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"The secrets of rare diseases: what lies behind mysterious diagnoses" type 2 neurofibromatosis (Recklinghausen's disease)

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Abstract: Neurofibromatoses (NF) are a group of hereditary diseases characterized by the development of multiple benign, and more rarely malignant, tumors in the central and peripheral nervous systems. Currently, this group includes three main conditions: type I neurofibromatosis (NF I), type II neurofibromatosis (NF II), and schwannomatosis (SWMT). Notably, neurofibromatosis, whose symptoms occur equally in both men and women, most commonly manifests in childhood, particularly during puberty.

Keywords: Type II neurofibromatosis, schwannomas, tumor process, neurofibromin.

Introduction: Neurofibromatosis (NF) is a hereditary disease characterized by the formation of tumors in nerve tissues, which subsequently leads to various bone and skin anomalies [1].

Type II Neurofibromatosis (NF II), formerly known as "central neurofibromatosis," is a condition associated with the development of tumors in the central nervous system (OMIM: 101000). A hallmark feature of NF II is bilateral vestibular schwannomas, which occur in approximately 90% of patients. Vestibular schwannomas are benign tumors that arise from Schwann cells of the vestibular portion of the VIII nerve. The clinical symptoms associated with the progression of vestibular schwannomas include tinnitus, hearing loss, and the development of vestibular ataxia [2,3]. Additionally, patients with NF II often develop non-vestibular schwannomas, ependymomas, and meningiomas. The long and complex structure of the NF2 gene contributes to the high frequency of spontaneous mutations. The gene is approximately 350,000 base pairs in length, consists of 60 exons, and is expressed not only in the nervous system but also in various other tissues. The gene codes for the protein neurofibromin, a tumor-suppressing factor [10].

Neurofibromin is produced by nerve cells and specialized glial cells (oligodendrocytes, Schwann cells). This protein contains a domain for interacting with guanosine triphosphatase (GTPase) activators. Through this domain, neurofibromin in healthy individuals interacts with the product of the oncogene ras, inhibiting its function and suppressing cell proliferation [11–15]. The clinical manifestations associated with NF II are determined by the localization of the tumors and the spread of the tumor process [4, 5].

The development of NF II is caused by a pathogenic mutation in the NF2 gene located on the long arm of chromosome 22. The disease is characterized by a high prevalence of somatic mosaicism, with varying frequencies of mosaic forms, ranging from 22.0% to 59.7%, according to different studies [6].

Clinical Features:

Bilateral vestibular schwannomas (neuromas) of the auditory nerve are the key feature of NF II, occurring in at least 90% of cases. These tumors primarily develop in late adolescence or early adulthood. NF II is rarely detected in children. The first symptom is usually

hearing loss. In most cases, café-au-lait spots are absent or occur in small numbers [7]. Other intracranial tumors, often multiple, are also common, but optic nerve gliomas are not typically found in patients with NF II. Schwannomas of cranial nerves V-XII, often bilateral and multiple, are frequently observed. Some authors note the possibility of sporadic cases of atypical NF II, characterized by multiple schwannomas in the skull or spine [8,15].

Tumors of the spinal cord may appear in two forms: schwannomas, which have the same histological structure as the auditory nerve neuromas, and ependymomas. These tumors can be multiple and lead to serious neurological complications (fig.1).

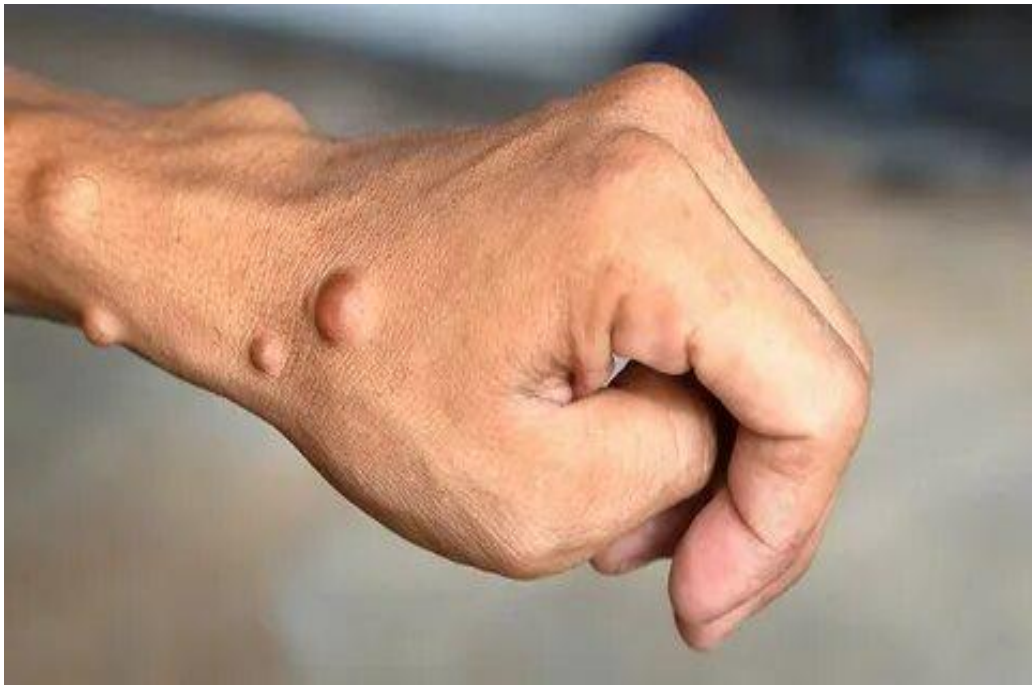

Figure 1. Subcutaneous schwannoma in type 2 neurofibromatosis on the finger [21].

The main treatment methods for patients in this group include surgical tumor removal and/or radiotherapy and/or radiosurgery, chemotherapy. Currently, a combination of these methods is used depending on the clinical manifestation of the disease, with surgery playing a leading role at all stages of disease development [16]. Ependymomas and low-grade gliomas in NF-II are much less common and are predominantly localized in the brainstem and upper cervical segments of the spinal cord. Malignant transformation of these tumors is rare and, in most cases, is associated with prior radiation therapy [17]. In cases of bilateral schwannomas with preserved hearing, treatment is recommended to start with the smaller tumor, and if hearing decreases, it should begin on the side with better hearing. If, after complete tumor removal, hearing on this side remains satisfactory, the other tumor should be removed. If hearing cannot be preserved, a wait-and-see approach is recommended for the remaining schwannoma, with surgery indicated if symptoms worsen (due to the high risk of deafness) [18].

Schwannomatosis (SWMT) is a rare hereditary disease characterized by the appearance of multiple peripheral and spinal schwannomas, and, less frequently, cranial nerve schwannomas, as well as meningiomas.

Schwannomatosis is often accompanied by a pronounced neuropathic pain syndrome (70%), with possible pathophysiological mechanisms for its formation including the loss of unmyelinated C-fibers, which play a key role in pain sensitivity (fig.2) [19].

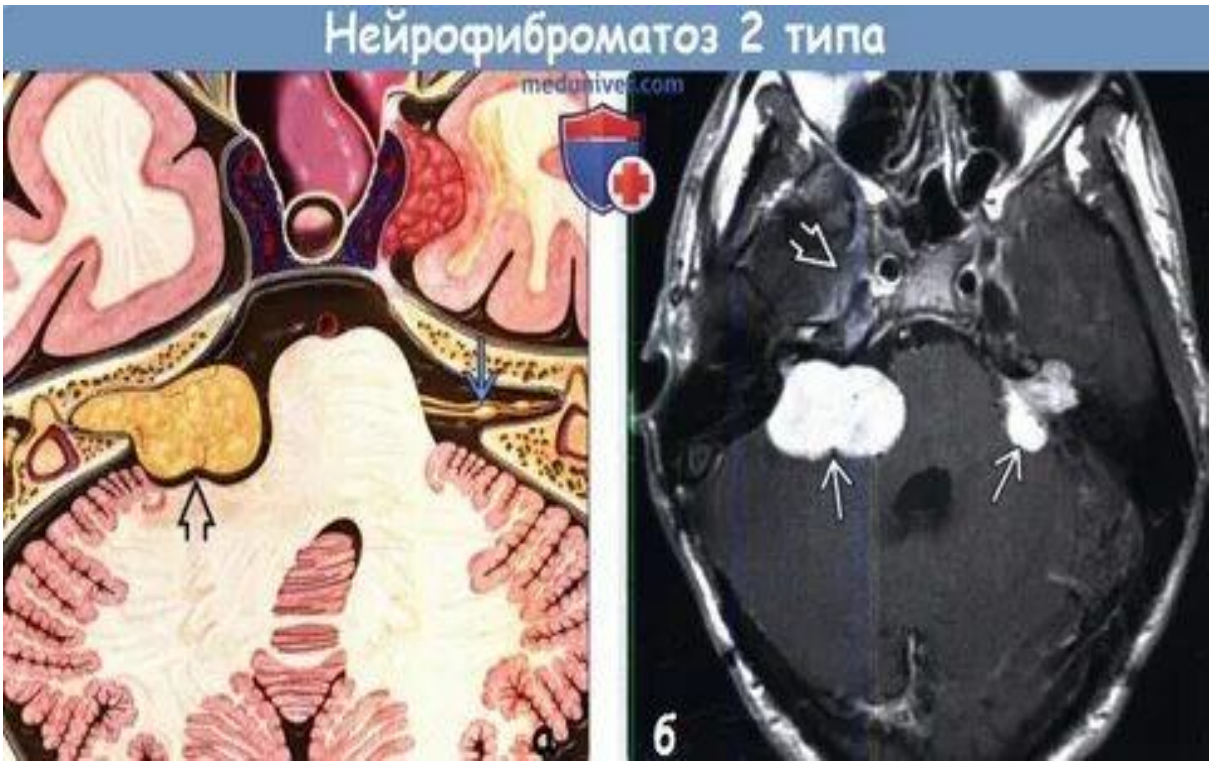

Figure 2. Type 2 Neurofibromatosis - MRI of the brain [20].

The majority of tumors consist of schwannomas of peripheral (89%) and spinal (74%) nerves. Meningiomas (5%), lipomas (11%), and angiomyolipomas (3%) are much rarer [22]. Phenotypically, schwannomatosis (SWMT) is most similar to NF II, and differential diagnosis between the two can sometimes be challenging. For a long time, it was believed that bilateral vestibular schwannomas occur only in type II neurofibromatosis, but the identification of genes involved in the development of SWMT has not only improved disease diagnosis but has also shown that patients with SWMT may have a phenotype that is completely identical to that of NF II [22].

CONCLUSION

One of the manifestations of neurofibromatosis in the neonatal period is the appearance of café-au-lait spots, and careful, long-term monitoring is required to exclude this disease. Diagnosis is not difficult. The prognosis depends on the localization, size of the neurofibromas, and the course of the disease. It is essential to enhance the professional training and vigilance of healthcare providers in primary care settings to identify the most common forms of phakomatoses. Additionally, continuity between specialists of different profiles is necessary for timely implementation of a comprehensive diagnostic approach and reducing the degree of disability in working-age patients.

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