Cowden's syndrome

Cowden syndrome, syn. **multiple hamartoma syndrome**, is an autosomal dominant inheritance disorder caused by a mutation in the tumor suppressor gene *PTEN*. The prevalence is estimated at 1 in 200.000. In addition to the sometimes noticeable disorders, the syndrome is associated with a high risk of developing breast, thyroid and endometrial cancers.

Lhermitte-Duclos disease is an extremely rare **dysplastic cerebellar gangliocytoma**. It is probably a hamartoma, usually as part of Cowden syndrome.

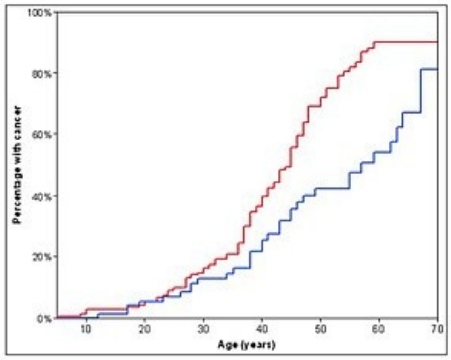
Clinical picture

The main feature of the disease are numerous hamartomatous lesions. A typical clinical picture includes mucocutaneous lesions (facial trichilemoms, acral keratosis and papillomatous papules), macrocephaly and an increased risk of breast cancer, thyroid cancer and endomentrial carcinoma. There are hamartomatous polyps often present in the gastrointestinal tract which cannot be histologically distinguished from polyps in juvenile polyposis. Also other polyps based on ganglioneuroma, lipoma, fibroma and inflammatory polyps have been described. Macrocephaly may also include hypoplasia of the maxilla and mandible and the resulting microstomy. Excessive ribs may appear, the chest may be deformed in the sense of pectus excavatum. Esophageal glycogen acanthosis is a relatively common finding. Lipomas can also occur subcutaneously. The syndrome may also include a brain development disorder; the syndrome may also include disorders of the autism spectrum or mental retardation.

Diagnostics

Diagnostic criteria for determining the working diagnosis (Pilarsky 2013) are based on the clinical picture. There are:

1. **Main criteria:**
   - **Lhermitte-Duclos disease**,
   - **gastrointestinal hamartomas of three or more**,
   - **macrocephaly** (97 percentile and more),
   - breast carcinoma,
   - endometrial epithelial tumor,
   - follicular carcinoma of the thyroid gland,
   - macular pigmentation on the glans penis,
   - multiple mucocutaneous lesions (at least one of the following):
     - multiple trichilemomas (three or more, at least one confirmed histologically),
     - acral keratosis (three or more lesions),
     - mucocutaneous neuromas (three and more),
     - oral papillomatosis.
2. **Secondary criteria:**
   - autism spectrum disorders,
   - colon malignancy,
   - esophageal glycogen acanthosis (three or more lesions),
   - lipomas (three and more),
   - mental retardation (IQ below 75),
   - conventional renal cell carcinoma,
   - testicular lipoma,
   - papillary thyroid carcinoma (incl. follicular variant of papillary carcinoma),
   - structural lesions of the thyroid gland,
   - vascular anomalies.



Cumulative risk of any cancer diagnosis in female (red) and male (blue) patients with Cowden syndrome from birth to age 70 (Kaplan-Meier). Riegert-Johnson et al. Hereditary Cancer in Clinical Practice 2010 8:6.

Cumulative risk of patients with Cowden's syndrome up to the age of 70 years.

In the case of a negative family history, the diagnostic criteria are met if one of the following situations occurs.

1. At least three main criteria are met. However, at least one of them must be Lhermitte-Duclos disease, gastrointestinal hamartomas or macrocephaly.
2. Any two main and three secondary criteria are met.

In the case of a positive family history (related to Cowden's syndrome or a proven *PTEN* mutation) the diagnostic criteria are met if one of the following occurs.

1. Any two main criteria are met.
2. One main and one secondary criterion is met.
3. Three secondary criteria are met.

Molecular biology

About 80% of patients with clinically diagnosed Cowden syndrome have a germline mutation in the *PTEN* gene (*phosphatase and tensin homolog*). The *PTEN* gene is located on chromosome 10q23.3. It encodes a protein with phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase activity, the activity of which leads to attenuation of the AKT/PKB signaling cascade. Thus, it is a tumor suppressor gene. Different mutations of the same gene also cause phenotypically different Bannayan-Riley-Ruvalcaba syndrome.

The syndrome with a proven *PTEN* mutation is referred to as Cowden syndrome 1. The remaining approximately 20% of cases without a proven mutation in the *PTEN* gene are caused by a mutation in another gene interfering with the AKP/PKB signaling cascade. Six molecular variants of Cowden syndrome are currently known:

- Cowden syndrome 1 – *PTEN* gene mutation,
- Cowden syndrome 2 – mutation of the B subunit of succinate dehydrogenase complex (*SDHB*),
- Cowden syndrome 3 – mutation of the D subunit of succinate dehydrogenase complex (*SDHD*),
- Cowden syndrome 4 – hypermethylation of the promoter of the *KLLN*gene, which shares a transcription site with *PTEN*,
- Cowden syndrome 5 – *PIK3CA* gene mutation,
- Cowden syndrome 6 – *AKT1* gene mutation.

Links

Related articles

- Mechanisms of tumor formation
- Tumor Supressor Genes

Used literature

-
- WOOD, L.D.. Update on colorectal polyps and polyposis syndromes. *Diag Histopathol.* 2014, vol. 20, no. 1, p. 12-18, ISSN 1572-0241.
- PILARSKI, R. – BURT, R. – KOHLMAN, W.. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst.* 2013, vol. 105, no. 21, p. 1607-16, ISSN 1460-2105.
- HANSSEN, A.M. – FRYNS, J.P.. Cowden syndrome. *J Med Genet* [online]. 1995, vol. 32, no. 2, p. 117-9, Available from <https://jmg.bmj.com/content/jmedgenet/32/2/117.full.pdf,>. ISSN 0022-2593.

References

External links

- -. *Online Mendelian Inheritance in Man : COWDEN SYNDROME 1* [online]. [cit. 8/2014]. <https://www.omim.org/entry/158350>.
- Kalkulačka na PTEN skóre (http://www.lerner.ccf.org/gmi/ccscore/)