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RESEARCH ARTICLE

The Different Characteristics of Neurofibromatoses and Their Neurologic, Cognitive and Psychiatric Alterations

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Abstract

Neurofibromatoses are neurocutaneous diseases with similar pathogenesis. The first description of NF1 is due to von Recklinghausen in 1882, while a NF2 case was known since 1822 but remained joined to NF since 100 years later as central variant; both display autosomal dominant transmission. Only in 1993 these diseases were recognized as totally different, being carried by different chromosomes (17 for NF1, 22 for NF2). NF1 is much more frequent than NF2, featuring cutaneous, sub-cutaneous and plexiform neurofibromas, Lish nodules, café-au-lait macules (CALMS), freckling, learning disabilities and skeletal malformations together with Central Nervous System and Spinal tumors (gliomas, astrocytomas and meningiomas); 10% possibility of malignant transformation exists. Neurologic, cognitive and Psychiatric abnormalities are reviewed much more deeply. The cardinal manifestation of NF2 is bilateral cochlear-vestibular schwannoma with additional tumors (cranial and radicular schwannomas, meningiomas, brain and spinal ependymomas); cutaneous signs are less frequent than in NF1, but the prognosis is worst. In Schwannomatosis several schwannomas arise on peripheral nerves with pain at pressure; VIII° nerve tumors are lacking. Legius syndrome is carried by chromosome 15, has cutaneous alterations like NF1, learning disabilities, but non tumor predisposition. Other syndromes featuring CALMS exists together with tissue abnormalities, while Proteus (or Elephant-man) syndrome is characterized by asymmetrical tissue overgrowth with deformities.

Keywords: Neurofibromatosis 1; Neurofibromatosis 2; Schwannomatosis; CALMS; Legius Syndrome; psychiatric disturbances

Neurofibromatoses (**NF**s) are neurocutaneous diseases (phakomatoses) that share a similar pathogenesis: the alteration of tumour growth mechanisms.

Although they have the same name "neurofibromatosis" (**NF**), type 1NF (**NF1**) and type 2NF (**NF2**) are quite different diseases, genetically and clinically, through with some common features. The first typical case of NF1 was reported by Tilesius (1793), [1] but the disease was fully described by in 1882 (von Recklinghausen, 1882) [2] and since then is known by this abbreviation. **NF2**was first described by Wishart since 1822 [3] and remained grouped with NF1 until 100 years later [4] Only later was it definitely recognized as a different disease [5,6].

Here we describe the common characteristics of these two conditions, highlighting the differences and the differential diagnosis from the few other similar cases.

Both diseases are inherited and transmitted with an autosomal dominant pattern; they are linked by similar pathogenic mechanisms, but are carried by different chromosomes. **NF1** is related to neurofibromin, a tumour suppressor gene encoded by chromosome 17; **NF2** is connected to merlin or schwannomin, a different tumor suppression protein coded by chromosome 22. For both conditions the so-called "two hit hypothesis" was proposed by Knudson in 1971 [7] patients are heterozygous and a second somatic event is needed to inactive both the alleles. In addition, both diseases have a high rate of penetrance with mosaicism; 20-30% NF2 cases show this feature.

Epidemiologically the incidence of the two diseases is quite different: **NF1** is seen in 1:3000-5000 people, while **NF2** is much rarer seen in approximately 1:50000 people.

The **clinical aspects** of **NF1** comprise cutaneous and subcutaneous neurofibromas, plexiform tumours, Lisch nodules, café au lait spots (CALS), freckling, skeletal malformations e.g. short stature, macrocephalia, tibialis pseudoarthrosis, sphenoid wing as well as CNS tumours (optic pathways glioma, astrocytomas and meningiomas) and spinal cord tumours. Regression toward malignant disease in reported in 10% of cases, with higher risk for plexiform tumours. Morbidity is linked to tumours growth, with compression of important tissues, and malignant transformation. Mortality is higher than normal and worse in women [8].

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Riccardi [9] described eight types of NF (Table 1), a classification no longer used since the *National Institute of Health* (1988) [10] criteria defined, possible and probable variants (Table 2). Recently a more detailed version of the classical "criteria" has been proposed [11].

The clinical manifestations of neurofibromatosis were classified by Huson [12] as "major", "minor" and associated complications: "major" manifestations are specific to NF, affect most patients, and are the basis of the diagnostic criteria NHI [10] - CALS, axillary freckling, peripheral neurofibromas and Lisch nodules; "minor" manifestations are also specific to NF and frequently appear, but are not considered diagnostic criteria. Macrocephaly and short stature are considered "minor".

The **Legius syndrome** [15] or **NF type 1-like syndrome** (**NFLS**), [16,17] is linked to an alteration of Sprouty-related, EVH1 domain containing 1 (SPRED1) on chromosome 15, characterized by cutaneous CALS and freckling without fibromas or other tumour predisposition but with learning disabilities and behavioural modifications. This form, transmitted with an autosomal dominant pattern, is clinically similar to NF1, but has a better prognosis as more is no risk of malignant transformation. Its frequency is not yet fully known (Table 5).

Behavioral and Neurological Abnormalities:

Learning disabilities and Scholastic difficulties are very common in young patients affected by NF1 (50-75 %) and often are a big concerns for parents [18,19]; much rare is a clear intellectual disability, reported in 6-7 % of patients; a condition belonging to Autism spectrum disorder, complete or partial, is seen in up to 25% of cases [20] (Figure 1,2). Behavioral problems [21] are seldom reported but are much more commons in presence of intellectual disability; frequently these patients bring also in adult age the problems linked to the ADHD syndrome which started in the young age.

Seizures may be encountered, with a frequency not dissimilar

Type	Inheritance	Characteristics
Neurofibromatosis NF1 others	AD	CALM, neurofibromas Lish, frecking, CNS neoplasms,
Acoustic NF2 few	AD	Bilateral 8th nerve Schwann, CALM and neurofibromas
Mixed NF3	?	1 and 2 combination
Variant NF4 neurofibromas,	?	Changes in CALS, CNS neoplasms, Lish nodules
Segmental NF5 and/or	Not known	Segmental neurofibromas CALS
Familial CLAS NF6	?	CALS
Late onset NF7	?	After the third decade of life, neurofibromas, few CALS
Unspecified NF8	?	Variable signs

NF1 - classical, NF2-acoustic, NF3 - mixed, NF4 – variant, NF5- segmental, phenotype, NF6 – familial CLS, NF7 –Schwannomatosis or late onset, NF8 – unknown and variable.
AD, autosomal dominant
CALS, Cafè-au-lait Spots
CALM, Cafè-au-lait Maculas.

Table 1: Classification of neurofibromatosis [9].

• Six or more CALS or hyperpigmented macules = 5 mm in diameter in pre-puneral children and 15 mm in post-puberal patients.
• Two or more axillary or inguinal freckles.
• Two or more typical neurofibromas or one plexiform neurofibroma.
• Optic Nerve Glioma.
• Two or more iris hamartomas (Lisch nodules), often identified only by slit-lamp examination by an ophthalmologist.
• Sphenoid dysplasia or typical long-bone abnormalities such as pseudo-arthrosis.
• First-degree relative (mother, father, sister, brother) with NF1.

Table 2: Two of the seven clinical criteria used to diagnose NF1 are needed for a definite diagnosis, in the absence of alternatives (neurofibromatosis. conference statement (from National Institutes of Health Consensus Development Conference. 1988) [10].

1. Bilateral Schwannomas of the eighth cranial nerve diagnosed by MRI or CT (biopsy is not necessary).
2. First-degree relative with F2 and: a) Unilateral schwannoma of the eighth cranial nerve, with early onset (age <30 years). b) Two of the following: Meningioma-Glioma-Schwannoma, Posterior sub-capsular lenticular opacity (juvenile cortical cataract) in children.
3. Unilateral schwannoma of the eighth cranial nerve diagnosed by CT or MRI with early onset (in a patient under 30 years) and two of the following: Meningioma-Glioma-Schwannoma, juvenile cortical cataract.
4. Multiple meningiomas (>2) and: a) Unilateral schwannoma of the eighth cranial nerve. b) 2 of the following: Glioma-Schwannoma, Juvenile cortical cataract

Table 3: NF2 is diagnosed in individuals with one of the following:

- Definite

1. Age >30 years and two or more non-intra-dermal schwannomas, at least one with histologic confirmation and no evidence of vestibular tumor on MRI scan and no known NF mutation, or
2. One non vestibular schwannoma plus a first-degree relative with schwannomatosis

- Possible

1. Age <30 and two or more non-intra-dermal schwannomas, at least one with histologic confirmation and no evidence of vestibular tumor on MRI scan and no known NF mutation, or
2. Age >45 and two or more non-intra-dermal schwannomas, at least one with histologic confirmation and no symptoms of 8th nerve dysfunction and no NF2, or
3. Non vestibular schwannoma and first-degree relative with schwannomatosis

- **Segmental.** Diagnosed as definite or possible but limited to one limb or no more than 5 contiguous segments of spine.

Another set of criteria are:

- Two or more non intra-dermal (cutaneous) schwannomas
- No evidence of vestibular tumour
- No known NF 2 mutation

or

One pathologically confirmed non vestibular schwannoma plus a first-degree relative who meets the above criteria.

Table 4: Diagnostic criteria for Schwannomatosis (from Ferner et al., 2011) [14]

Syndrome	Inheritance	Chromosome	Cutaneous	Other
Legius	AD	15	CALM frecking	Learning disabilities, behavioral modifications
Familial cafè au Lait spots	?	17? Ring11	CALM	None
Noonan	AD?	12	Frecking	Palpebral ptosis, fissuration, hypertelorism, cardiomyopathy, pulmonary stenosis, short neck, coagulopathy, short stature.
Watson	AD	15q11.2	Frecking CALM	Neurofibromas, pulmonary stenosis, Lisch, short stature
Leopard	AD	?	Frecking CALM	Cardiomyopathy, hypertelorism, pulmonary stenosis, deafness, genital abnormalities.
Turcot (M.R.C.S.)	?	17		Colon-rectal cancer medulloblastoma
Proteus	?	10 or 16	Nevus	Tissue overgrowth
McCune Albright	?	20q13.3	Large spot	Polyostotic fibrous dysplasia, precocious puberty

AD, Autosomal Dominant; CALM, Cafè-au-Lait Maculas; M.R.C.S., Mismatch-Repair-Cancer-Syndrome.

Table 5: Frequency of Syndrome.

Figure 1: For years neurofibromatosis was wrongly associated to the condition of elephant-man “as it is frequently stereotyped, misunderstood and often unheard of” (The Independent, 21 may 2015) [19].

Figure 2. Reconstruction of the CRO-Magnon facial aspect with the characteristic benign tumor.

from the one observed in the general population; again, they might appear as comorbidity when other neurologic or psychiatric problems are present [22].

Unidentified Bright Objects (UBO) are frequently well identified at MRI and are related to abnormalities of myelin sheaths due to increased content of water or to other dysplasia; the functional significance of these quite visible alterations is at present unknown, since they are not related to any of the clinically relevant problems. Moreover, it has been shown that

demyelination is not so rare in NF: Multiple Sclerosis has been calculated in higher frequency in NF than in population [23].

Minor clinical complaints are sleep disturbances or Headache [24]; in these cases, one should carefully evaluate if the pain is related to a real condition like migraine or tension headache, typical or atypical facial pain syndrome versus a conversion or others functional disturbance much related to the complex discomfort generated by the presence of fibromatous lesions and to their appearance. Pain in association with plexiform neurofibromas is also common and must be distinguished from the pain that may be the first sign of transformation to a Malignant Peripheral Nerve Sheath Tumor (MPNST). Pain is a rule in Schwannomatosis due to the particular origin of tumors but isn't always related to nerve compression by the growing cells [25,26].

At peripheral level is possible to observe the signs of neuropathy, or mono neuropathy linked to single fibromas compressing the nerve or limiting the free space around it at canonical tunnels, or frank peripheral neuropathy with marked muscular atrophy and loss of strength in the four limbs with distal and symmetrical distribution [27]; in around 10-15% of patients is possible to encounter painful and growing mass with expansive and malignant transformation (MPNST).

As minor general complaints one should not forget the Macrocephaly [28] and the Short stature [29].

The main problem is to define a clear structural abnormality that could play an important role in the pathogenesis of the relevant clinical problems:

- Acqueductal stenosis
- Cerebrovascular diseases
- Spinal meningoceles
- Tumors in NF1 (meningiomas, astrocytomas, gliomas)
- Optic Pathways Glioma
- Hydrocephalus
- Cortical Dysplasias
- Sphenoid Dysplasia
- Spinal Myelo or Meningocyele
- NF1 Multiple Sclerosis

Molecular Pathogenesis could be searched in intrinsic pathology, GABAergic dysfunction, Dysmielination, increased fluid of White Matter, abnormal functional connectivity [30], abnormal resting state, reduced Gray Matter Volume (GMV) in amygdale, frontal subcortical brain vulnerability, functional connectivity alterations, gyrification alterations, oligodendrocytes abnormalities or reduced neural activation.

The **cardinal manifestation** of **NF2** is bilateral vestibular schwannoma in cases with several additional CNS tumours (schwannomas of other cranial, radicular or peripheral nerves, meningiomas, gliomas, ependymomas in the CNS and spinal cord). The final criteria (Table 3) were set by National Neurofibromatosis Foundation Clinical Care Advisory Board (NNFCC) in 1997 [13].

Cutaneous neurofibromas and other manifestations like CLS and plaques are less frequent than in NF1; the site and the growth of tumours, despite surgery and antiblastic therapy (bevacizumab trials) cause high mortality (mean age at death is around 30 years).

Diagnostic imaging is extremely useful to locate focal areas of T2 hyper intensity corresponding to **NF1** tumours though the widespread use of MRI remains controversial in this disease on account of its costs. However, close cranial and spinal MRI follow-up of lesions in **NF2** is always required.

Schwannomatosis is a third form of neurofibromatosis: several schwannomas grow on peripheral, intracranial and spinal nerves, without vestibulo-cochlear lesions or cutaneous manifestations. The pain related to lesions' pressure is the other common feature of this disease. Incidence and rate of transmission are similar to that of NF2 but the schwannomatosis gene is not clear. The criteria for the diagnosis of Schwannomatosis are shown in (Table 4) [14].

The last clinical syndromes (**Noonan, Watson, Leopard, Turcot**, **Inherited familial CLS Spots, McCune-Albright**) involve similar cutaneous manifestations (CALS) with other organ or systemic abnormalities (Table 5) but their incidence is far less frequent [18] and few cases has been described. The first three syndromes (Noonan, Watson and Leopard) are inherited as autosomal dominant, show evidence of CALS or maculas (CALM) with Freckling and varying degrees of pulmonary stenosis, cardiomyopathy and dysmorphic changes or abnormalities of several tissues. Turcot syndrome (or Mismatch-Repair-Cancer-Syndrome) combines colon-rectal polyposis with medulloblastoma, while McCune-Albright features a large brown spot with polyostotic fibrous dysplasia and endocrine dysfunction with precocious puberty.

Proteus, or elephant-man syndrome, requires few words of comment; it features asymmetrical tissue overgrowth with deformities. It is linked to Joseph Merrick, a 19th-century Englishman who suffered extreme disfigurement from an unknown disease now believed to be Proteus. He tried finally to profit from his own deformities but died at 27 years of age, probably choked during sleep. He was the hero as protagonist of the famous movie by David Linch (1980) as the apotheosis of a stigma. "for years neurofibromatosis was wrongly associated to the condition of elephant-man "as it is frequently stereotyped, misunderstood and often unheard of" (The Independent, 21 may 2015) [31].

A recent observation regards the frontal bone erosion in the CRO-magnon ancestral skeleton interpreted as caused by schwannoma or, most probably neurofibroma [32].

For an exhaustive description of neurocutaneous syndromes see M. Ruggieri et al [33] and R. Ferner, Huson and Evans [34].

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