Nervous system: Neurofibroma

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Identity

Numerous cutaneous neurofibromas (A.) and a large plexiform neurofibroma (B.).
Classification

Neurofibromas are benign tumors of the peripheral nerves. Dermal neurofibromas are well circumscribed solid cutaneous tumors with limited size. Plexiform neurofibromas (PNF) originate from subcutaneous or visceral peripheral nerves and involve multiple fascicles extending along the length of a nerve. In contrast to dermal neurofibromas, plexiform neurofibromas vary in size and can be extremely large. Multiple dermal neurofibromas are the hallmark of neurofibromatosis type 1 (NF1), an autosomal dominant genetic disease with an incidence of approximately 1 in 3000. Plexiform neurofibromas develop in approximately 30% of NF1 patients. While dermal neurofibromas also occur in non-NF1 patients, PNFs are almost exclusively associated with NF1.

Clinics and pathology

Disease

Neurofibromatosis type 1 (NF1) is an autosomal genetic disease caused by heterozygous dysfunction of the NF1 tumor suppressor gene on the long arm of chromosome 17.

Embryonic origin

Neurocrest.

Etiology

The genetic cause for neurofibromas is the bi-allelic inactivation of the NF1 tumor suppressor gene.

Epidemiology

Both sexes can be affected. Neurofibromas are rare in children, but start develop in puberty. Up to thousands of neurofibromas can develop in one adult NF1 patient. In contrast to dermal neurofibromas, PNF are often congenital and may develop already before birth.

Clinics

Neurofibromas are mostly benign. These tumors can lead to transient stinging, itching, and pain. Multiplicity of these tumors often causes disfigurement with psychological impact on the individual's self-esteem, partnerships and social relations. However, dermal neurofibromas usually do not cause any further serious dysfunction. There is no evidence for malignant transformation of dermal neurofibromas. In contrast, PNF often lead to pain, disfigurement, neurological and other clinical deficits. PNF mostly show net-like growth pattern along nerve roots extending from a main nerve root to a small distal branch, and can be divided into two main types: internal tumors and superficial ones.

Superficial PNF do not cross tissue planes and are amenable to complete or nearly complete surgical resection. Internal PNF extend through multiple tissue planes and can not be completely removed in most cases without damaging tissues and organs. PNF located in the chest, abdomen or pelvis are frequently detected as paraspinal masses that involves multiple spinal levels. These tumors may also appear as anterior mediastinal masses, sciatic nerve lesions with pelvic extension, and perirectal plexiform and uterine tumors, all leading to sever clinical complications. Furthermore, there is a risk of malignant progression in PNF, especially the internal ones. While dermal neurofibromas mostly appear during adolescence, PNF are mainly congenital though some of them become apparent later. Growth of PNF is slows down with increasing age.

Pathology

According to the WHO classification dermal and plexiform neurofibromas are grade I tumours. Histologically they consist of transformed Schwann cells with wavy contours and ovoid to elongated nuclei with fine dense heterochromatin. The tumours show a diffuse growth or an arrangement of cells in streams. The Schwann cells are intermingled with fibroblasts and perineurial-like cells in a matrix of mucous substances and a varying amount of collagen fibres. Within the tumour, especially in dermal neurofibromas, mast cells and perivascular lymphocytic infiltrates may be demonstrated. In some patients focal palisading of small groups of nuclei may resemble Meissner corpuscles and arrangement of cells in dense whorls may resemble Pacini corpuscles. Plexiform tumours typically show a low cellularity, loose texture and an abundant myxoid matrix. Degenerating nerve fibres may be seen within the tumour. There are no signs of malignancy and proliferative activity is low or absent in both, dermal and plexiform neurofibroma. Some cases may show a mixed Schwannoma-neurofibroma differentiation, these tumours are termed 'Schwannoma in Neurofibroma'.

Immunohistochemical labelling of tumour cells with antibodies against S-100 protein is particularly helpful in tumours with extremely low cellularity like in dermal neurofibromas of the mamilla.

Treatment

Surgery: Plastic surgeons should be consulted for surgical resection of neurofibromas, especially for those of face and neck. The result of the surgery dependends on the size, localization, and structure (diffuse, nodular, or pendunculated) of the tumors. Pendunculated neurofibromas can be excised with a very satisfactory result. Various techniques can be applied for resection of neurofibromas: conventional scalpel, laser or electrocauterization.
According to our experience, conventional scalpel is suitable for larger, exophytic tumors. Laser and electrocauterization are useful for tumors with intracutaneous localization with abundant blood vessels. There is no proven benefit for carbon dioxide laser treatment for neurofibromas. No relapse will occur upon completely resection. Anti-histamine is not always satisfactory as a treatment for itching of neurofibromas.

**Hormones:** Hormonal factors seem to contribute to the growth of neurofibromas, as neurofibroma growth is stimulated by puberty and pregnancy. A recent study has shown that 75% of neurofibromas carry progesterone receptors. However, there is no evidence that progesterone and combined oral contraceptive pill stimulate growth of neurofibromas. For pregnant NF1 patient, obstetrician and clinicians should be aware that spinal and pelvic neurofibromas may progress rapidly and thus need to be monitored closely.

**Plexiform neurofibromas:** Deeply located tumors PNF often lead to pain and neurological deficits and thus need special attention and closely monitoring. Patients developing deficits or pain should undergo surgery whenever a positive outcome is suggested. Annual examination helps to detect first indication of possible spinal cord compression. Regular MRI is important for early detection of malignant transformation.

Results of surgery of PNF are usually unsatisfactory because of the network-like growth of the tumors often involve multiple nerve fascicles and other adjacent tissues. Typically surgical interventions for PNF are restricted to debulking procedures of large tumors causing significant clinical complications or aesthetic disfigurement. However, successful subtotal resections of the superficial PNF with significant improvement in cosmetic appearance are possible. Furthermore, a recent study reported the advantage of early surgical intervention of small PNF in children under 15 years of age. Total resection was achieved in all 7 cases without causing any neurological or organic deficit. Annual control within four years with magnetic resonance tomography did not reveal any relapse of the tumors.

**Prognosis**

Neurofibromas are benign tumors. However, there is a risk of malignant transformation in PNF, leading to malignant peripheral nerve sheath tumors.

**Cytogenetics**

*Note:* Neurofibromas are benign and usually do not have gross chromosomal abnormality beside allelic loss of chromosome 17.

**Genes involved and Proteins**

**NF1**

**Location:** 17q11.2  
**Note:** The direct genetic cause for neurofibromas is the bi-allelic inactivation of the tumor suppressor gene NF1. The NF1 gene is located on 17q11.2.

**DNA/RNA**

It encompasses 335 kb genomic DNA, consists of 60 exons, and gives rise to an 11-13-kb transcript.

**Protein**

The NF1 gene product, neurofibromin, has a RAS GTPase-activating region (GAP) and is likely involved in RAS-signaling pathway.


**Germinal mutations**

The first inactivation of the NF1 gene in a neurofibroma is the constitutional mutation in the patient. Constitutional mutations are mostly minor lesions such as point mutations in exons and in conserved splicing sites, and deletions/insertions of one to few base pairs, mostly leading to frameshift of the transcript.

**Somatic mutations:**

The 2nd inactivation of the NF1 gene in neurofibromas is somatic and specific to each tumor which does not exist in non-tumor tissues of the patient. Somatic inactivation involves small lesions and loss of the 2nd NF1 allele. Neurofibromas are composed mainly of Schwann cells and fibroblasts. By selectively culturing Schwann cells and fibroblasts, respectively, from an neurofibroma, it has been demonstrated that the somatic NF1 alterations only exist in the former but not in the later cell type. These results provided genetic evidence that Schwann cells are the progenitor tumor cells in neurofibromas.

**Result of the chromosomal anomaly**

**Hybride Gene**

**Note:** Loss of chromosome 17 leads to bi-allelic inactivation of the NF1 gene.

**References**


This article should be referenced as such: