Clinical case of a woman with Multiple Endocrine Neoplasia Syndrome type 1

Nikolay Botushanov, Dimitar Troev, Maria Pavlova, Dimitar Georgiev
Clinic of Endorinology and Metabolic Diseases- Medical University Plovdiv

Absract

The multiple endocrine neoplasia (MEN) syndromes represent heterogeneous type of familial diseases characterized with adenomas of different endocrine glands. There are three main types of MEN. MEN type 1 / Wermer`s syndrom/ is uncommon. The population prevalence is about 1 in 30,000. Both sexes are equally affected. Adenomas of the parathyroid glands, pituitary and pancreas are most typical. Tumors are due to two consecutive mutations resulting in inactivation of a tumor-suppressive gene located in 11 chromosome /11q13/. MEN -1 is inherited as autosomal dominant trait with incomplete penetration.

We represent a 39 years old female with MEN-1. The first presentation of the syndrome were hypoglycemic episodes with no obvious provocation and reason. Later adenoma of the pancreatic tail was discovered. Due to hypercalcemia and increased parthyroid hormone hyperparathyroidism was diagnosed and two surgical removals of two enlarged parathyroid glands were undertaken. Investigating other possible locations of endocrine adenomas we found functionally inactive pituitary adenoma. Investigating patient's family we found no clinical signs of the syndrome.

Introduction. The multiple endocrine neoplasia (MEN) syndromes were described in the early part of the 20-th century and subsequently classified into two principle categories: MEN type 1 and MEN type2. They affect multiple types of hormone-secreting organs and produce multiple hormonal syndromes. Currently we accept that there are at list six MEN syndromes with several subvariants: MEN-1, MEN-2, von Hippel-Lindau disease, neurofibromatosis type1, Carney` complex and McCune-Albright syndrome. The first five of this are transmitted in the germline with autosomal-dominant transmission. The last one McCune-Albright syndrome, developes as a result of very early somatic mutations leading to involvement of multiple endocrine and nonendocrine cell types. Often it is misunderstood that every one of these syndromes can produce variety of nonendcrine symptoms which can dominate the clinical picture.

MEN -1 is uncommon. The population prevalence is about 1 in 30,000. Both sexes are affected equally . It is transmitted in autosomal-dominant way with high penetration and different expression. MEN-1 gene was mapped to chromosome 11q13. It is a tumor suppressor gene and is composed of 10 exones. It can be found in different endocrine and nonendocrine cells. This gene encodes a 610-amin-acid protein called menin, which participates in the cell control in different tissues.

The most typical for MEN-1 combination of features represents the association of parathyroid, enteropancreatic endocrine and pituitary neoplasia but many other features can be seen /table 1/.

Table 1. Features of multiple endocrine neoplasia type 1 in adults.

Endocrine features (estimated average penetrance)

1. Parathyroid adenoma (95%)
2. Enteropancratic
   - Gastrinoma (40%)
   - Insulinoma (10%)
   - Nonfunctioning (20%)
   - Other: glucagonoma, VIPoma, somatostatinoma, etc. (each < 2%)
3. Foregut Carcinoid
   - Thymic carcinoid nonfunctioning (2%)
   - Bronchial carcinoid nonfunctioning (4%)
   - Gastric enterochromaffin-like tumor nonfunctioning (10%)
4. Anterior Pituitary
   - Prolactinoma (25%)
   - Other: nonfunctioning (10%), Growth hormone +prolactin (5%), ACTH (2%), Thyrotropin(5%)
5. Adrenal
   - Cortex: Nonfunctioning (30%), functioning or cancer (2%)
   - Medulla: Pheochromocytoma (<1%)

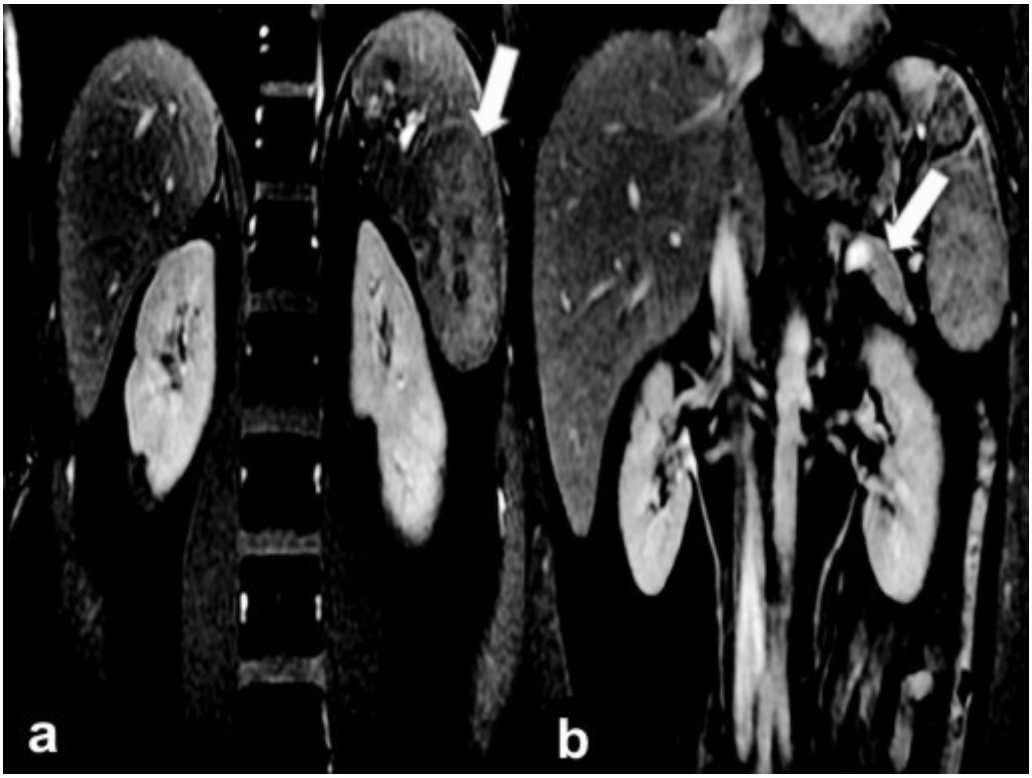
Nonendocrine features (estimated average penetrance)

1. Facial angiofibroma (85%)
2. Lipoma (30%)
3. Leiomyoma (5%)
4. Meningioma (5%)

Many nonfunctioning MEN-1 tumors synthesize a peptide hormone or other factor, but they are in small quantity and can not produce symptoms of hormonal expression.

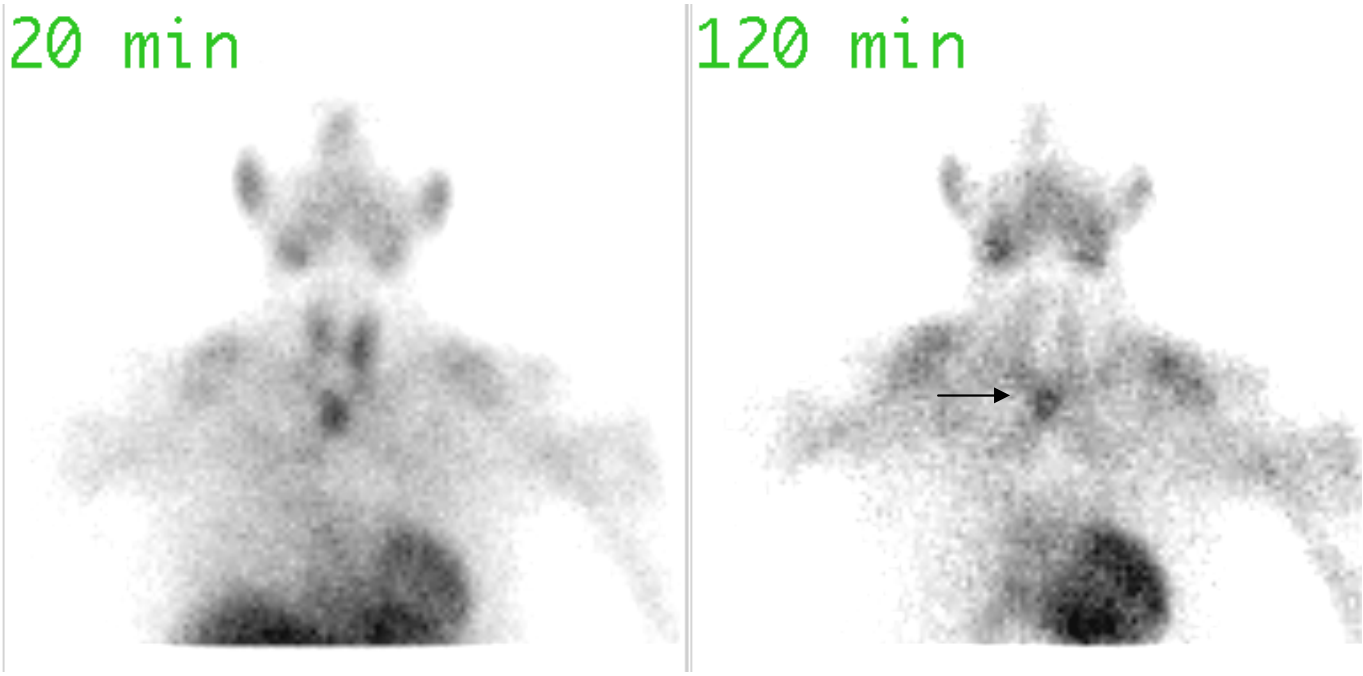
Clinical Case. We represent a 39 years old woman with typical features of MEN-1 : hyperparathyroidism, insulinoma and nonfunctioning pituitary adenoma. The first clinical signs began in 1999 , when she was 29 years old. She complained of frequent episodes of serious hypoglycemia which she was not able to overcome alone and some of them led to hospitalization. Because she was not diabetic and did not take any oral hypoglycemic drugs or insulin, and hypoglycemia and inappropriately high insulin and C-peptide were found diagnosis insulinoma was put. At the beginning we were not able to visualize any pathologic changes in the pancreas , that`s why we undertook treatment with oral drugs which suppressed insulin secretion to control hypoglycemia. She was taken Diazoxide /Proglycem/ 100 mg t.i.d. Later on we managed to discover on CT a solid tumor mass 17 /18 mm located between the spleen and the pancreas /fig.1/. Currently she is preparing to undergo surgical removal of the tumor.

Фиг. 1 CT of abdomen of the patient



In the year of 2000 a nodule in the right lobe of the thyroid gland was found. Due to the existing hypercalcemia, hypophospahtemia and high PTH it was interpreted as parathyroid adenoma and was surgically removed. Histological result proved the diagnosis parathyroid adenoma. High serum calcium persisted after the operation and recurrence of the hyperparathyroidism was suspected. A scintigraphy with ^{99m}TcMIBI was performed /fig 2/ and another parathyroid adenoma was found. In 2007 she has undergone another surgical removal of the existing parathyroid neoplasia.

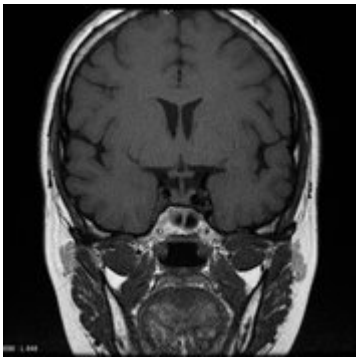
Fig 2. Scintigraphy with ^{99m}TcMIBI of the thyroid and parathyroid glands



In the early phase /20 min/ a relatively homogenous radionucleotide captation in the thyroid gland can be seen. A large nodule can be found adjacent to the lower part of the left lobe. In the late phase /120 min/ o focus of residual radionucleotide accumulation can be seen in the above described zone.

In an effort to discover other manifestations of MEN-1 we performed an MRI of the brain and found adenoma of the anterior pituitary /fig 3/. Hormonal secretion of the pituitary hormones were normal and we classified it as nonfunctioning.

Fig 3 MRI of the brain



In this patient we found the typical combination of features of MEN-1. The first presentation of the syndrome were the hypoglycemic episodes, but we consider that hyperparathyroidism was the real first presentation but because asymptomatic remained undiagnosed. The patient has undergone two surgical procedures of removal of parathyroid adenomas. Despite all the symptoms of hyperparathyroidism still persisted after the two operations. May be a more radical approach was necessary to explore all the parathyroid glands during one of the past operations and to remove all with pathological changes. Hyperparathyroidism in MEN-1 differs in some ways from that caused by a sporadic adenoma: has an earlier age of onset, has no gender imbalance and almost never progress to parathyroid cancer.

The discovered adenoma of the pituitary gland, due to its size 3 mm and no hormonal overproduction was not operated at that moment.The patient must undergo surgical removal of the insulinoma in an attempt to stop the persistent hypoglycemic episodes, which are difficult to control with diazoxide.

It is normal a patient with MEN 1 to undergo two or more operations during his life.

A screening program for MEN-1 patients should routinely meet three main objectives: identify MEN-1 carriers; identify MEN-1 tumors at a treatable stage, and be cost effective. When carrier testing with DNA is not possible, streamlined and periodic tumor surveillance becomes the preferred method for carrier ascertainment. Representative protocol of tests and schedules to survey for tumor expression in a highly likely carrier of MEN type1 is shown in table 2

Table 2. Representative protocol of tests and schedules to survey for tumor expression in a highly likely carrier of MEN type1.

Tumor	Age to begin testing (yr)	Biochemical Tests Annually	Imaging Tests Every 3-5 yr
Anterior pituitary	5	Prolactin;IGF-1	MRI
Foregut carcinoid	20		CAT
Gastrinoma	20	Gastrin	-
Insulinoma	5	Fasting glucose	-
Other enteropancreatic	20		CAT, MRI, In-DTPA-octreotide
Parathyroid adenoma	8	Calcium (especially Ca^{+2}), PTH	-

From Brandi ML, GAGEL rf, Angeli A et al. Guidlines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658-5671

Conclusions. When we have a patient with symptoms that suggest neoplasia of one endocrine gland we should have in mind that another endocrine and non endocrine organs can also be affected. So thorough examination should be done in order to discover these lesions at an early and treatable phase of there development.