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# Introductory Chapter: Neurofibromatosis - Current Trends and Future Directions

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## 1. Introduction

Neurofibromatosis (NF) is a rare genetic-hereditary syndrome with autosomal dominant transmission and complete penetrance yet variable clinical expression. It is precisely this genotypically defined but phenotypically variable behavior of the NF which is of particular interest as it is able to influence not only the timeliness of clinical diagnosis but also the prognosis of the disease. Indeed, in most cases clinical diagnosis is early (within the first 3 years after birth), but in particular forms with a low phenotypic expression, especially in the mosaic forms of mild neurofibromatosis type 2 (NF2), it can be later, with clinical manifestation of the syndromic features in early adulthood [1, 2].

The known syndromic features of NF, although still framed in the context of rare diseases, differ in their incidence and clinical manifestations. Neurofibromatosis type 1 (NF1) is the most frequent, with an incidence of 1 individual per 2500/3500 live births, without significant gender differences and at least 50% related to de novo mutations [3]. Neurofibromatosis type 2 has an incidence of new cases/year equal to 1 individual for every 25,000/30,000 live births, correlating in 80% of cases to de novo mutations, and a prevalence of around 1/100,000 which has, over the past 20 years, been increasing hand in hand with the introduction of new and more sophisticated diagnostic methods [2].

It is well documented that NF1 is characterized by the presence of an autosomal dominant mutation of a gene on chromosome 17 in position q11, which codes for a protein known as *neurofibromin*, which acts as a tumor suppressor in the pro-proliferative pathway RAS/MEK-MAPK. The total absence of functional protein therefore cancels the inhibitory activity on the RAS proto-oncogene with consequent hyperactivation of the transduction mechanism and the pro-proliferative and pro-mitotic cellular response.

Different mutations have been described on the gene which codes for neurofibromin [4]. In recent years, questions have been raised as to whether the presence of one particular type of mutation rather than another might affect the prognosis of the disease. A study published in Lancet in August 2014 [1] highlighted the possible prognostic role of multiple genomic microdeletions in the context of the entire gene, the presence of which seems to be associated with a more severe phenotypic expression, characterized by the appearance of plexiform neurofibromas at an early age, a significant reduction in IQ, multiple craniofacial anomalies, and a higher risk of malignant degeneration of peripheral neurofibromatous lesions.

On the other hand, the mutation associated with NF2 is autosomal dominant of a gene located on chromosome 22 in position q12.2, which codes for a protein known

as *merlin* or *schwannomin* which seems to have a role, not yet fully clarified, as a tumor suppressor in the contact inhibition mechanism of the proliferative stimulus. The alterations of schwannomin seem to be phenotypically expressed exclusively in Schwann cells [5] which would justify, from the molecular point of view, the almost total absence of other neoplastic entities in patients with NF2 or NF3.

Neurofibromatosis type 3, better known as Schwannomatosis, can be considered a variant of NF2 characterized, however, by the total absence of vestibular schwannomas and neurofibromas and by the lower presence of tumors of the central nervous system. NF3 is, rather, characterized by the presence of multiple schwannomas along the course of the peripheral nerves [6].

It has therefore been understood over time that while those gene mutations related to the various NF conditions have complete penetrance, there is considerable variability in terms of the phenotypic expression of the disease, not only between the three syndromic forms of NF but also within each type of neurofibromatosis. Hence the interest of this book, which aims to offer the reader a perspective on neurofibromatosis that goes beyond academic descriptions of what is already known with respect to the different clinical manifestations of NF, instead focuses interest on specific clinical disease patterns, related neurocognitive aspects, and therapeutic developments that in recent years have been emerging in the management of the various types of neurofibromatosis, especially in the direction of new targeted molecular therapies.

As is well documented, the diagnostic criteria for NF1 have, since 1987, been defined by the National Institutes of Health [7], which includes a variable combination of the following manifestations: *abnormal pigmentation of epithelial and mucous membranes* (café-au-lait macules, axillary and inguinal freckling, Lisch nodules of the iris); *multiple peripheral neurofibromas*; *bone abnormalities and deformities* (osteopenia, scoliosis, sphenoid wing dysplasia, congenital tibial dysplasia); *cardiovascular anomalies and malformations* (congenital heart disease, vasculopathy, and hypertension); and *neurocognitive deficits*.

Even more variable are the clinical manifestations associated with NF2, whose most commonly used diagnostic criteria are the “Manchester diagnostic criteria” [8]. Such criteria include *multiple central nervous system tumors* (intracranial meningiomas, 43–58%); *intramedullary spinal cord tumors* (ependymomas in more than 75%); *benign tumors of the cranial nerves* (vestibular schwannoma, 90–95%) that may or may not be bilateral; *peripheral nerve schwannomas*; *ophthalmological changes*; *dermal-epidermal skin tumors of varying natures*; and moreover, a familiar history of NF2.

Following clinical examination and ultrasound diagnostics for skin and subcutaneous lesions, the gold standard in the diagnosis of neurofibromatosis is magnetic resonance imaging with gadolinium of the brain and spinal cord. It has been observed that in patients with NF1, it is not uncommon to locate focal hypointense lesion areas in T1-weighted and slightly hyperintense lesions in T2-weighted sequences, the so-called unidentified bright objects (UBOs), the actual nature of which is still discussed in the literature, although their presence can correlate with cognitive dysfunction [9]. A previous study by Griffiths et al. speculated that they could correspond to areas of subclinical glial proliferation, having hypothesized an association between their early diagnosis in resonance and the relative risk (around 80%) of subsequent development of central tumors of the glial series at between 5 and 10 years of age [10].

Malignant forms of neurofibromas and, more rarely, peripheral schwannomas degenerated into sarcomas are termed as “malignant peripheral nerve sheath tumors” (MPNSTs) and are more frequently associated with the malignant evolution of plexiform neurofibromas more commonly in the third decade of life and with poor prognosis [11, 12].

The treatment of the syndrome is mainly surgical with the removal of both central and peripheral lesions causing functional or evolving damage during follow-up diagnostics. The support that intraoperative neurophysiological monitoring can provide to the surgical resection technique is of fundamental importance, not only for saving the nerve but also in preventing the onset of neuropathic pain. Much more invasive is the surgical resection of MPNSTs, which can sometimes involve amputation or disarticulation to ensure surgical radicalism, followed by adjuvant radiotherapy.

Ultimately, while surgery is still considered the first approach to neurofibromatosis, interest in medical therapeutics for this syndrome has grown considerably in recent years, and numerous clinical trials are still ongoing, as will be explained in detail in the chapters of the book.

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