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Neurofibromatosis – Diagnostic Assessment

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1. Introduction

Descriptions of individuals supposed to have neurofibromatosis have been discovered in manuscripts dating from 1000 AD (Zanca, 1980). However, it was not until 1881 that Von Recklinghausen coined the term “neurofibroma” when he observed that this benign tumour arose from the peripheral nerve sheath. His colleagues honored his contribution by naming the condition Von Recklinghausen’s disease. However, the different forms of neurofibromatosis were not separated and delineated until the latter part of the twentieth century (Ferner et al., 2007a). Neurofibromatosis is one of the called “neurocutaneous disorders” or “phakomatoses”, genetic diseases that involve both skin and the nervous system. They share some features: hereditary transmission, involvement of organs of ectodermal origin and a tendency to develop certain types of central and peripheral nervous system tumours. Advances in clinical genetics allowed to separate neurofibromatosis in two diseases, each caused by a different gene, although recognition still requires an appreciation of the cutaneous and systemic symptoms. (Ferner 2007a, 2010)

2. Clinical manifestations and diagnostic criteria

2.1 Neurofibromatosis 1

Neurofibromatosis 1 (NF1) is an autosomal dominant disorder with an incidence of 1 in 3,500 live births. Half of all cases are spontaneous mutations. The gene was cloned on chromosome 17q11.2 in 1990. Neurofibrin, the protein product, is widely expressed with high levels in the nervous system. It acts as a tumour suppressor which explains why NF1 patients are prone to developing benign and malignant tumours (Ferner, 2010). Although recent advances in genetic testing may permit the laboratory diagnosis in as many as 95%, for the majority of patients the diagnosis is made on the basis of clinical manifestations. Diagnosis requires the presence of 2 or more major criteria: 6 or more *café au lait* spots, axillary or inguinal freckling, 2 or more cutaneous neurofibromas, 1 plexiform neurofibroma, characteristic bony lesions (pseudarthrosis, sphenoid wing hypoplasia), an optic glioma, 2 or more iris Lisch nodules, or a first-degree relative with NF1 (Table 1). Diagnosis can be made at birth in some cases, whereas others must be monitored for a few years for the presence of additional criteria (Ferner et al., 2007a, b, 2010; Tonsgard, 2006).

6 or more <i>café au lait</i> spots (>0,5 cm in prepubertal children, >1,5 cm in postpubertal individuals) Axillary or inguinal freckling 2 or more cutaneous neurofibromas 1 plexiform neurofibroma 2 or more iris Lisch nodules An optic glioma Characteristic bony lesions (pseudarthrosis, sphenoid wing hypoplasia) A first-degree relative with NF1
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Table 1. Diagnostic Criteria for NF1

2.1.1 Cutaneous manifestations

Café au lait spots are generally the heralding feature of NF1. *Café au lait* spots are hyperpigmented flat spots that are oval or rounded with fairly smooth borders (Fig 1a). They are present at birth in many individuals and increase in size and number over the first 5 to 7 years of life. Most, but not all patients with NF1, have *café au lait* spots (Tonsgard, 2006).

Freckling is reported in children of about 3 years of age in the axillae, groins, around the neck, on the eyelids, and under the breasts. However it may not appear until 5 to 7 years of age (Tonsgard, 2006).

Cutaneous angiomas and hypopigmented maculae are described, and xanthogranulomas (Fig1b) can appear fleetingly during childhood as orange papules. Cutaneous or dermal neurofibromas are tumors of the nerve sheath comprised of Schwann cells, fibroblasts, perineural cells, mast cells, axons, and blood vessels (Lott & Richardson, 1981). They may become visible in childhood but more commonly develop in adolescence or adulthood (Fig 1a). They may be purplish depressions in the skin or pedunculated lesions. Plexiform neurofibromas are histologically similar to cutaneous neurofibromas but have more extracellular matrix (Fig 1c). Often, they arise from the dorsal spinal roots, nerve plexus, large nerve trunks, or sympathetic chains. Plexiform tumours may be discrete, homogeneous, well circumscribed or diffuse, heterogeneous, and infiltrative. They may involve superficial skin or be entirely internal. They occur in at least 50% of patients and are probably present at birth. Many are asymptomatic (Tonsgard et al., 1998).



Fig. 1. A - *Café au lait* (black arrows) and pedunculated cutaneous neurofibromas (white arrow) B - Xanthogranuloma. C - Plexiform neurofibroma (blue arrow)

Individuals with NF1 harbor a 7–13% lifetime risk of developing malignant peripheral nerve sheath tumors (MPNST), which usually arises in a pre-existing plexiform or a focal subcutaneous neurofibroma. Cutaneous neurofibromas do not become malignant. MPNSTs metastasize widely and often presage a poor outcome. Vigilant monitoring is recommended for patients with a past history of malignancy or radiotherapy, a family history of MPNST, internal neurofibromas, lesions in the brachial or lumbosacral plexus, or neurofibromatous neuropathy. Individuals with neurofibromatous neuropathy have a mild axonal sensory and motor neuropathy with diffuse neurofibromatous change in the nerves. (Ferner, 2007a)

Diagnosis of MPNST is problematic within the context of NF1 because the emergence of a lump is not unusual. The clinical symptoms of malignancy are intertwined with the symptoms of benign tumours. Plexiform neurofibromas that are associated with persistent or nocturnal pain, rapid increase in size, change in texture, or new or unexplained neurological deficit require urgent assessment at a specialist unit. Targeted biopsy with 18-fluorodeoxyglucose (FDG) PET is the best method for diagnosis (Ferner et al., 2000).

2.1.2 Ocular/orbit manifestations

NF1 may affect the iris, retina, optic nerve, and the bony and soft tissue of the orbit. Lisch nodules are proliferations of melanocytes and fibroblasts that appear as reddish brown spots in the iris of blue- or green-eyed people and hypopigmented spots in brown eyed people. They are commonly found in the lower pole of the iris and have no effect on vision (Fig 2). Onset is usually in the teenage years. They are present in 90% of adults. Retinal hamartomas occur in a small percentage of patients. Optic gliomas (visual pathway tumors) are grade I pilocytic astrocytomas found in 15% of patients. They produce thickening of the optic nerve (Fig 3). Frequently bilateral and often involving the chiasm, they may extend to the optic tracts or inferiorly into the hypothalamus. They may present as decreased color vision or an afferent papillary defect and later with pallor of the optic disc or a decrease in visual acuity between 15 months to 7 years of age. Plexiform neurofibromas of the orbit are frequently found in patients with optic gliomas (Liternick et al., 1989; Tonsgard, 2006; Ferner, 2010).

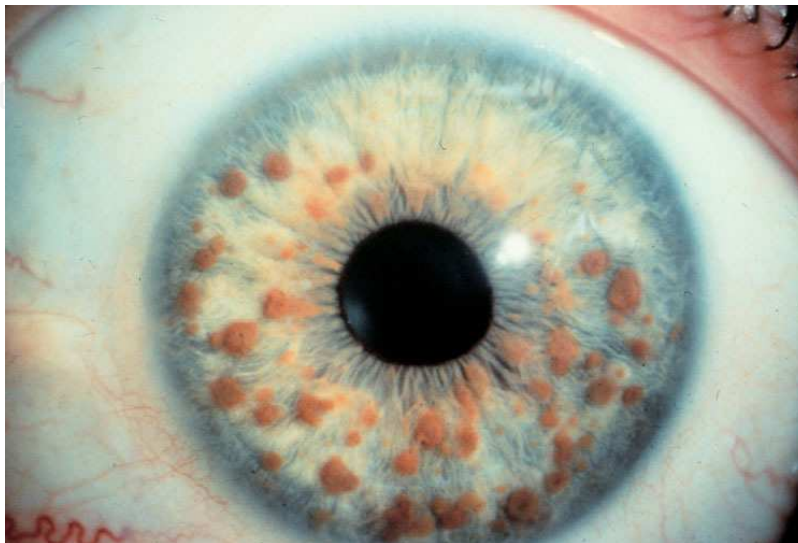


Fig. 2. Lisch Nodules

2.1.3 Bone abnormalities

Orthopedic problems arise in patients with NF1 from inherent abnormalities in the maintenance of bone structure and from reduction in bone mineral density. Individuals with NF1 have an increased risk of developing osteoporosis and osteopenia, which predominantly affect the load-bearing parts of the body (Crawford & Bagamery, 1986; Ferner, 2007).

Complications can also result from bony overgrowth or destruction caused by underlying plexiform neurofibromas. Bony dysplasia, bony erosion, demineralization, non ossifying fibromas, and scoliosis are all features of NF1. Dysplastic bony lesions include splayed ribs, vertebral anomalies, hypoplasia of the sphenoid or mandible, and pseudarthrosis. Pseudarthrosis most commonly involves the tibia and presents in early infancy with bowing of the affected limb followed by pathological fracture and impaired healing. The disorder represents thinning of the long bone cortex and the development of a false joint in a long bone (Crawford & Bagamery, 1986; Ferner, 2007).

Scoliosis affects 10% of those with NF1, most commonly involves the lower cervical and upper thoracic spine, and can be either idiopathic or dystrophic. The latter does not usually develop before 6 years of age and is rare after the first decade of life. Typically, there is a short curve with severe apical rotation, distortion of the vertebral bodies and ribs, and rapid disease progression (Crawford & Bagamery, 1986; Ferner, 2007).

2.1.4 Cardiovascular problems

An international database review identified cardiovascular malformations in 2% of patients with NF1 and most individuals had pulmonary stenosis. Hypertension occurs with increased frequency and is associated with premature death in adults with NF1. High blood pressure can be idiopathic or the result from dysplastic renal artery stenosis or pheochromocytoma. Dysplasia of blood vessels is usually multifocal and bilateral. The most common sites are kidney and brain (Lin et al., 2000; Ferner, 2007).

2.1.5 Neurological manifestations

Neurological complications affect both the peripheral and central nervous system, accounting for significant morbidity and mortality in NF1.

As already described, cutaneous neurofibromas are tumours of peripheral nerves, and plexiform neurofibromas can involve large nerves, plexus, spinal roots, sympathetic nerves, or small peripheral nerve fibers. Involvement of large nerves such as the sciatic may be asymptomatic or suggested only by hypertrophy of the affected extremity. When the sacral plexus is involved, there can be massive proliferation of tumor with infiltration of the bladder and compression of the ureters, rectum, and uterus. Plexiform tumours of the spinal roots may cause pain and erosion of the neural foramen or cord compression. High cervical nerve root neurofibromas are prone to compress the cord but the neurological deficit is frequently mild in comparison with the neuroimaging appearances. Involvement of the lumbar roots causes back pain that is aggravated by exertion (Tonsgard, 2006; Ferner, 2007).

Neurofibromatous neuropathy affects at least 1% of NF1 adults. They present with mild distal sensory and motor symptoms. Thickened peripheral nerves are infiltrated with neurofibromatous tissue. Although NF1 neurofibromatous neuropathy is not progressive, affected individuals require assiduous monitoring because they are at risk of developing malignant peripheral nerve sheath tumors (Ferner, 2010).

Cognitive disability is the commonest neurological symptom in children with NF1 and does not improve in adulthood. Characteristically, the intelligent quotient (IQ) is in the low-average range but mental retardation (IQ<70) is uncommon. Children with NF1 have specific learning difficulties that include visual spatial problems, impaired visual motor integration with abnormal ocular saccades, language deficits, and disorder of executive function. Problems that are typically associated with the NF1 phenotype include attention deficit hyperactivity disorder, which responds to methylphenidate medication, and poor socialization (Hyman et al., 2005).

Chiari 1 malformation and aqueduct stenosis due to subependymal glial cell proliferation are encountered in 1.5 % of NF1 patients (Valverde et al., 2007). Hydrocephalus is an uncommon complication. Sphenoid wing dysplasia is noticeable as pulsating exophthalmos without visual compromise; the absent sphenoid wing allows the temporal lobe to prolapse forwards into the orbit but surgical correction is not usually undertaken (Ferner et al., 2007a).

Epilepsy is diagnosed in about 6% of NF1 patients, it is frequently mild and it tends to start between childhood and middle age. There are several underlying causes, comprising brain trauma, infection unrelated to NF1, mesial temporal sclerosis, NF1 related gliomas and anecdotal reports of dysembryoblastic neuroepithelial tumours. All seizure types occur but complex partial seizures predominate.

Cerebrovascular problems have been reported in 2.5% of children with NF1 and include stenosis or occlusion of the internal carotid and cerebral arteries, aneurysms, and Moyamoya disease (Rosser et al., 2005).

Headaches occur in 20% of patients; most of these are consistent with migraine and respond well to prophylactic medications (Tonsgard, 2006).

Gliomas occur in all parts of the brain but have a predilection for the optic pathways, brainstem, and cerebellum. They are usually indolent pilocytic astrocytomas, but those that arise outside the optic pathways, which are symptomatic lesions or that release in adulthood, are more aggressive and are associated with a worse prognosis. About 15% of NF1 children have optic pathway gliomas but only 5% develop symptoms or signs (figure 3). They usually present before the age of 6 years and can cause impaired visual acuity and color vision, squint, proptosis, afferent pupillary defect, optic atrophy, visual field defects and precocious puberty. Adult onset or tumor progression, are unusual and visual screening is not required in adulthood. Young children rarely complain of visual loss and the best method of diagnosis is regular visual screening, at least until the age of 7 years. Grade III and IV astrocytomas occur in NF1 and require aggressive treatment. They are invariably symptomatic. The best outcome implies complete surgical removal coupled with chemotherapy. The outcome for malignant brain tumors in patients with NF1 is generally better than in not affected individuals (Laternick et al., 1989; Tonsgard, 2006; Ferner, 2010).



Fig. 3. Optic pathway gliomas involving both optic nerves (black arrows)

Primary progressive multiple sclerosis occurs with increased frequency in NF1 and relapsing remitting disease has also been reported. Although NF1 is a tumour suppressor condition, immunosuppressant therapy is not contraindicated and so far, there is no evidence of an increase in malignancy in NF1 patients with multiple sclerosis (Ferner, 2007b).

2.2 Neurofibromatosis 2

Neurofibromatosis type 2 (NF2), primarily known as acoustic neurofibromatosis or central neurofibromatosis is an autosomal dominant disorder caused by mutations on the NF2 gene, a tumour suppressor gene located on chromosome 22q12 that encodes a protein termed Merlin/Schwannomin, causing diminished or loss of function of these protein (Asthagiri et al, 2009; Ferner, 2007b; Gareth & Evans, 2009). It is less common than NF1, accounts for 5 to 10% of all cases of Neurofibromatosis and has an incidence of 1 in 25,000 livebirths and a prevalence of 1 in 60,000 (Asthagiri et al, 2009; Ferner, 2007b; Pérez-Grau et al, 2010). The average age of onset is 22 years of age (Asthagiri et al, 2009; Ferner, 2007b) (Gareth & Evans, 2009). There is a risk of 50% of an affected individual to transmit the mutation to their offspring and the penetrance will be complete at 60 years of age, however there is a high phenotypic variability between individuals, even within the same family (Asthagiri et al, 2009; Gareth & Evans, 2009). About one third of NF2 patients are mosaic, which means that the mutation took place after conception and that only certain cells of the body will be affected and these patients will have a milder form of the disease (Ferner, 2007b; Gareth & Evans, 2009; Pérez-Grau et al, 2010).

The characteristic feature is bilateral vestibular schwannomas (on cranial nerve VIII) that occur in 90-95% of patients. They present most commonly with progressive sensorineural hearing loss as the first sign, frequently unilateral at onset (Ferner, 2010; Gareth & Evans, 2009; Pérez-Grau et al, 2010). Since schwannomas usually do not develop before adolescence, in children the first manifestation, contrary to what occurs in adulthood, can be

cranial, orbital or spinal meningioma, spinal or cutaneous schwannoma, mononeuropathy, focal amyotrophy or cataracts (Ferner, 2007b, 2010; Gareth & Evans, 2009; Pérez-Grau et al, 2010). Contrarily to tumours in NF1, schwannomas are benign tumours and the morbidity and early mortality rates are due to the multiple tumours in central and peripheral nervous system (Asthaigiri et al, 2009; Ferner, 2007a; Pérez-Grau et al, 2010)

The efficiency of the set of existing criteria was compared in a study selecting 163 people from NF2 registry without bilateral vestibular schwannomas. (Baser et al., 1996) They evaluated the criteria for “definite NF2” and “probable NF2” at two points: initial assessment and the most recent clinical evaluation. (Baser et al., 1996) For both points, the Manchester criteria and the NNF (National Neurofibromatosis Foundation) criteria identified a higher proportion of people than with the NIH (National Institute of Health) criteria. The Manchester criteria identified an even higher number of people because they are based on the number of disease features of any types and a determined age is not necessary for diagnosis, contrary to NNFF which requires a certain number of different feature types and the existence of unilateral vestibular schwannomas with less than 30 years of age. The 1987 and the 1991 NIH Criteria each require a positive family history for the diagnosis of NF2 in people who do not have bilateral vestibular schwannomas, therefore, the proportion of these people identified with “possible NF2” is low and even lower with “definite NF2”. (Baser et al., 1996) For people who do not have a family history of NF2 or bilateral vestibular schwannomas, a diagnosis can be made based on the Manchester and the NNFF criteria. (Baser et al., 1996) The Manchester criteria are more sensitive for identifying mosaics than all the other criteria. They considered that a new set of criteria should be created including the evidence of mononeuropathy (foot drop, wrist drop, facial palsy, or III nerve palsy) and the results of genetic testing.

2.2.1 Cutaneous manifestations

Three types of cutaneous tumours, all histologically schwannomas, are identified: cutaneous plaque-like lesions (raised, hyperpigmented and hairy), subcutaneous tumours (fusiform swelling) and intradermal tumours. (Asthaigiri et al, 2009; Ferner, 2007b). These occur in about 70% of NF2 patients, though less prominent than in NF1 patients. (Gareth & Evans, 2009; Pérez-Grau et al, 2010)



Fig. 4. Cutaneous schwannoma

Generally these tumours grow on or around a peripheral nerve (more frequently sensory nerves) and subcutaneous tumours usually cause pain and are sensitive to pressure. (McClatchey, 2007; Pérez-Grau et al, 2010) Rarely a cutaneous neurofibroma may appear or a dermal tumour may be confused with a neurofibroma. (Asthaigiri et al, 2009; Ferner, 2007b; Gareth & Evans, 2009; McClatchey, 2007)

Café au lait patches are reported in almost 40% of patients with NF2, being more common than in the general population, but less numerous than in people with NF1 and generally they are singular and inconspicuous. (Asthagiri et al, 2009; Ferner, 2010)

2.2.2 Neurological manifestations

Although schwannomas on cranial nerve VIII are the cardinal feature of NF2, they can also grow on other cranial nerves (CN). The next most affected CN are III (oculomotor), V (trigeminal) and VII (facial), but they can affect IX-XII also (Ferner, 2010; Gutmann et al, 1997). When tumours arise in III and V CN, they are usually asymptomatic, opposite to tumours of the lower cranial nerves, mostly symptomatic (Asthagiri et al, 2009). The initial symptom associated with vestibular schwannomas usually is progressive sensorineural hearing loss, which can be preceded or accompanied by tinnitus (Ferner, 2010; Gareth & Evans, 2009). Other symptoms associated are: vertigo, gait instability, facial weakness, twitching, sensory deficit and headache (Ferner, 2010; Pérez-Grau et al, 2010). The growth rates of vestibular schwannomas are variable, but higher in patient under 30 years of age.

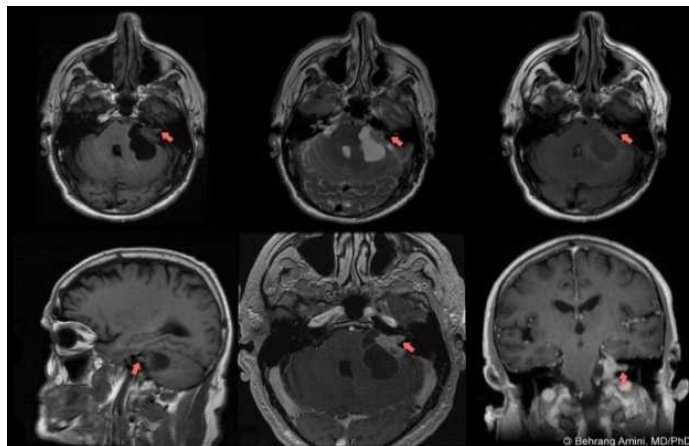


Fig. 5. Vestibular schwannoma (red arrows)

Meningiomas are the second most frequent tumour in NF2 patients. They are generally multiple, can occur in brain or spine, and the symptoms vary according to the location (Goutagny & Kalamarides, 2010). Cranial meningiomas have a high rate of neurological problems and mortality (Asthagiri et al, 2009; Ferner, 2010). Optic meningiomas may cause vision loss due to compression of the optic nerve, especially in children (Bosch et al, 2006).

Spinal schwannomas can occur and are regularly multiple (Ferner, 2010). These tumours and optic meningiomas can be found in about 90% of patients with NF2 (Ferner, 2010). For 20-30% of NF2 patients the initial symptoms have their origin in intracranial meningiomas, spinal or cutaneous tumours (Gareth & Evans, 2009).

Ependymomas (low-grade CNS malignancies) can be present, mostly in the brainstem and upper cervical cord and may be associated with a syrinx (fluid-filled cavity within spinal cord), with symptoms that could appear throughout life (Aguilera, 2011; Ferner, 2010; Gareth & Evans, 2009). For spinal cord ependymomas, the intramedullary lesions may present themselves as back pain, weakness or sensory disturbances (Asthagiri et al, 2009).

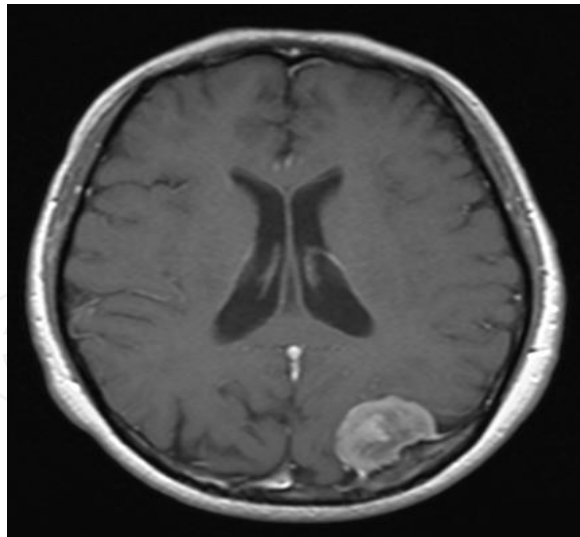


Fig. 6. Cranial meningiomas in NF2 patients

Also associated to NF2 is an axonal peripheral neuropathy (Asthağiri et al, 2009; Ferner, 2010). The majority of the cases are associated to tumours within or compressing the nerve, but in others the mechanisms are not yet fully understood as there is no evidence of a tumour and are probably related with compression from multiple Schwann cell tumourlets. (Asthağiri et al, 2009; Ferner, 2010). In children a clinical presentation with mononeuropathy (in particular facial nerve palsy) before the appearance of vestibular schwannomas is common, but also common is a polio-like illness (Ferner, 2007; Gareth & Evans, 2009). In both presentations full recovery is unusual. (Ferner, 2007a; Gareth & Evans, 2009).

2.2.3 Ocular manifestations

Usually lens changes appear in infancy or childhood (earlier than vestibular schwannomas) and most commonly include juvenile posterior subcapsular cataracts, cortical wedge cataracts and mixed cataracts and all can reduce visual acuity. (Gareth & Evans, 2009) They should be considered as specific of NF2 only in people younger than 50 years of age. They are present in about 60-80% of NF2 patients (Asthağiri et al, 2009; Gareth & Evans, 2009).

Other manifestations are epiretinal membranes and retinal hamartomas. The first, opposite to the second, don't usually affect visual acuity even in patients with severe disease, and may be present in more than a third of patients with NF2 (Asthağiri et al, 2009; Pérez-Grau et al, 2010).

The onset at a young age of ophthalmologic symptoms is a risk factor for marked disease progression. (Bosch et al, 2006) Therefore people at risk of developing NF2 should be screened for these abnormalities in infancy (Gareth & Evans, 2009; Baser, 1996).

Regarding diagnostic criteria, the National Institute of Health (NIH) Consensus Panel established in 1987 clinical guidelines for the diagnosis of Neurofibromatosis type 2, which were revised in 1991. However, these criteria were considered too rigid and leading to exclusion of patients that should be screened for NF2. Therefore, in 1997, a consensus review of published data was proposed by researchers in the neurofibromatosis field by the National Neurofibromatosis Foundation (NNF) (Gutmann et al., 1997; McClatchey, 2007). In

order to promote higher specificity and sensitivity, in 2002 new diagnostic criteria were established, based on a comparison of this four different sets of criteria for NF2 (Table 2) (Baser et al., 1996; Ferner, 2007a).

<p>1987 NIH criteria</p> <p>A. Bilateral vestibular schwannomas</p> <p>B. First-degree family relative with NF2 <i>and</i> unilateral vestibular schwannoma <i>or</i> any two of: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lenticular opacity</p>
<p>1991 NIH criteria</p> <p>A. Bilateral vestibular schwannomas</p> <p>B. First-degree family relative with NF2 <i>and</i> unilateral vestibular schwannoma <i>or</i> any one of: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity</p>
<p>Manchester criteria</p> <p>A. Bilateral vestibular schwannomas</p> <p>B. First-degree family relative with NF2 <i>and</i> unilateral vestibular schwannoma <i>or</i> any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</p> <p>C. Unilateral vestibular schwannoma <i>and</i> any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</p> <p>D. Multiple meningiomas (two or more) <i>and</i> unilateral vestibular schwannoma <i>or</i> any two of: schwannoma, glioma, neurofibroma, cataract</p>
<p>NNF criteria</p> <p>A. Confirmed or definite NF2</p> <ol style="list-style-type: none"> 1. Bilateral vestibular schwannomas 2. First-degree family relative with NF2 <i>and</i> unilateral vestibular schwannoma at less than 30 y of age <i>or</i> any two of: meningioma, schwannoma, glioma, juvenile lens opacity (posterior subcapsular cataract or cortical cataract) <p>B. Presumptive or probable NF2</p> <ol style="list-style-type: none"> 1. Unilateral vestibular schwannoma at less than 30 y of age <i>and</i> at least one of: meningioma, schwannoma, glioma, juvenile lens opacity (posterior subcapsular cataract or cortical cataract) 2. Multiple meningiomas (two or more) <i>and</i> unilateral vestibular schwannoma at less than 30 y of age <i>or</i> at least one of: schwannoma, glioma, juvenile lens opacity (posterior subcapsular cataract or cortical cataract)

Table 2. Clinical diagnostic criteria for NF2 (Baser ME, 2002)

3. Differential diagnosis

The differential diagnoses of NF1 includes other forms of neurofibromatosis, conditions with *café au lait* patches or with pigment changes confused with *café au lait* patches. Likewise, tumors or localized body overgrowth can be mistaken for neurofibromas (table 3). It should be emphasized that one or two *café au lait* patches occur in 10% of the general population. Children with 3–5 *café au lait* patches but no other signs of NF1 should be followed up in a specialist neurofibromatosis clinic as they might have mosaic NF1 or NF2 (Ferner., 2007b).

Mosaic NF1 occurs as a result of a somatic mutation in the NF1 gene. The body's proportion affected depends on mutation's timing in embryonic development. The importance of making the diagnosis is that NF1 complications are relatively infrequent in segmental NF1 and there is a much lower risk of recurrence in offspring. Homozygotes for one of the genes causing hereditary non-polyposis cancer of the colon have *café au lait* patches and an affected first degree relative. However, the affected relative is a sibling and the parents are normal (Ruggierei & Huson, 2001).

The only subtype of NF1 that is distinct and has a uniform phenotype in families is Watson syndrome. It is characterized by pulmonary stenosis, cognitive impairment, *café au lait* patches and few, if any, cutaneous neurofibromas (Korf & Huson, 2006).

There is no clear evidence that neurofibromatosis-Noonan syndrome exists as a distinct phenotype with features of both syndromes. It is likely that some individuals with NF1 simply have facial features similar to those of Noonan syndrome and these characteristics are not consistent within families. Molecular studies indicate that neurofibromatosis-Noonan syndrome is caused by mutations of the NF1 gene, some of which have been identified in patients with classical NF1 (De Luca et al., 2002).

<p>Other forms of neurofibromatosis:</p> <ul style="list-style-type: none"> Segmental/mosaic NF1 Watson syndrome Autosomal dominant multiple <i>café au lait</i> alone Neurofibromatosis 2 Schwannomatosis
<p>Other conditions with <i>café au lait</i> patches:</p> <ul style="list-style-type: none"> McCune-Albright syndrome DNA repair syndromes Homozygosity for one of the genes causing hereditary non-polyposis cancer of the colon
<p>Conditions with pigmented macules confused with NF1:</p> <ul style="list-style-type: none"> LEOPARD syndrome Neurocutaneous melanosis Peutz-Jehers syndrome Piebaldism
<p>Localized overgrowth syndrome:</p> <ul style="list-style-type: none"> Klippel-Trenauny-Weber syndrome Proteus syndrome
<p>Conditions causing tumors confused with neurofibromas:</p> <ul style="list-style-type: none"> Lipomatosis Banaya-Riley-Ruvalcuba syndrome Fibromatoses Multiple endocrine neoplasia type 2B

Table 3. Differential diagnosis of neurofibromatosis 1

NF2 is clinically and genetically distinct from NF1, and is characterized by bilateral vestibular schwannomas. Affected individuals also develop schwannomas on other cranial, spinal, peripheral and cutaneous nerves. *Café au lait* patches are less numerous than in NF1, and the skin lesions are predominantly schwannomas. Central nervous system

meningiomas and gliomas are observed, and slit lamp examination reveals juvenile subcapsular lens opacities in the majority of patients. Subcutaneous, peripheral nerve and spinal schwannomas lead to schwannomatosis without vestibular schwannomas or the ophthalmological features of NF2 (Ferner, 2007a).

Multiple lipomas occur primarily on the trunk, proximal thighs and distal arms, and are inherited in an autosomal dominant fashion. Biopsy is sometimes necessary to differentiate cutaneous neurofibromas from schwannomas and lipomas (Ferner et al., 2007a).

4. Diagnostic workup

The diagnosis of NF 1 is mainly clinic and (Baser et al, 1996; Ferner, 2007b), as explained before, two of the major criteria based on the modified NIH criteria must be fulfilled. Given the variety of clinical symptoms and the fact that these are age-dependent, it is sometimes difficult to make the diagnosis of NF1 at an early age because children might have, for example, the typical “café au lait” spots but only develop other features of the disease years later (Korf, 2011). Therefore, a complete physical and neurological exam together with a family history, ocular and cognitive (addressing learning skills) assessment and appreciation of bone deformities and cardiovascular alterations (with measurement of blood pressure) should be performed when a hypothesis of NF1 is considered or in an at-risk descendent.

Brain MRI is considered important at an early age for the exclusion of optic pathway glioma but for some aspects as sedation, costs and parents anxiety must be beared in mind. Bones imaging to look for bone dysplasia must also be assessed whenever a pain complaint occurs (Korf, 2011).

Because half the cases are familial, genetic counseling is very important in NF1 due to the high morbidity and mortality associated to this disease. Parents of affected children should know that a 50% risk of NF1 mutation transmitting is associated to each pregnancy (Tonsgard, 2006). Attention should be paid to the possibility of the subject being a mosaic, because a simple blood sample may miss the affected cells. A tissue sample from a tumour must be ideally collected in these situations.

For NF2 diagnosis the Manchester Criteria are the most commonly used. Therefore, as presented in Table 2, patients do not need to have a family history of NF2 or bilateral vestibular schwannomas but may have multiple other related lesions. Peripheral neuropathy and the presence of a constitutional NF2 mutation are not yet included in the diagnostic criteria of NF2 (Asthagiri et al, 2009; Baser et al., 1996; Gareth & Evans, 2009). Genetic testing could aid to rule out mutations in individuals from families with NF2 avoiding additional exams (Baser et al., 1996; Gareth & Evans, 2009).

The diagnostic evaluation as well, should always incorporate a thorough clinical and family history, a physical (including cutaneous), neurologic and as in NF1, ophthalmologic examination and a brain and spinal MRI with and without gadolinium (Gareth et al, 2009). MRI is the ideal imaging method when vestibular schwannomas are suspected but also to explore the presence of other cranial nerve tumours or meningiomas (Gutmann et al., 1997). The median age of NF2 diagnosis is 20-30 years with hearing loss as initial symptom. However, the clinical manifestations are age dependent and about 30% of children begin with other symptoms (Asthagiri et al, 2009; Gareth & Evans, 2009).

The screening of children with NF2 suspicion from an affected parent should include ophthalmologic examination (in the first ten years of life), neurologic examination (annually), audiology with auditory brainstem evoked potentials yearly from infancy (annually) and presymptomatic genetic testing (not before 10 years of age) (Evan et al., 1995; Gareth & Evans, 2009). MRI screening should be performed every 2 years when younger than 20 years of age and every 3 to 5 years when older than 20 years of age. However, if tumours are present screening should be done annually. For spinal MRI, the frequency should be every 3 years (Baser et al, 1996; Gareth & Evans, 2009).

5. Molecular genetic diagnosis of neurofibromatosis

5.1 Neurofibromatosis type 1

NF1 is an autosomal dominant genetic disorder. The gene locus discovered by linkage analysis and subsequently positional cloning in 1990, is found on chromosome 17 (Barker et al., 1987; Viskochil et al 1990; Wallace et al, 1990). It is a large gene that spans greater than 350-kb of genomic DNA, and it is composed of 60 individual exons (Gutmann et al 1999). The gene locus has a spontaneous mutation rate that is 100 times greater than average, and approximately half of NF1 cases appear to represent new mutations (Lewis and Riccardi 1981). The reason for the unusually high mutation rate and the mechanism of mutation are unknown. However, the vast majority of new mutations occur on the paternally derived chromosome. This phenomenon does not appear to be linked to paternal age as in other genetic diseases (Jadayel et al., 1990), and it is known as “genomic imprinting” (Hall, 1990). The mechanism by which genomic imprinting may play a role in the spontaneous mutation rate, may involve hypermethylation of the sperm genome, which is then at higher risk for mutations through the spontaneous deamination of 5-methylcytosine (Rodenhiser et al., 1993).

The most common gene product is a polypeptide of 2,818 amino acids, called neurofibromin (Gutmann & Collins 1992; Danglot et al 1995; Li et al., 2002). Neurofibromin is expressed in neurons, oligodendrocytes, Schwann cells, the adrenal medulla and white blood cells (Daston et al 1992; Gutmann, 1998). Sequence analysis of the full length NF1 gene cDNA revealed a portion that codes for a 360 amino acid peptide with structural and functional similarities to some guanosine triphosphatase activating proteins (GAP) in other mammalian and yeast cells (Xu et al 1995). The portion of the gene that codes for this protein interacts with the protooncogene, p21ras (Martin et al., 1990; Shen et al., 1996). The abovementioned proteins have the ability to accelerate hydrolysis of ras-guanosine triphosphate to ras-guanosine diphosphate, thus, activating the proto-oncogene. In some sporadic tumors of non-NF1 patients, ras activating mutations are implicated in malignant transformation (Reed & Gutmann 2001). This was the first hypothesis to the possible function of neurofibromin (Gutmann & Collins 1992). Loss of neurofibromin activity through mutation could lead to cellular proliferation, and thus to some of the disease expression of NF1. The NF1 gene is thus considered a tumor-suppressor gene as loss-of-function mutations have been associated with benign and malignant tumors in neural-crest-derived tissues in patients with NF1 (Coleman et al 1995; Serra et al 1997), being neurofibromin a tumor suppressor by down-regulating or inhibiting intracellular ras activity (Gutmann and Collins 1992). But beyond ras regulation, important intracellular signaling pathways are probably regulated by neurofibromin as cAMP generation that

modulates cell growth and differentiation in the brain (Tong et al 2002). On the other hand, neurofibromin is highly expressed in Schwann cells, and may play a critical role in the formation of neurofibromas (Rutkowski et al., 2000).

There may be basic differences in how NF1 gene expression influences the development of tumors or the cognitive manifestations. Some tumors occur when both copies of the gene are functionally inactivated or defects in growth regulation are caused by reduced protein expression.

Some of the non-tumor features, including cognitive and learning problems, may be related to microenvironmental interactions between haploinsufficient astrocytes and neurons (Gutmann et al., 1999).

Finally, neurofibromin has been shown to play a crucial role on modulating mesenchymal stem and progenitor cell differentiation into osteoblasts, and this effect may contribute to the osseous abnormalities seen in NF1 (Wu et al 2006)

The factors that determine the genotype/phenotype correlations are not well understood (Ainsworth et al., 1993; Shen et al., 1996), and the discordance for several defining features of NF1 among pairs of monozygotic twins suggest that some manifestations are not entirely genetically controlled (Huson, 1994).

Cloning of the NF1 gene brought hope for routine prenatal diagnosis, but the large size of the gene and large number of potential mutations make this unlikely for at least several years (Marchuk & Collins 1994).

Genetic diagnosis is sometimes possible in NF1 families with two or more affected individuals by linkage analyses. Available polymorphic DNA markers, however, do not always have sensitivity enough to achieve it in all families (Marchuk & Collins, 1994). Conventional approaches to the identification of disease-causing mutations in individuals with NF1 have been limited because of the large size of the gene and the wide diversity of mutations, no clustering in any one region of the gene (Gutmann et al., 1999). For these reasons, identification of a mutation in a suspect case requires a variety of techniques to thoroughly examine DNA for mutations, most of them point mutations or small lesions leading to premature termination codons (Upadhyaya & Cooper, 1998). Some tests as the protein truncation test (in-vitro transcription-translation of the whole NF1 coding sequence (Heim et al., 1995) have been used to identify mutations, but it seems that a combination of approaches will be necessary (Gutmann et al., 1999). In addition, even when a mutation is identified, an individual risk is confirmed, but not how severely he will be affected. This point limits the usefulness of currently available technology for prenatal test.

5.2 Neurofibromatosis type 2

NF2 is now well characterized as an autosomal dominant inherited disease caused by mutation of a gene located on the long arm of chromosome 22(q11-13.1), distinct from NF1 (Rouleau et al., 1987; Wertelecki et al., 1988).

The abnormal gene product for NF2, merlin or Schwannomin identified in 1993 (Rouleau et al., 1993; Trofatter et al., 1993), functions as a tumor suppressor gene (Rouleau 1994). Unlike

protooncogenes, which cause tumors by producing a protein that stimulates cellular proliferation and requires only one abnormal copy of the gene to produce the abnormal gene product, a tumor suppressor gene requires a critical mutation of both copies (alleles) of the gene for the normal suppressor gene product to be absent or inactive. As with other tumor suppressor genes, the germ-line mutation produces 1 abnormal allele in all the cells of an affected individual, and presumably, a “second hit” of the other allele occurs later, in the tissue from which a tumor arises (Knudson 1985). Indeed, evidence for somatic inactivation of both NF2 alleles is found in the majority of schwannomas and meningiomas that arise in these patients (Hung et al., 2000; Lamszus et al., 2000).

The protein product, merlin, has a high degree of homology with a family of cytoskeletal proteins (ERM proteins) that link the actin skeleton of the cell to cell adhesion membrane proteins important for cellular remodelling and growth regulation (Trofatter et al., 1993). These proteins function looks like essential for the formation of specialized subcellular structures as well for adhesion and migration activities (McClatchey et al., 1998). Schwann cell cultures isolated from schwannomas of NF2 patients with identified germ-line mutations have shown striking differences in morphology, cell-cell contacts, and growth compared to normal control Schwann cells (Rosenbaum et al 1998). These findings permit to theorize that disruption of cytoskeletal organization by alteration in NF2 gene and protein product is involved in the genesis of tumors. Another approach to determine merlin functions, has involved molecules that interact with it and potentially transduce its growth suppressive signal. Merlin, like the ERM proteins, has an amino-terminal cell surface glycoprotein-binding domain (called FERM domain) with 3 subdomains that may mediate specific interactions with critical protein binding partners (Kang et al 2002; Shimizu et al 2002). Several candidate proteins include: CD44 (Herrlich et al., 2000; Morrison et al., 2001), actin (Xu & Gutmann, 1998), beta II-spectrin (Scoles et al., 1996), SCHIP-1 (Goutebroze et al., 2000), HRS (Scoles et al., 2000), NHE-RF (Gonzalez-Agosti et al., 1999) and beta1-integrin (Obremski et al., 1998). The merlin-actin association is tightly regulated by protein phosphorylation (Morrison et al 2001; Kissil et al 2002), and it is important for localizing merlin to the proper subcellular location (Fernandez-Valle et al., 2002). The association of merlin with CD 44 raises the possibility that merlin could function as a molecular switch. The merlin’s ability to associate with CD44 may be influenced by merlin’s phosphorylation state, intramolecular complex formation, and its interactions with other binding partners. With these influences, merlin may determine whether it traduces a growth stimulatory or inhibitory signal (Pearson et al 2000). Merlin also associates with other Schwann cell growth regulators. Hepatocyte growth factor-regulated tyrosine kinase substrate binds through residues in the C-terminal domain not shared with ERM proteins (Scoles et al 2000). This factor is one of the most potent stimuli for Schwann cell proliferation and motility (Gutmann et al 2001).

Approximately half of the cases of NF2 appear to be the result from a new gene mutation (Evans et al., 1992a) although the mutation rate is lower than of NF1. The mechanism of mutation is currently unknown, but has been shown to be related to increased paternal age (Evans et al., 1992a). Further analysis has shown a clearer link between the risk of mosaicism inheritance by offspring and age of vestibular schwannoma diagnosis (Evans & Wallace, 2009). Patients who inherit NF2 from their mothers generally have an earlier age of presentation and a more rapidly progressive course (Eldridge, 1990; Evans et al., 1992a).

This suggests the possibility of gene modification by a mechanism of maternal imprinting (Hall, 1990). On the other hand, different NF2 mutations result in varying disease courses. Point mutations are found in about 55% of cases clinically diagnosed, and genotype-phenotype correlations have been established based on the relationship between NF2 mutations and clinical severity (Parry et al., 1996; Evans et al., 1998a). Patients with constitutional mutations that produce a truncated protein with loss of merlin expression (generally nonsense or frameshift mutations) have an earlier onset, number and rate of growth of CNS tumors (Selvanathan et al 2010). Missense, in-frame mutations or large deletions result in the generation of merlin proteins defective in their negative growth regulatory ability (Gutmann et al., 1998b), with milder disease (Parry et al., 1996; Evans et al., 1998). However, exception to these correlations have been reported (Scoles et al 1996), suggesting that other factors different to the class of mutation are likely to be responsible for a portion of the clinical symptoms (Welling 1998).

Currently, linkage analysis using tightly-linked genetic markers has been available to determine NF2 mutations carrier status in at-risk individuals in families with this disease from at least two generations. The relatively low detection rate of mutations (55%) may be partially related to somatic mosaicism in sporadic cases (Bijlsma et al., 1997; Evans et al., 1998; Kluwe et al., 1998), as well as a significant number of gene deletions observed.

The child of a parent with NF2 has a 50% risk of having the disease (Evans et al 1992a), and even no mutation was detected due to the common gonosomal mosaicism found, penetrance is thought to be complete, with initial symptoms until age 35 to 60 (Evans et al 1992b; Eldridge 1990). Newer techniques for detection of protein truncations have been developed, but they are not still validated for NF2 patients without bilateral vestibular schwannomas, and its ability to detect mosaic mutations remains untested (Gutmann et al, 1998b). Since RNA mismatch cleavage method is available, tumors mutations are detected with higher sensitivity, so this technique could be used as a convenient method for germline NF2 mutations screening (Faudoa et al 2000; Hung et al 2000)

These and possibly other streamlined methods may eventually make the genetic diagnosis of NF2 in suspected cases, including sporadic ones in the future (Bourn et al 1994; Rouleau, 1994; Merel et al 1995; Legoix et al 1999). At present, in most families with more than one affected individual, linkage analysis still remains the test of choice, as this will provide a greater than 99% certainty of NF2 diagnosis.

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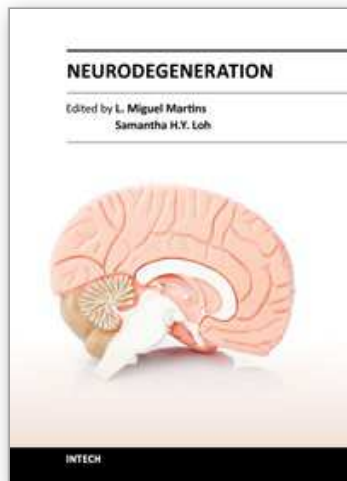
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Neurodegeneration

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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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