NEUROFIBROMATOSIS – ONE DISEASE FOR A MULTIDISCIPLINARY TEAM

NEUROFIBROMATOSA – O BOALĂ PENTRU O ECHIPĂ MULTIDISCIPLINARĂ

Abstract

Neurofibromatosis is a genetic disease with an autosomal dominant inheritance pattern, mainly characterised by neurologic and cutaneous findings. Several types of neurofibromatosis have been identified and there have been several attempts to classify them. Among them, two are more frequent: type 1 (von Recklinghausen) and type 2 (central/acoustic). Both sexes and all races are affected, type 1 being more frequent than type 2. The mutations are situated for every type on different chromosomes, affecting different genes and different proteins. These mutations have high penetrance, but variable expressivity. There are also sporadic cases which are caused by new gene mutations. The pathogenesis is also different as the pathways are not the same. The clinical findings vary between the two types, as well as between patients within a certain type. Different organs and systems can be affected: nervous, eyes, skin, mucosae, bones, endocrine glands, a.s.o. However, for an accurate diagnosis, certain diagnostic criteria, specific for each type should be considered by a multidisciplinary team. Usually additional workup tests are not needed for the diagnosis, but sometimes can be useful, especially if differential diagnoses are taken into consideration. There is no ethiological treatment available for neurofibromatosis; therefore the only options are symptomatic treatments associated to the information and education of the patients regarding the disease and the complications as well as a genetic counselling.

Keywords:
neurofibromatosis type 1, neurofibromatosis type 2, schwannoma, genetic disease, dermatologic, neurologic, multidisciplinary team

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Introduction

The neurofibromatoses are genetic diseases with an autosomal dominant inheritance pattern, which is mainly characterised by cutaneous and neurological findings. It is part of the big family of phacomatoses (neurocutaneous syndromes). Phakomatoses (“phakos” = lentil, spot, lens; “oma” = tumour) represent a heterogeneous group of diseases that associate different malformations of the nervous system and benign tumours of the skin, mucosae, eye and nervous system, with ectodermic origin.

Neurofibromatosis, is part of the phakomatoses, together with the tuberous sclerosis of Bourneville, Sturge-Weber syndrome, Von Hippel-Lindau syndrome, ataxia-telangiectasia, and some others with lower incidence.

In neurofibromatosis, neuroectodermal abnormalities are frequently found in the skin and nervous system, but also in other tissues (bones, eyes, endocrine glands and others) and the signs and symptoms can vary from one patient to another, needing a multidisciplinary approach in order to establish the type of each neurofibromatosis.

Classification

Several types of neurofibromatosis (NF) have been identified. In 1982, Riccardi has proposed one classification that included 8 forms, based on the clinical findings and on the inheritance pattern: NF1 (von Recklinghausen), NF2 (acoustic), NF3 (mixed NF1 and NF2 or schwannomatosis), NF4 (variant), NF5 (segmental), NF6 (familial café-au-lait spots), NF7 (late onset) and NF8 (unspecified)(1). Once the genetic diagnosis was possible, based on it and the clinical particularities of the disease, Carey et al. proposed in 1986 a new classification including only 5 types of neurofibromatosis: NF1 (classical/ von Recklinghausen), NF2 (acoustic), NF3 (segmental/mosaic), NF4 (familial café-au-lait spots) and NF5 (NF-Noonan phenotype)(2,3).

The consensus conference of the National Institute of Health in Bethesda (MD, USA) defined in 1988, 7 main criteria for the diagnosis of NF1. Despite all this, due to the rarity of the other forms than type 1 and 2, there isn’t a consensus regarding a final and universal classification.

Epidemiology

It is estimated that globally this disorder affects at least one million individuals(4). Among the neurofibromatosis types that have been described, the most frequent forms are type 1 (NF1, von Recklinghausen) and type 2 (NF2, central/acoustic). The incidence of NF1 is 1:3,000 births(5) (one of the most common genetic diseases), while NF2 is much rare (1:33,000 births)(6).

This disease affects all races, men and women equally and almost a half of the cases have a family history of neurofibromatosis, the rest developing the disease due to a new genetic mutation(7).

Etiopathogenesis

The two most frequent types of neurofibromatosis (NF1 and NF2) are both genetic diseases, with an autosomal dominant inheritance pattern, but the mutations are situated at different levels and on different chromosomes.
Neurofibromatosis type 1 (Von Recklinghausen’s Disease)

NF1 is a multisystem neurocutaneous disorder, and the most common phakomatosis. It is caused by a genetic mutation localised on the long arm of the chromosome 17, at 17q11.2. The affected gene is NF1, encoding neurofibromin, a 327kDa protein, composed of 2818 amino acids (8, 9). This protein is found in many types of cells (neurons, oligodendrocytes, Schwann cells) and has an important role in regulating cellular proliferation and differentiation, being required especially during the embryonic development, in the differentiation of the cells derived from the neural crest (cells for the peripheral and enteric nervous system, glia but also non-neural cell types including smooth muscle cells of the cardiovascular system, melanocytes – pigment cells in the skin, and craniofacial bone cells, cartilage and connective tissue) (10). After birth, the main role of this protein is to regulate by negative feedback the RAS-mitogen-activated-protein kinase (MAPK) pathway which allows cellular proliferation and supports the cells survival (11). If neurofibromin is deficient, the RAS-MAPK pathway is no longer blocked, it becomes hyperactive, the cells proliferate uncontrollably, and the final result is the appearance of tumours.

Over 1400 different pathogenic mutations of the NF1 gene have been discovered (12). The penetrance is high (almost 100% - autosomal dominant transmission), but the expressivity is variable (13). 30-50% of the cases are sporadic, being caused by new gene mutations, neither of their parents having NF1 (14-16). A patient afflicted with NF1 has a 50% chance of transmitting the disease to each of his/her children, regardless of sex.

Neurofibromatosis type 2

Neurofibromatosis type 2 (NF2) is caused by a genetic mutation situated on the short arm of the chromosome 22, at 22q12.2. The affected gene is NF2, encoding merlin (neurofibromin 2 or schwannomin), a 69.7 kDa protein, composed of 595 amino acids. This protein is produced in the nervous structures and is part of the cytoskeleton. It is a tumour suppressor protein and regulates different processes in Schwann cells (17, 18). The sequence analysis of this protein resembles with that of the protein family Ezrin-Radixin-Moesin so that the name merlin protein is an acronym for Moesin-Ezrin-Radixin-Like Protein. All its action mechanisms are not very well understood, but most of the data show that it is involved in cell signalling and migration pathways. It seems that merlin regulates the surface receptors’ activity and turnover by modulating their interactions with the actin cytoskeleton, acts at the adherence junctions and suppresses tumour development, probably by inhibiting cell growth (18). Due to its dysfunction, tumours in the nervous system develop and more frequently bi-laterally vestibular schwannoma (acoustic neurinoma) can be diagnosed. Like NF1, NF2 is also a genetic disease with high penetrance (almost 100% - autosomal dominant transmission), but with variable expressivity (19). Still, over 50% of the patients are developing the disorder due to a novel mutation and almost a third has mosaic mutations, responsible for the appearance of the disease (20).

Clinical findings

The diagnosis will start with a family history/medical history and sometimes photographs of family members can be useful. Genetic prenatal tests are necessary in selected cases. Due to the fact that the clinical manifestations and diagnostic criteria are different, the two main forms of the disease (NF1 and NF2) will be described separately and due to the multifaceted appearance and its complexity a team work, (a multidisciplinary team) is very useful in diagnosing, monitoring and managing patients with NF.

A. Neurofibromatosis type 1 (Von Recklinghausen’s Disease)

The onset of NF1 is much earlier than that of NF2 and NF3 and the clinical findings of NF1 vary, as
different organs or systems can be affected such as nervous system, eye, skin, mucosae, bones, endocrine glands and other. The diagnosis of NF1 is more easy to be done in adults, as the symptoms and signs develop with age, but it is more difficult to be done in children under 5 years of age, where café-au-lait spots (macules) can be the only pathological sign, increasing in number and size with the age and associating other diagnosis criteria. The diagnosis criteria take into consideration the cutaneous, ocular, neurologic and skeletal manifestations to which the genetic component is added. These criteria have been established in 1988 during the Neurofibromatosis - National Institutes of Health Consensus Development Conference (21). Clinical diagnosis of NF 1 requires the presence of two or more of the following criteria:

1. 6 or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals,
2. 2 or more neurofibromas of any type or at least one plexiform neurofibroma,
3. freckling in the axillary or inguinal region (Crowe sign),
4. optic nerve glioma,
5. 2 or more Lisch nodules (iris hamartoma),
6. a characteristic bone lesion such as sphenoid wing dysplasia or thinning of long bone cortex with or without pseudarthrosis,
7. a first-degree relative (parent, sibling or offspring) with NF-1 diagnosed using the above criteria.

Clinical manifestations
As shown, NF is affecting, is affecting a variety of organs and systems, this is why, the clinical manifestations will be described separately taking into account the affected organ or system.

i. The skin is frequently affected in NF1.
From the diagnostic criteria mentioned above, 3 out of 7 are assessed by the dermatologist, but some others can be added, not so characteristic but also important. The café-au-lait spots (macules) are well-demarcated, uniformly hyperpigmented macules which may vary in colour from light brown (the colour of coffee with milk - „café-au-lait”) to dark brown, depending on the patients’ phototype. They can be localised anywhere on the skin, but they usually spare the scalp, genital region, palms and soles. Their shape is usually oval, but the size differs in diameter from 5 mm to 500 mm, commonly being under 100 mm (10cm) (22). Café-au-lait spots are usually the first sign of the disease and can be present at birth or can appear later in life. Generally they develop during the first year of life, but they may also appear at older ages, regardless of the moment, having normally a tendency to grow though some authors have described lesions that diminished or disappeared spontaneously in older individuals (23). A correlation between the number of café-au-lait spots and the severity of the disease hasn’t been proven, but the number and appearance of café-au-lait spots has to be monitored yearly by the dermatologist. Larger café-au-lait spots, especially if associated with hypertrichosis, should always be palpated in order to exclude an underlying plexiform neurofibroma (24). Axillary or inguinal freckles are smaller café-au-lait spots, having the same characteristics (colour, borders), but smaller sizes. They resemble solar lentigines, but are localised on non-photopen exposed areas, such as axillary and inguinal regions, as well as in other intertriginous areas (e.g. inframammary fold). The most common location is the axillary fossa, axillary freckling, also referred to as Crowe’s sign, being present in almost 80% of the cases (25, 26). They appear after development of the café-au-lait spots, at 4-6 years of age, but before the development of neurofibromas (27). Neurofibromas are benign peripheral nerve sheaths tumours (formed of Schwann cells, fibroblasts, perineural cells and mast cells). They can be situated more superficially (cutaneous neurofibromas) or deeper (subcutaneous, deep nodular
The size of the tumours may vary, the larger the nerves originating in the cervical spinal cord but more frequently on the trigeminal nerves and neurofibromas can be found almost anywhere, excess hair (hypertrichosis). Superficial plexiform neurofibromas can be situated anywhere on the body surface, but they are mostly found on the trunk and limbs. Women can have larger lesions if situated on the breast. The total number of lesions may vary from one case to another, and sometimes it can reach hundreds.

Subcutaneous neurofibromas are localised more profusely than the cutaneous ones, in the dermis and subcutaneous tissues. Clinically they are more firm and less well defined. Subcutaneous neurofibromas can be found anywhere on the body surface, and if present in the cervical region they can be easily misdiagnosed as lymph nodes. Almost 20% of the patients diagnosed with NF 1 have at least one subcutaneous neurofibroma.

Plexiform neurofibromas are fibromas that are localised along the length of cranial, peripheral and enteric nerves, histologically similar to the other neurofibromas but involving one or more nerve bundles. There are two types of plexiform neurofibromas, regarding their location: superficial and deep. The superficial type of plexiform neurofibromas present as nodules or firm masses situated in the subcutis, with firm cords which can be palpated inside, giving the feeling there is a “bag of worms”. The overlying skin can be pigmented (including a café-au-lait macule) and it can be covered with excess hair (hypertrichosis). Superficial plexiform neurofibromas can be found almost anywhere, but more frequently on the trigeminal nerves and the nerves originating in the cervical spinal cord. The size of the tumours may vary, the larger ones generating overhanging folds of loose skin that produce deformities of the face, neck or limbs, sometimes with functional impairment (eyesight, movement). Sometimes, in its most extreme form, thickening of the skin and underlying tissues may occur, and the affected region can become very large and deformed, condition known as “elephantiasis neuromatosa”.

The deep type of plexiform neurofibroma (or visceral, enteric, plexiform neurofibroma) can reach deeper, to the muscles fascia, muscles and even internal thoracic or abdominal structures (blood vessels, organs). The consequences can be very serious if these tumours produce an invasion of the vital structures such as the spinal cord, gut or ureters. Almost 25% of the patients have visible and superficial plexiform neurofibromas, most of them being observed from the birth or developing in the first years of life (on an average at 4-5 years of age). However, the deeper ones can remain unnoticed / undetected or can be found accidentally during imaging tests (e.g. ultrasound, magnetic resonance imaging MRI). The plexiform neurofibromas’ growth is variable, there can be times of rapid growth alternating with stationary periods, but the probability of developing a new plexiform neurofibroma after childhood is low. In about 3-15% of the young adult cases there is the risk for a plexiform neurofibroma to undergo malignant transformation, turning into a neurofibrosarcoma. The tumour is growing fast, becomes firmer and may associate persistent local pain or some neurological deficits. However, sometimes, these signs are absent and the malignant transformation is discovered only after the tumour has metastasized. The evolution of neurofibrosarcomas is very aggressive, often fatal. There are some other rare forms of neurofibromas with different manifestations, they either look like blue-red macules (due to the thickening of the vessel walls and presence of fibromatous tissue in the papillary dermis) or like pseudoatrophic macules (due to a replacement of the collagen in the reticular dermis with fibromatous tissue). Other cutaneous findings, which may also occur, are represented by pruritus (itch), juvenile xanthogranulomatosis (almost 18% of the cases, especially in the first three years of life) and benign glomus tumours (modified smooth muscle cells in blood vessels under the hand of foot finger nails). In 5-10% of the cases patients may develop lesions on the oral mucosa, usually symmetric, like papillomatous tumours on the palate, membranes on the buccal mucosa, tongue or lips, or macroglossia frequently diagnosed by stomatologists.

II. The nervous system (peripheral, enteric or cranial nerves) may also be affected, as partially described, and this is the reason why patients need a neurological examination yearly, to establish new clinical findings and to monitor the evolution of the older diagnosed problems. Neurofibromas can be associated with other nervous system tumors such as single or multiple gliomas of the optic nerve and hemispheric visual pathways or hamartoma of the iris (Lisch nodules), glioblastoma, meningioma. Brain computed tomography (CT) or Magnetic resonance imaging (MRI) can be useful for the diagnosis in detecting the tumors. Other neurological findings can be macrocephaly without hydrocephalus, stenosis of the Sylvius aqueduct which causes non-communicating hydrocephalus, Chiary type 1 malformations, mild mental retardation and learning disabilities. 60% of the patients have impaired learning and thinking skills, speech impairment and visual-spatial skills, or may...
develop attention deficit hyperactivity disorder (ADHD), attributed to dysplasia of the cortex. Cognitive tests, head circumference measurements, neurological and psychiatric evaluation for ADHD can be useful in these children. Uncommon, 4-7% of patients may present with epilepsy (seizures) diagnosed using the electroencephalogram, hydrocephalus or stroke (imagistic diagnosis by brain CT scan or MRI). Nerve tumors in the facial area, large neurofibromas of the trigeminal or facial nerve or extensive café-au-lait spots may generate concern with the patients’ appearance, resulting in anxiety and emotional distress. Gliomas in other parts of the brain and spinal cord (usually low grade astrocytomas) also occur. Peripheral nerve neurofibromas (e.g. on the spinal nerve roots) are diagnostic. Of note, high T2W1 MRI lesions are seen in 80% of children, commonly in basal ganglia, internal capsule, optic radiation and brainstem or cerebellum. These lesions are of unknown clinical significance and usually regress after 10 years of age. More than 1% of patients with NF1 develop a symmetric sensory axonal neuropathy, and some cases may associate polyneuropathy. Nerve conduction studies may be helpful for the diagnosis.

III. Bones – or bone tissue abnormalities can be present. Signs of abnormal development in children can suggest orthopedic evaluation and further investigations (X-rays, CT, MRI) or sometimes a specialized clinical examination may be sufficient. Long bones may present deformities due to abnormalities in bones growth, formation, and deficiency in bone mineral density (thin cortical layer, bowed legs, decreased bone mineral density, angulations of the long bones). Sometimes fractures don’t heal, and there is a high risk of osteoporosis, rising a diagnosis problem. The spine can be abnormal curved and scoliosis may be diagnosed, or bones’ growth is abnormal leading to a short stature (height below average) associated or not with sphenoid wing dysplasia. Enlarged mandibular canal or mandibular foramen can be seen, especially by stomatologists. Pseudoarthrosis is frequently associated with bone development problems.

IV. Endocrine glands – the cells with ectodermal origin can be also affected. Pheochromocytomas (tumors of the adrenal glands) can be diagnosed by CT or MRI, or using the plasma or urine catecholamine level, and 10% of them can be cancerous. Puberty, menopause and pregnancy increase the risk of appearance of neurofibromas, or the dimensions of the existing ones. Precocious puberty with growth acceleration can cause disruption of the hypothalamic-pituitary axis.

V. The eyes – may also be involved, due to the presence of optic nerve or optic pathway gliomas causing visual difficulties, or hamartomas of the iris (tiny bumps of the iris, called Lisch nodules) which are to be monitored yearly after diagnosis by the ophthalmologist. This pathologic situations may associate cataracts.

VI. Other organs affected are represented by the blood vessels, due to the smooth muscles involved, present in their walls, causing increased risk of high blood pressure, blood vessel abnormalities (rarely) and hepatomegaly. Gastrointestinal stromal tumors, often multiple, localized more frequent in the proximal part of the small bowel can be found after an episode of gastrointestinal bleeding or intestinal obstruction.

B. Neurofibromatosis type 2 (acoustic neurinoma / vestibular schwannoma)

Much less common than NF1, NF2 (central NF) is characterized by the presence of schwannomas (benign tumors) bilaterally. The diagnosis criteria for NF2 are established by a consensus of experts:

Definite (confirmed) NF2 - bilateral vestibular schwannoma (acoustic neurinoma)

Probable NF2:
- family history of NF2 and
- unilateral vestibular schwannoma or
- any 2 of the following tumor types: meningioma, glioma, schwannoma, neurofibroma, juvenile posterior subcapsular lenticular opacity, juvenile cortical cataract

Possible NF2:
- unilateral vestibular schwannoma and at least 2 of any of the following: meningioma, glioma, schwannoma, neurofibroma, juvenile posterior subcapsular lenticular opacity, juvenile cortical cataract
- multiple (2 or more) meningiomas and unilateral vestibular schwannoma or any 2 of the following: glioma, schwannoma, neurofibroma, cataract.

Clinical manifestations and diagnosis

The main clinical findings in NF 2 are the neurologic ones, while the cutaneous manifestations are less specific. However, the skin may help the diagnosis.

I. The skin – cutaneous lesions in NF 2 are usually tumours (most frequently schwannomas) and are present in 70% of cases, but in small numbers/patient (90% of the patients have less than 10 tumours).

There are at least 3 types of tumours:
- cutaneous plaques, slightly elevated, hyperpigmented and with their surface covered with hair (the most frequent type).
- nodular fusiform tumours situated in the subcutis which cannot be noticed at the skin surface unless the skin is palpated
- cutaneous tumours, similar to those found in NF 1 (relatively rare).

There have also been described café-au-lait spots (fewer and smaller than those found in NF1) and hypopigmented patches.
II. Cranial and peripheral nerves are usually affected by the presence of tumours. Signs and symptoms may appear in the late teens and early adult years. The signs and symptoms may be different, and will be described separately, regarding the affected cranial nerve. Schwannomas (neurinomas) on the VIII-th cranial nerve (acoustic-vestibular) are characteristic and can induce gradual hearing loss (partial/total deafness) and tinnitus if the acoustic nerve is affected and balance impairment, vertigo or dizziness and uncoordinated walking, if the vestibular nerve is affected. If the schwannoma grow, they can compress the brainstem, inducing focal neurological problems (weakness, foot drop, pathologic reflexes, cranial nerve palsies, headache). The clinical examination may be completed with paraclinical investigations including: hearing and balance tests (audiometry, acoustic reflex testing, electroneystagmography, brainstem auditory evoked potentials, balance tests – computerized dynamic posturography, walking tests, CT scan and MRI – 3D of the brain can be used for diagnosing and monitoring the dimensions and risk of complications of the schwannoma).

The II-nd cranial nerve (optic nerve) can be affected by the presence of tumors, the retina by specific retinal hamartomas or epiretinal membranes that cause visual difficulties. The visual problems can be increased by the presence of lens opacities and juvenile cataracts that may develop, even before a child shows clinical signs or symptoms of vestibular schwannoma. That’s why ophtalmologic examination yearly is necessary in order to monitor the patients if diagnosed before, or diagnose if they are still undiagnosed with ophtalmologic problems. If the patients are young children who do not cooperate for an ophtalmologic examination (being too young or with cognitive disorders), MRI of the optic nerve pathways and brain must be performed in order to detect a potentially aggressive glioma. If the V-th cranial nerve (trigeminal nerve) is affected, the patient may complain about numbness of the face, maybe on the side and in the distribution territory of the only trigeminal branch which is affected or about weakness of the muscles used for chewing (masticator muscles).

If the VII-th cranial nerve (facial nerve) is affected bilaterally, we will find facial drop, due to weakness of the muscles of the face (mimic muscles). Spinal nerve roots and peripheral nerves may also be affected by the presence of schwannomas, producing numbness or weakness in the upper or lower limbs and sometimes pain. If symptomatic, MRI of the spinal cord and spinal nerves is indicated in order to establish the diagnosis and appreciate the treatment options. Schwannomas are slightly hyperintense on T2W1 MRI. There is no cognitive impairment in patients with NF2.

III. Cerebral and spinal tumors can be present as meningioma, glioma, astrocytoma, ependymoma. Meningiomas are more frequent and may develop in 50-75% of the patients, being localized inside the skull and/or spine. MRI can be used in order to establish the diagnosis. Schwannomas are slightly hyperintense on T2W1 MRI, and meningioma hypointense, often multiple and in atypical locations. Both enhance with contrast substance administration.

Ependymoma are more common than meningioma in the spinal cord.

The genetic diagnosis can be used, the detection rates for molecular-based testing approaches 72% in simplex cases and 93% in familial cases. When a parent has NF2, prenatal testing can be done on amniocytes or chorionic villi, either through direct gene mutation analysis, when such a change has been identified or through linkage analysis. Prenatal testing may not be possible if the affected parent is the first affected person in the family and a mutation cannot be found.

Paraclinical Diagnosis

Usually the skin lesions of NF1 don’t need additional paraclinical tests for diagnosis, as this can be easily established by the dermatologist just by clinical examination. A biopsy is useful in the case of plexiform neurofibromas, when a malignant transformation is suspected.

If a biopsy is performed from a characteristic lesion, the histological findings can show one of the following:

- The café-au-lait spots show histopathologically a high quantity of melanin in the epidermis and sometimes a greater number of melanocytes (compared to the rest of the skin) and giant melanosomes.

- Cutaneous neurofibromas are characterised histopathologically by the presence in the dermis of groups of well-defined, but nonencapsulated small nervous fibres with interfacing bundles of elongated cells. These cells have a pale cytoplasm and elongated nuclei and are fibroblasts, Schwann cells and perineural cells. All of them are found within a stroma composed of collagen, mucin and scattered mast cells.

- Plexiform neurofibromas are quite similar histopathologically to cutaneous neurofibromas, except that the number and size of the nervous fibres is larger, as they show hypertrophy. These nervous bundles are encircled by fibroblasts and Schwann cells, all in a myxoid matrix.

Malignant transformation of a plexiform neurofibroma into a neurofibrosarcoma shows histopathologically cellular pleomorphism, nuclear atypia with hyperchromasia and increased mitotic activity. The cells are located around the vessels, in a wavy pattern and immunohistochemistry is positive for S-100. NF2 tumours histopathologically don’t differ from the sporadic lesions (e.g. cutaneous schwannoma). Molecular testing may be helpful in patients with a single clinical finding and no positive family history of neurofibromatosis. Sequencing of the neurofibromin gene offers the highest detection rate. Prenatal diagnosis of NF1 using...
amniocentesis or chorionic villus sample if one parent is affected or preimplantation genetic diagnosis for couples using in vitro fertilization when a specific mutation is known. Urinary free catecholamines (norepinephrine and epinephrine) and their metabolites in the 24 hour urine collection or plasma catecholamines can be used to investigate a suspected pheochromocytoma.

**Differential diagnosis (NF1 and NF2)**

Using the clinical criteria, the positive diagnosis of neurofibromatosis is easy, but at the beginning, especially in young children, when not all the criteria are met, establishing the diagnosis can be quite difficult.

From dermatological point of view the differential diagnosis can be made with some other diseases presenting with café-au-lait spots, axillary or intertriginous freckling or neurofibroma. Café-au-lait spots are the first and, at the beginning, the only signs of disease that appear. Initially they can be less than 6 and a differential diagnosis can be made with isolated café-au-lait macules (found in 10-20% of the normal population)(14, 39), spilus and Becker naevi. Café-au-lait spots can also appear in other syndromes such as McCune-Albright, Westerhof, Legius, tuberous sclerosis and Fanconi anaemia. Until the whole clinical picture is revealed the only tests that can be helpful for diagnosis are the genetic ones.

McCune-Albright syndrome is a genetic sporadic disease that has café-au-lait spots present from birth or which appear from infancy, but usually the macules are more asymmetrical and larger in comparison with those in NF1 and also the borders are more imprecisely defined and they never cross the median line. The syndrome also associates bone problems (polystotic fibrous dysplasia) and endocrine problems (more often early puberty).

Westerhof syndrome is a rare disorder characterised by the presence of hypo- and hyperpigmented macules on the trunk and limbs, without other systemic manifestations.

Legius syndrome is a genetic disorder, with autosomal dominant inheritance, which resembles to NF1, due to the presence of the café-au-lait spots and axillary freckling, but without the other clinical findings (40).

Tuberous sclerosis can also have café-au-lait spots, but without the presence of intertriginous freckling or the neurofibromas and the other associated clinical findings, dermatologic as well as systemic. Fanconi anaemia is a rare form of aplastic anaemia that associates abnormalities of the bones, microcephaly, hypogonadism, ocular, renal and cutaneous abnormalities, among which café-au-lait spots are present.

Intertriginous freckling may also appear within other syndromes: LEOPARD, Watson or Carney syndromes. LEOPARD syndrome, whose name is a mnemonic and stands for the characteristic signs and symptoms of this disease (Lentigines, Electrocardiographic (ECG) conduction defects, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth and Deafness) presents with multiple lentigines on the face, neck and trunk.

Watson syndrome can have café-au-lait spots as well as freckling in the axillary or inguinal region and neurofibromas, but is associated with pulmonary stenosis, short stature and mental retardation. Carney complex is an autosomal dominant transmitted syndrome that associates cutaneous findings, endocrinopathy and tumours (myxomas of the heart, breast, psammomatous melanotic schwannomas, testicular tumours, etc). Dermatologically hyperpigmented macules can be found on the skin and mucosae, lentigines and blue naevi, as well as cutaneous myxomas, the latter presenting as translucent or skin-coloured papules.

Neurofibromas have very characteristic features, clinically as well as histopathologically, but sometimes, especially the plexiform hyperpigmented ones, covered excessively with hair, in children, can clinically resemble to congenital melanocytic naevi.

Cutaneous tumours in NF 2 can be mistaken for the ones found in neurofibromatosis type 1 (NF1) or type 3 (NF3). In NF3 (Riccardi classification), also known as schwannomatosis, the patients have multiple cutaneous schwannomas and different tumours of the central nervous system, but they spare the VIII-th cranial nerves, so the vestibular tumours of NF 2 are not present (41).

Among the differential diagnoses of NF1 and NF2, one should never forget the other forms of neurofibromatosis: NF3 Riccardi (discussed above), type 5 Riccardi or type 3 Carey (known as segmental neurofibromatosis as the lesions are situated on one or more dermatomes or in a mosaic fashion on one segment of the body that is limited by the Blaschko’s lines), type 6 Riccardi or 4 Carey (familial café-au-lait spots, without other stigmata or systemic involvement), type 5 Carey (NF-Noonan phenotype which presents, besides the NF 1 features the characteristic clinical elements of the Noonan syndrome, such as short stature, peculiar facial features, skeletal malformations and cardiac abnormalities) (34, 42, 43).

The neurological differential diagnosis can be made with brainstem glioma, low grade astrocytoma, meningioma, cauda equina and conus medullaris syndromes, vascular lesions of the spinal cord.

**Complications**

Though apparently a benign disease, complications may appear in the evolution of the disease so monitoring the patients for complications is mandatory. The complications may have very different etiologic mechanisms like distorting nerve tissue or compression on internal organs (in the thoracic-abdominal cavity) due to tumor growth, or malignant transformation of the tumors.

Tumors (neurofibromas under the skin or plexiform neurofibromas involving multiple nerves) can
Neurofibromatosis – one disease for a multidisciplinary team

Neurofibromatosis can’t be cured, there is no specific treatment available! As a predominantly genetic disease, there is no etiological treatment available for this disorder but it requires life-long management adapted to the form and age; therefore the only option is a symptomatic treatment associated with the information and education of patients regarding the disease and its complications, the necessity to be monitored for evolution and complications yearly by a multidisciplinary team as well as a genetic counselling.

Dermatologic treatment
The dermatologist can excise bigger tumours which produce functional discomfort or deformities. Simple surgical excision is the most frequent method, but ablative lasers (such as C02 Laser) or electrodesiccation can also be used, with a higher risk of recurrences and hypertrophic or keloid scars [44-46]. Deeper tumours are treated by surgeons due to the fact that the tumour may extend to the internal structures. However the results are often unsatisfactory because of the deeper infiltration and the higher risk of recurrences. Chemotherapy, antifibrotic agents, antiangiogenic therapy and genetic and cytokine modulators are studied [47]. For plexiform neurofibromas that arise suspicions for malignancy (see above) biopsy and histopathological analysis are mandatory and if malignancy is confirmed, early specific treatment must be prescribed. Treatment of the café-au-lait spots can be tried due to cosmetic reasons, but they respond badly to non-invasive treatments, such as lasers (they do not disappear completely or they reappear) [48]. If intense itching is present, antihistaminic treatment can bring relief, some authors considering that ketotifen is the best option [48].

Symptomatic treatment
Pain relief can be often needed as pain may be one of the most bothering symptoms in patients with affected peripheral or spinal nerves. Monitoring of blood pressure and specific treatment in order to lower high blood pressure may be useful, if smooth muscles of the blood vessels are involved. Surgery (laparoscopic/classical methods), in order to remove compressing or invasive tumors, or tumors affecting nerves, recidivating tumors in order to reduce complications or cutaneous large tumors in order to help in recovering self-esteem. Microsurgery and stereotactic radiosurgery are used to remove vestibular schwannomas or schwannomas with other localization. Meningiomas are growing slower than schwannomas, and surgical treatment can be considered only if they are causing serious disabling symptoms. Radiation therapy can be used for localized tumors or malignant ones, but there is a risk, as it can cause radiation induced cancer if applied repetitively and especially in young patients. Orthopedic treatments for scliosis and other treatable bone deformities can be used, as well as medical treatment for osteoporosis in order to reduce complications. Implants (cochlear, auditory brainstem implants) are used for augmentation and amplification of hearing, and in young children with NF1 and speech problems and learning disabilities speech therapy can be a choice. Treatment for cancer, disabling ependymoma, unresectable schwannoma may include surgery, chemotherapy (lomustine, vincristine, prednisone, or carboplatin and vincristine, or erlotinib) and radiation therapy [49].

Evolution and prognosis
NF1 and NF2 are progressive and generalized diseases. For NF1 the overall life expectancy may be reduced by on average 8 years due to complications (hypertension, malignancy, spinal cord or brain lesions) [46]. Prenatal diagnosis is difficult, not only because of the high costs, but also as the disease has a wide variability of clinical expressions within the same family, so it is difficult to predict the severity of the disease in a given patient.

Conclusions
A multidisciplinary team represented by dermatologist, neurologist, ophthalmologist, orthopedist, pediatrician, geneticist will be very efficient in diagnosing and monitoring on an annual basis for changes in the evolution of the disease. Together they are preventing, treating symptoms and complications. The team can be enlarged with neurosurgeon, plastic surgeon, oncologist, otolaryngologist, endocrinologist or some other specialists if necessary as neurofibromatosis is a rare but multifaceted disease.