NEUROFIBROMATOSIS - CLINICAL CHALLENGES

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S u m m a r y. Neurofibromatosis (NF) is a group of inherited diseases characterized by the occurrence of tumors of the nervous system. The present article reviews scientific reports on neurofibromatosis. We focused on the literature about neurofibromatosis type I (NF1) and neurofibromatosis type II (NF2). We present etiology, genetics, clinical and diagnostic challenges in neurofibrosis. Genetic alteration in the main two variants is different, affecting chromosome 17-17q11.2 in NF1 and chromosome 22-22q12.2 in NF2. NF2 is characterized by a much worse prognosis affecting mostly the central nervous system. For NF2 mainly bilateral tumors from the Schwann cells of the vestibular nerve are characteristic. Meningiomas are often present. Generally, NF1 is more frequent than NF2 and affects mainly the skin. Patients suffering from the disease need special attention. Ideally, they should be under constant care of a team consisting of a neurosurgeon, otolaryngologist, neurologist, geneticist, and a nurse. It is expected that new therapies, especially those aimed at signaling pathways, over time will revolutionize the treatment of the disease in the future.
K e y w o r d s: neurofibromatosis type 1, neurofibromatosis type 2, central system nervous.

INTRODUCTION

Neurofibromatosis (NF) is a group of inherited diseases characterized by tumors affecting the nervous system. There are two types of neurofibromatosis, and those are are often confused. Neurofibromatosis type II (NF2) is characterized by a much worse prognosis affecting mostly the central nervous system (CNS). Neurofibromatosis type I (NF1) is generally more frequent than NF2 and affects mainly the skin [1, 2, 3, 4].

The first clinical NF case was presented in 1592 by Italian doctor Ulisse Aldrovandi, who described a man of short stature with a large tumor resembling probably an isolated plexiform neurofibroma [5]. NF1 was described in detail in the nineteenth century by Friedrich Daniel von Recklinghausen, and the disease was named after him. In 1916, the famous neurosurgeon Harvey Cushing described a patient with bilateral vestibular nerve tumors connecting this case with Recklinghausen disease, and until the 1980s there was no clear distinction between NF1 and NF2, and many cases of type 2 of NF were described as a variety of Recklinghausen disease [6, 7]. Today, this name refers only to NF1.

MATERIALS, METHODS AND AIM

The present article reviews scientific reports on neurofibromatosis. We focus on the literature about NF1 and NF2. We present etiology, genetics, clinical and diagnostic challenges in neurofibrosis.

EPIDEMIOLOGY AND GENETICS

Despite their mutual name, both types of the disease are characterized by a completely different epidemiology as well as the etiology of the underlying genetic pathology. NF1 is much more common and occurs in 1 in every 3 000 births [8]. It affects both sexes and all races. NF1 is caused by a mutation causing the loss of the NF1 gene function. The gene encodes neurofibromin and is localized at

17q11.2 [9]. The penetration is complete, but the expression is varied. In half of cases the mutation is spontaneous, and in the other half is inherited [10]. Neurofibromin, the coding of which is damaged as a result of these changes, is a tumor suppressor acting in the RAS/MAPK pathways and mTOR [11].

NF2 occurs in, depending on sources, from 1 in 33,000 to 1 in 87,410 births which is respectively 10% to 3% of all cases of neurofibromatosis worldwide [12, 13] disregarding race and gender. The symptoms differ between individuals and families. Quite unlike NF1, NF2 is caused by the mutation of the *NF2* gene located at 22q12 and encoding merlin (neurofibromin 2) [14]. Merlin is a protein of cell membranes, also a tumor suppressor on the pathways of PI3kinase/Akt, Raf/MEK/ERK and mTOR [8]. However similar, molecular bases for the development of both types of disease are different, which also results in a different clinical picture.

MAJOR CLINICAL DIFFERENCES BETWEEN NF1 AND NF2

NF1 is often called not quite adequately but quite accurately peripheral [15]. The reason for this is, *inter alia,* is the occurrence of numerous tumors, most of which develop from the peripheral nerves. They are usually benign, however, from 3% to 13% may be malignant (even the adverse effect of neurosurgeries on the malignancy of these tumors was suggested). These tumors are predominantly neurofibromas (and fibromas less frequently), which are primarily composed of Schwann cells (which surround the neurons building the peripheral nervous system), as well as perineural cells and fibroblasts (forming fibrous tissue) [16]. The less important component of these tumors are mast cells and collagen matrix [8]. Gliomas can also be found in NF1, and those come mainly from astrocytes. Of the various locations, the visual path is often quite common (optic gliomas). The symptoms suggesting the appearance of the tumor are exophthalmoses, decreased visual acuity, and even (in 15%) visual field defects [17]. Tumors from other tissues (mediastinal tumors for example) are much rarer [18]. One of the typical characteristics and immediately obvious changes are color abnormalities appearing on the skin and referred to as 'coffee-with-milk' (café-au-lait) spots [3, 4]. They concern almost all patients suffering from NF1, and their appearance is usually accompanied by general hyperpigmentation. Hamartomatic nodules appearing on the iris are also characteristic. They are called Lisch nodules, and although they often do not appear until some time, finally they affect a vast majority of patients with NF1 [19].

In contrast, NF2 is called central, which in fact is not always anatomically justified (after all, the most frequently occupied vestibular nerve is the peripheral nerve), but roughly defines different character of this type of disease [15]. Symptoms of NF2 usually appear later than in NF1, but the prognosis is usually much worse. The basic symptom crucial in the diagnosis is bilateral (or unilateral, however it sooner suggests their idiopathic nature) tumors from Schwann cells occurring primarily on the vestibular schwannoma [20]. They can lead to hearing loss even complete at some stage (which is also a frequent complication after surgery) as well as disturbances of balance, sometimes they manifest as tinnitus [21]. These tumors, apart from said Schwann cells, also contain spindle cells, Verocay cells, and hyalinized vessels. Under the microscope the characteristic arrangements of Antoni A and Antoni B can be seen [8]. Although these tumors mainly concern the eighth nerve, they can affect all other cranial nerves, but those are also much rarer cases [1]. A frequent type of tumors in NF2 are meningiomas, especially those appearing in the anterior fossa of the skull, where they very often oppress the visual intersection (thus leading to blindness, deterioration of sight and may be the first symptom of the disease) [2]. Tumors compressing the cortex of the brain may interfere with structural neuronal wounding enough to cause symptomatic epilepsy, on the other hand, epileptic seizures can also be a result of gliosis and disorders of the brain structure resulting from surgeries (generally symptomatic epilepsy is on average in 4 out of 10 cases, and brain tumors are its third cause after stroke and injury [22]. One of the first symptoms of NF2 frequent in congenital form or immediately after birth is cataract [7]. Skin changes, if present, are similar to those in NF1, however, they are much rarer [21]. Table 1 summarizes the differences in both types of neurofibromatosis.

Table 1. Main differences between NF 1 and NF 2 [11, 12, 13, 19, 23, 24, own elaboration]

Type of neurofibromatosis	Neurofibromatosis type 1	Neurofibromatosis type 2
Genetics	loss of the function of *NF1* gene (17q11.2) encoding neurofibromin	loss of the function of *NF2* gene (22q12.2) encoding neurofibromin 2 (merlin)
Frequency of occurrence	1 / 3, 000 births	from 1 / 30, 000 to 1 / 87 410 births
Skin manifestations	skin manifestations such as cafe-au-lait, domed tumors on the skin and general hyperpigmentation	rare and less visible
Tumors	neurofibromas throughout the body, optic nerve glioma, Lisch nodules	bilateral or unilateral vestibular nerve tumors, rarely tumors of other cranial nerves, meningiomas and other tumors of the nervous system

CONCLUSIONS

NF1 is characterized by a better prognosis affecting mostly the CNS, and is generally more frequent than NF2. Surgery remains the preferred method of treating symptomatic tumors, another option is radiation. Considering surgery, it is important to weigh potential benefits and risks in comparison to the potential damage that the surgery could cause. Better control and early detection of individual symptoms and, consequently, early treatment implementation and prevention of complications seem to be the key to the most effective battle against the disease. Patients with neurofibromatosis need special attention. Ideally, they should be under constant care of a specialist team consisting of a neurosurgeon, otolaryngologist, neurologist, geneticist and a nurse. Permanent auditory, visual and head imaging tests are required (magnetic resonance once a year), and monitoring the disease aside its early detection and subsequent symptoms remains the most important challenge in the whole NF treatment process.

It is expected that new therapies, especially those aimed at signaling pathways, over time will revolutionize the treatment of the disease in the future. Nevertheless, it is worth remembering that the extension of life span of patients with NF unfortunately often reduces its quality. Therefore, each therapeutic decision should be made individually and should be adjusted to individual patient's needs, which makes the care of a patient with NF difficult and challenging.

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