MULTIPLE ENDOCRINE NEOPLASIA TYPE 4

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ABSTRACT

MEN4 (OMIM #610755) has many similarities with MEN1 but is caused by germline mutations in *CDKN1B*. MEN4 is rarer than MEN1. Clinical manifestations of MEN4 encompass primary hyperparathyroidism, pituitary adenomas, and gastroenteropancreatic neuroendocrine neoplasms. In line with MEN1 other neoplasms may occur.

INTRODUCTION

MEN4 (OMIM #610755) was initially named MENX and was first described in rats (1-3). MEN4 is caused by germline mutations in *CDKN1B* (*Cdkn1b* in rats), a tumor suppression gene encoding for the protein p27Kip1 (commonly referred to as p27 or as KIP1) (4). The *CDKN1B* gene is located on chromosome 12p13.1 (5). p27 is a member of the cyclin-dependent kinase inhibitor (CDKI) family which regulates the cell cycle (6, 7). Germline mutations in *CDKN1B* lead to reduced expression of p27, thereby resulting in uncontrolled cell cycle progression. To date, most of the reported human mutations were missense. These mutations were deemed pathogenic due to their *in vivo* or *in vitro* effects on the function of p27. In humans, two CDKI families have been identified: the INK4a/ARF family and the Cip/Kip family (8). Natalia Pellegata and colleagues reported in 2006 a three-generation family with apparently MEN1-related tumors, but this kindred turned out to become the first reported cases of MEN4 in humans (2). The incidence of *CDKN1B* mutations in patients with a MEN1-related phenotype is likely to be in the range of 1-4% (9-11). MEN4 screening has been recommended for all patients with a MEN1-related phenotype without the presence of a MEN1 gene mutation, but the yield seems to be extremely low (< 0.1%) (12, 13). All first-degree relatives of patients with MEN4 should be offered genetic testing (14-16). The offspring of an individual with MEN4 has a 50% chance of inheriting the *CDKN1B* pathogenic variant (17). Possible genotype-phenotype correlations might exist (18).

CLINICAL FEATURES OF MEN4

Primary Hyperparathyroidism

Primary hyperparathyroidism has been reported in up to 80%-90% of cases with MEN4 (3). The indications for parathyroid surgery in MEN4 are the same as for MEN1 and the approach in MEN4-related primary

hyperparathyroidism may be similar to that in MEN1 (19-22). It is suggested that screening for hyperparathyroidism with serum calcium measurements (and parathyroid hormone levels (PTH) if indicated) should start at the age of 15 years in MEN4 mutation carriers (23, 24).

Pituitary Adenomas

Pituitary involvement in MEN4 is the second most common manifestation of the disease, affecting approximately 1/3 of the reported cases to date. The types of pituitary disorders in MEN4 include: nonfunctional pituitary adenoma, acromegaly and gigantism, prolactinoma, or Cushing's disease (16, 22, 25-36). Pituitary tumors in MEN4 generally present with less aggressiveness and smaller size compared to those in MEN1 (28). The management of pituitary tumors in MEN4 is similar to other sporadic or familial cases (19). Routine surveillance for the development of pituitary tumors in patients with MEN4 should be performed on a case-by-case basis and follow the current guidelines for MEN1 (19, 24).

Gastroenteropancreatic Neuroendocrine Neoplasms (GEP NENs)

The prevalence of GEP NENs in MEN4 is approximately 25%. These include gastroduodenal or pancreatic NENs (panNENs), which are either nonfunctioning or secreting several peptides and hormones, including gastrin, insulin, adrenocorticotropic hormone (ACTH), or vasoactive intestinal polypeptide (VIP) (11, 20, 22, 25, 37-39). It appears that there is a decreased penetrance of gastroduodenal NENs or panNENs in MEN4 as compared to MEN1. The clinical syndromes associated with these hormonal overproductions can be found elsewhere in *Endotext* (40-43). The diagnosis and management of panNENs in MEN4 is similar to that in MEN1 (19). Screening for gastroduodenal NENs and panNENs should be initiated according to MEN1 screening protocols (19).

Other Neoplasms

Cervical neuroendocrine carcinoma (NEC), secreting and nonsecreting adrenal tumors, testicular cancer, breast cancer, papillary and medullary thyroid cancer, colon cancer, thymic and lung carcinoids, and meningioma have been reported incidentally in MEN4 cases (2, 9, 11, 15, 22, 23, 34, 36, 44, 45).

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