndrome (6).

At the beginning of the past century, autopsy findings of a patient with acromegaly and four enlarged parathyroid glands were reported (7). In 1953, Underdahl et al. published the first review of MEN1 syndrome in which they described 14 cases in the literature and eight cases from the Mayo Clinic (8). In 1954, Wermer et al. suggested that this syndrome followed an autosomal-dominant inheritance pattern with high penetrance (9). The name MEN1 syndrome has replaced the original name, Wermer’s syndrome. The MEN1 clinical phenotype was fully characterized in the 1960s. In 1988, the MEN1 locus was mapped to chromosome 11q13 using recombinant DNA probes in two brothers with MEN1 syndrome (10). Linkage analysis in MEN1 families confirmed the 11q13 locus. In 1997, the MEN1 gene was identified by positional cloning, and mutations causing MEN1 syndrome were confirmed (11,12).

CLINICAL FEATURES

MEN1 is characterized by a combination of tumors of the anterior pituitary, parathyroid, gastrointestinal tract, and pancreas. Some patients may also develop adrenocortical tumors, carcinoid tumors, facial angiofibromas, collagenomas, and lipomas. Tumors of the parathyroid are the first manifestation of MEN1 in more than 85% of patients. In the remaining patients, the first manifestation may be an insulinoma or prolactinoma. Gastrointestinal and pancreatic...
tumors are gastrinomas, insulinomas, pancreatic polypepti-
domas (PPomas), glucagonomas, and vaso-active intestinal
polypeptidomas (VIPomas).

The most frequent MEN1-associated endocrinopathy, which occurs in 90% of individuals with MEN1 between the ages of 20 and 25 years, is primary hyperparathyroid-
ism, and it manifests as hypercalcemia in 100% of affected individuals by 50 years of age. It is a multi-glandular
disorder with enlargement of all parathyroid glands asynchroneously and asymmetrically (7). Thus, increased
calciu levels, renal calculi, and bone demineralization should be actively searched for in suspected cases (13).

MEN1 patients usually have a family history of MEN1, and MEN1 gene mutations can be identified in 70% to 95% of
cases (1). Several endocrine tumors in MEN1 are benign and
cause symptoms by hypersecretion of hormones or local mass effects, while other MEN1-related tumors are
associated with a very high risk of malignancy as gastrinomas and carcinoid tumors (1,4). About one-third of
cases affected with MEN1 will die early from an MEN1-related cancer or metabolic disturbance (14–16).

Consequently, the average age of death in individuals with
MEN1 is significantly lower than that in the general population. MEN1 syndrome occurs in approximately 1 in
30,000 individuals, with an equal sex distribution, and there
is no ethnic or racial predilection (14).

MOLECULAR AND GENETIC CHARACTERISTICS

MEN1 gene is a tumor suppressor gene localized on
chromosome 11q13. It contains 10 exons spanning about 10
kb and encodes menin, a 610-amino-acid protein. The first
exon and part of exon 10 are not translated. A major
transcript of 2.8 kb has been described in a wide variety of
human tissues such as the pancreas, thymus, adrenals,
thyroid, testis, leukocytes, heart, brain, lung, muscle, small
intestine, liver, and kidney (7).

Menin is a nuclear protein with a wide variety of molecular
interactions with proteins that are involved in transcriptional
regulation, genome stability, proliferation, and cell division
(17,18). It acts as a scaffold to regulate gene transcription by
coordinating chromatin remodeling and is an essential
component of the histone methyltransferase complex. The
proposed mechanism by which MEN1 mutations lead to
tumor formation is by disruption of the interactions between
menin and other proteins, thus altering critical events in cell
cycle regulation and proliferation (19,20).

Over 1,300 mutations have been reported, scattered in
and around the open reading frame without significant clustering, predominantly in coding exons but also within
intrinsic sequences (21,22). The majority of the mutations result in premature stop codon generation (>70%). Most of
the mutations are unique, and only a few are reported in
more than 2% of cases. About 45% of the mutations are
deletions, 25% are nonsense mutations, 15% are insertions,
10% are missense mutations, and less than 5% are splice-site
mutations (22). MEN1-founding mutations have been
described in Europe (France, Finland, and Sweden), North
America (United States, Canada), South America (Brazil),
and Oceania (Australia) (7,23–26).

The MEN1 mutations inactivate the gene and are consistent
with those expected for a tumor suppressor (22). More
than 90% of tumors from MEN1 patients have loss of
heterozygosity (LOH), and this has been taken as evidence
that the disease follows Knudson’s two-hit model of
tumorigenesis (27). The first hit is a heterozygous MEN1
germinal mutation inherited from one parent (familial
cases) or developed in an early embryonic stage (sporadic
cases) and is present in all cells at birth. The second hit is an
MEN1 somatic mutation that occurs in the predisposed
endocrine cell, giving the survival advantage needed for
tumor development (28).

MEN1 syndrome has high penetrance. Half of patients
develop signs and symptoms by 20 years of age, and more than 95% will have symptoms by 40 years of age (29). There
is significant variability in the age of onset, severity of
disease, and tumor types. Despite numerous studies, no
pheno-genotype relation has been established, and no correlations have been detected between MEN1 mutations
and clinical manifestations (1).

Ten percent of patients with the MEN1 syndrome may
not harbor mutations in the coding region of the MEN1
gene, and whether these individuals have whole gene
deletions or mutations in the promoter or untranslated
region remains to be investigated. One study showed that
33% of patients who do not have mutations within the
coding region have large deletions involving complete
exons not easily detected by DNA sequence analysis (30).

MEN1 families without inactivation of the MEN1 gene
may also present mutations in other genes. Pellegata et al.
first reported a CDKN1B-inactivating germline mutation in
a family with an MEN1-like phenotype (MEN4 syndrome)
involving cases with acromegaly, primary hyperparathy-
odism, renal angiomylipoma, and testicular cancer (31). A second CDKN1B germline mutation was described in an
apparently “sporadic” MEN1 patient with adrenocortico-
tropic hormone secreting pituitary adenoma (Cushing’s
disease) (32). Recently, other CDKN1B mutations were
identified in a very large cohort of patients with MEN1-
related states in whom no detectable MEN1 mutation was
found (33). Of note, none of these CDKN1B-mutation
positive patients had developed pituitary adenomas. These
data suggested that the tumoral susceptibility caused by
CDKN1B inactivation needs to be further evaluated and that
the association of CDKN1B mutations with pituitary disease
may be less common than initially thought. Agarwal et al.
demonstrated that patients with MEN1 states may rarely
harbor germline mutations in other genes encoding cyclin-
dependent kinase inhibitors (CDKIs), such as CDKN2B/
p15INK4b, CDKN2C/p18INK4C, and CDKN1A/p21
CIP1 (33). A mutation in the CDKN1A/p21CIP1 gene was
associated with pituitary tumors (macrolactinomas) in
two relatives. In conclusion, our knowledge about the role of
the CDK1 genes in the susceptibility to familial pituitary
adenomas is still limited owing to the small number of
patients with mutations reported so far (31–33).

PITUITARY TUMORS IN MEN1

Prevalence

The prevalence of pituitary tumors may vary widely,
in 10% to 76% of MEN1 cases, depending on the studied
series (26,29,34). Of note, the prevalence of pituitary tumors in
MEN1 in several large series consisting of small families
affected by MEN1 (less than five affected cases per family)
differs markedly from the few very large MEN1 genealogies
(>20 affected cases per family) so far reported (26). MEN1
cases in the latter families are usually caused by a founding MEN1 gene, and some of them may present very high frequencies of pituitary tumors, such as those reported in Newfoundland and Brazil (26,35).

**General characteristics**

Amongst 1,500 pituitary adenomas surgically resected at the Mayo Clinic, 41 (2.7%) occurred in the setting of MEN1 (36). In patients with MEN1, the frequency of functional adenomas, mainly prolactin and growth hormone-producing tumors, was higher than that of sporadic adenomas. There was, however, no difference in age, gender, tumor size, or invasiveness.

In 1980, Farid et al. described a syndrome of prolactinoma, carcinoid, and hyperparathyroidism in four large families from Newfoundland (37). This variant is now referred to as MEN1-Burin, for the region the affected patients were from (the Burin Peninsula). These patients presented frequently with prolactinoma and carcinoid. A nonsense mutation of the MEN1 gene, which was responsible for the disease in these patients, was found later (35).

Burgess et al. described another prolactinoma variant, MEN1-Tasman (34). In this case, prolactinomas occurred in 76% and nonfunctional adenomas in 24% of patients. Recently, a founding MEN1 gene mutation was detected in a large MEN1 Brazilian family, and a high frequency of pituitary tumors was verified (26).

In a France-Belgium multicenter study, 324 MEN1 patients were analyzed; 136 MEN1 patients with a pituitary adenoma were compared to 110 control patients with sporadic pituitary adenomas. No significant differences were detected in the types of adenomas, but the mean age of patients with pituitary disease as the initial manifestation of MEN1 was significantly lower (33.9 ± 14 years) than that of patients showing a primary endocrine, intestinal, or pancreatic tumor (41.6 ± 14 years). The study also showed that the delay between initial and subsequent MEN1 endocrine lesions was significantly longer when pituitary disease was the initial MEN1 manifestation (9.0 ± 8.1 years) than when the initial manifestation was intestinal and pancreatic tumors (4.1 ± 4.0 years) or hyperparathyroidism (5.2 ± 5.1 years) (38).

**Clinical characteristics**

In the France-Belgium multicenter study, the frequency of pituitary macroadenomas was significantly higher in MEN1 patients than in non-MEN1 subjects (85% vs. 42%) (38). Clinical manifestations related to the size of pituitary adenoma were significantly more frequent in MEN1 patients than in non-MEN1 subjects (29% vs. 14%). Pituitary adenomas with initial manifestation occurred in 17% of patients and were more frequent in women than in men. Normalization of pituitary hypersecretion was much less frequent in MEN1 patients than in non-MEN1 subjects (42% vs. 90%). In a recent publication, the authors found a gender-related difference showing that the prevalence and probability of developing pituitary tumors were significantly greater in females than in males (39). A family history of MEN1 was more frequently found in men than in women at the time of diagnosis. Pituitary tumors occurred as the first clinical manifestation of MEN1 syndrome in 25% of sporadic and in 10% of familial cases (7).

**Morphologic characteristics**

In a study by Trouillas et al. of 211 MEN1 patients, 77 surgically removed pituitary adenomas were described and compared with 2,509 unselected non-MEN1 sporadic pituitary tumors (40). These authors also compared a control subgroup of 296 cases from the latter group in which non-MEN1 cases were matched with MEN1 cases at the time of surgery and the immunoprofile of the tumor. The results showed that patients with MEN1 were younger and had larger tumors. The tumors of patients with MEN1 syndrome were more often invasive. The types of lesions were significantly different in MEN1 and non-MEN1 patients owing to the higher frequency of multiple adenomas (4% vs. 0.1%) and hyperplasia (4% vs. 0%) in the MEN1 patients. The frequency of functional pituitary adenomas was identical in the two groups (72% MEN1 vs. 64% non-MEN1), but the proportion of plurihormonal adenomas was significantly higher in the MEN1 group. Regarding immunoprogression, they did not find predominance of any functional subtype. It is important to note that in patients with pituitary hyperplasia, tumors producing a releasing hormone such as growth-hormone-releasing hormone must be investigated. Adenoma multiplicity may underlie surgical failure in cases in which one adenoma is removed and the other is left behind (41).

**Treatment**

Treatment of pituitary tumors depends on clinical presentation, and its aims are tumor volume diminution, normalization of hormone hypersecretion, and preservation of normal pituitary function. Surgery, medication (dopamine agonists, somatostatin analogs, growth hormone receptor antagonists) and radiotherapy are used. The choice of treatment depends on hormone hyperproduction (prolactin or growth hormone), the size and invasion of the tumor, presence of visual impairment, the presence of associated comorbidities, the response or lack of response to medical treatment, contraindications, and the patient’s preference. The treatment is the same for sporadic and MEN1-associated pituitary tumors. There are insufficient data in the literature to propose a different approach at present. A closed surveillance is recommended.

**Risk of malignant progression**

Although it was reported that pituitary tumors were larger and more often invasive in patients with MEN1 syndrome than in patients with sporadic tumors, malignant tumors were not more frequent. However, three cases of pituitary carcinomas were recently reported in patients with MEN1. The first one was a female with sporadic MEN1 and gonadotroph pituitary carcinoma (42). The second was a male with prolactin-producing carcinoma with familial MEN1 (43), and the third was a male with a thyrotropin-producing carcinoma in sporadic MEN1 (44). Owing to the low frequency of pituitary carcinomas, which represent about 0.1–0.2% of all cases of pituitary tumors, it is intriguing that three MEN1-associated cases have been reported.

**FUTURE PERSPECTIVES**

Despite significant efforts in the past decade, little is known about genetic alterations in patients with sporadic pituitary tumors. Recent interest in genetics and molecular alterations in patients with pituitary tumors has led to a
better understanding of the different syndromes involved in the development of MEN1, Carney complex, McCune-Albright syndrome and familial acromegaly (20,28,43,46). A number of genetic factors, hormones, growth factors, adhesion molecules and cell cycle regulators may be involved in these syndromes. Their study could help to elucidate the process of pituitary tumor initiation and progression.

Information related to human genes is accumulating at an ever-increasing pace, and the growing inventory of genetic variations is facilitating our understanding of the same disease among individuals and populations. MEN1-identified mutations have been described in different places around the world. The prevalence, severity, and resistance to treatment could differ among ethnic groups as a consequence of inherited and noninherited causes. It will be important in the future to analyze whether or not these groups possess ancestral similarities that could explain differences in clinical characteristics (47). Comparison of the prevalence of the two most important components of human genetic variation, single-nucleotide polymorphisms and copy-number variants, among these populations will provide us with better insight into MEN1. The use of ancestry in mapping genes that contribute to the development and progression of pituitary tumors in MEN1 may help us to understand the causes of disease and health disparities between these patients all around the world. Genomic data present a new array of opportunities and challenges, and data collection should be extended to as many diverse populations as possible.

Future study of MEN1 and pituitary tumors includes the application of “omic” technologies (genomics, transcriptomics, proteomics, and metabolomics). Contrary to traditional molecular biology methods that were used to study the role of a single gene and single protein, “omic” data along with a systems biology approach will help us to apply a multiple-factor model of disease and to clarify the network of interactions and regulatory events that contribute to disease (48,49).

Finally, the use of exome sequencing will offer new opportunities for research on Mendelian disorders. Exome sequencing has now been applied in multiple situations individually where the causal variants for a number of Mendelian disorders have been successfully identified. In addition, exome sequencing has been shown to be more rewarding in the study of disorders with genetic and phenotypic heterogeneity such as MEN1 (50–52). High-throughput sequencing may also be helpful in uncovering new genetic variants among MEN1 patients with no mutations apparent from conventional PCR and exon sequencing.

CONCLUSION

MEN1 is a complex syndrome in which a large number of endocrine and non-endocrine neoplasias may occur. The occurrence of anterior pituitary tumors in MEN1 syndrome may range between 10% and 60%. Pituitary involvement includes the initial manifestation of MEN1 syndrome in 10% to 25% of individuals (38,53). Pituitary adenomas are significantly more frequent in women than in men. Approximately 65% to 85% of pituitary tumors in MEN1 syndrome are macroadenomas. Plurihormonal adenomas occur more frequently than monohormonal adenomas in MEN1. Most cases are prolactinomas, somatotropinomas, and non-secreting tumors, although three cases of pituitary carcinoma were reported. In some families, including four families from Newfoundland reported as the so-called MEN1-Burin variant, prolactinoma is unusually common. Specific family presenting isolated familial prolactinomas or somatotropinomas need to be differentiated from cases with familial acromegaly/gigantism owing to germline mutations in the AIP gene (54).

When pituitary adenomas present as the initial manifestation of MEN1, they occur at an earlier age than when the initial manifestation is an endocrine, intestinal, or pancreatic tumor. Pituitary tumors in patients with MEN1 syndrome tend to be larger, more frequently invasive and more symptomatic, and they occur in younger patients. The normalization of pituitary hypersecretion occurs much less frequently in MEN1 functional adenomas than in sporadic adenomas. They are more frequently multi-hormonal and mixed tumors. Pituitary hyperplasia and multiple tumors are more frequently found in MEN1 pituitary tumors than in sporadic cases, although no significant differences were noticed.

In summary, pituitary tumors associated with MEN1 may differ markedly from sporadic tumors, and these differences are usually very helpful in performing the differential diagnosis between these entities. Briefly, pituitary tumors in MEN1 (a) are usually diagnosed at earlier ages than sporadic pituitary adenomas and occur more frequently in females; (b) have a higher degree of aggressiveness and invasiveness; (c) have a higher prevalence of macroadenomas; (d) more frequently present as multi-hormonal and mixed tumors; (e) are more often resistant to medical therapy; and (f) have higher tumor recurrence rates. Furthermore, pituitary hyperplasia and multiple pituitary tumors are more frequently found in MEN1 than in sporadic tumors, although no significant differences were noticed.

Finally, it is important to obtain genetic MEN1 mutation screening in MEN1 family members at risk to present with disease. This has a strong clinical impact that can lead to decreased morbidity rates and possibly decreased mortality rates, and this screening should be routinely performed (55,56).

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Author Contributions

Syro LV, Scheithauer BW, and Kovacs K conceived the study. Londoño FJ, Ortiz LD, and Rotondo F searched the literature and extracted the data. Syro LV, Londoño FJ, Ortiz LD, and Uribe H wrote the manuscript. Scheithauer BW, Rotondo F, Horvath E, and Toledo RA contributed to the initial revision of the manuscript. All authors contributed to the critical revision of the manuscript before publication and approved the final version.

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