The multiple endocrine syndromes are inherited autosomal dominantly and consist of two superior groups (I and II). The second group can be further divided into three subgroups (IIa, IIb and FMTC-only). The respective upper groups have different causes on moleculargenetic level. Characteristic signature diseases i.a. appear as part of these syndromes.

**MEN 1**
- Pituitary adenoma
- Parathyroid hyperplasia
- Pancreatic tumors

**MEN 2A**
- Parathyroid hyperplasia
- Medullary thyroid carcinoma
- Pheochromocytoma

**MEN 2B**
- Mucosal neuromas
- Marfanoid body habitus
- Medullary thyroid carcinoma
- Pheochromocytoma

### MEN-1 Syndrome (Wermer’s Syndrome)

The MEN-1 syndrome belongs to the multiple endocrine syndromes and is inherited autosomal dominantly.

### Etiology of the MEN-1 syndrome

Cause of the development of MEN-1 syndrome is a mutation of the *menin* gene. The
The menin gene is located on the long arm of chromosome 11 (11q13).

The menin gene is a so-called tumor suppressor gene. Proteins that regulate i.a. the cell cycle as well as apoptosis, belong to this group. The risk of development of neoplasias is increased due to the mutation of a tumor suppressor gene.

**Note:** The MEN-1 syndrome is caused by a mutation of the menin gene.

### Diseases as part of the MEN-1 syndrome

The signature disease of the MEN-1 syndrome in 95% of the cases is the primary hyperparathyroidism. As a part of this, an increased level of parathormone occurs due to parathyroid hyperfunction.

**Note:** The signature disease of the MEN-1 syndrome is the primary hyperparathyroidism.

### Tumors of the MEN-1 syndrome

The possible tumors that evolve from a MEN-1 syndrome, can be tumors of the pancreas like gastrinoma and insulinoma for example. These two tumors belong to the spectrum disorders of endocrine pancreatic tumors. These appear in 50% of the cases. Tumors of the hypophysis as a part of MEN-1 syndrome are rarer (about 30-50% of the cases) but still common.

### MEN-2 Syndrome

The MEN-2 syndrome is also inherited autosomal dominantly and can further be divided into the Sipple’s syndrome (2a), the Gorlin’s syndrome (2b) and the FMTC-only (familial medullary thyroid carcinoma).
The **FMTC-only** is a special form of MEN-2 syndrome since in this case, only **medullary thyroid carcinomas** appear. That is why it is also called **non-MEN syndrome** since no multiple endocrine tumors are present.

**Etiology of the MEN-2 syndrome**

The etiology of the three subgroups of the MEN-2 syndrome is identical. All three are caused by a mutation of the **Ret-protooncogene**. This codes for a transmembranous tyrosine kinase. The locus of the mutation is on the long arm of **chromosome 10** (10q11.2) here.

**Clinical presentation of the MEN-2a syndrome (Sipple’s syndrome)**

Sipple’s syndrome with 70 % of MEN-2 cases is notably more common than the Gorlin’s syndrome (about 10 % of all cases).

**Diseases as part of MEN-2a syndrome**

In about 50 % of the cases, a **phaeochromocytoma** and in 20 % of the cases, **primary hyperparathyroidism** occurs as a part of Sipple’s syndrome.

**Note:** A primary hyperparathyroidism can be part of a MEN-1 syndrome as well as part of a MEN-2a syndrome.

**Tumors of the MEN-2a syndrome**

The most common tumor and therefore signature disease of MEN-2a syndrome is the **medullary thyroid carcinoma (C-cell carcinoma)**. This occurs in almost 100 % of the cases.

**Note:** The signature disease of the Sipple’s syndrome is the medullary thyroid carcinoma.

**Clinical presentation of the MEN-2b syndrome (Gorlin’s syndrome)**

Gorlin’s syndrome is the least often occurring subgroup of the MEN-2 syndrome with 10 % of the cases. In about 60 % of the cases, the Gorlin’s syndrome evolves as part of a new mutation which means that it is not inherited autosomal dominantly. These cases are called **sporadic cases**.
Diseases as a part of MEN-2b syndrome
Similar to Sipple’s syndrome, a phaeochromocytoma also occurs in 50 % of the cases of Gorlin’s syndrome.

Note: In contrast, primary hyperparathyroidism does not belong to Gorlin’s syndrome. Further clinical characteristics that appear as a part of Gorlin’s syndrome, are mucosal neurinomas, ganglioneuromatoses in organs like the tongue or the intestine, as well as marfanoid habitus. Characteristics of marfanoid habitus are for example a lean, tall body shape with long extremities as well as hyperextension of joints.

Tumors of the MEN-2b syndrome
Similar to Sipple’s syndrome, the medullary thyroid carcinoma is also the signature disease of Gorlin’s syndrome (about 100 % of the cases).

Clinical presentation of FMTC-only syndrome (non-MEN syndrome)
Like mentioned above, an FMTC-only syndrome is a special form as only medullary thyroid carcinomas occur.

Note: Always think of a MEN-2 syndrome at familial occurring, medullary thyroid carcinomas. With a molecular genetic diagnosis, not yet affected family members can also be tested for the mutation to consider a prophylactic thyroidectomy afterward.

Review Questions
Find the answers below the references.

1. Which assertion about multiple endocrine neoplasias is not correct?
   A. The MEN-1 syndrome is caused by a mutation of the menin gene.
   B. The MEN-2 syndrome is caused by a mutation of the Ret-protooncogene.
   C. The Ret-protooncogene codes for a tyrosine kinase.
   D. The menin gene is a tumor suppressor gene.
   E. The multiple endocrine neoplasias are inherited autosomal recessively.

2. Which assertion about MEN-1 syndrome is correct?
   A. A synonym for MEN-1 syndrome is Gorlin’s syndrome.
   B. Endocrine pancreatic tumors like insulinoma can occur.
   C. Primary hyperparathyroidism occurs in 30 % of the cases.
   D. Hypophyseal tumors are present in over 90 % of the cases.
   E. Medullary thyroid carcinomas often occur.

3. Which assertion about MEN-2 syndrome is not correct?
   A. It can be further divided into Sipple’s, Gorlin’s and the FMTC-only syndrome.
   B. The majority of the cases of MEN-2 syndrome are Sipple’s syndrome.
   C. The signature disease of MEN-2 syndrome is the medullary thyroid carcinoma.
   D. Mucosal neurinomas can occur as part of the Gorlin’s syndrome.
   E. Primary hyperparathyroidism occurs in about 20 % of the cases of MEN-2b syndrome.
References


Correct answers: 1E, 2B, 3E

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