

Cutaneous manifestations in neurofibromatosis type 1

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Abstract

Objective. To better understand the real prevalence of cutaneous manifestations, in Neurofibromatosis type 1.

Materials and Methods. We reviewed all clinical charts of 1102 NF1 patients followed by February 1983 to February 2020 at the "Sapienza" University of Rome, Italy. NF1 patients are seen usually every year by a dermatologist.

Results. Café-au-lait macules were shown in 1063 patients (96.5%), axillary and inguinal freckling in 991 (90%) and neurofibromas in 861 (78.1%). Other skin manifestations included: lipoma (6.2%), nevus anemicus (3.9%), psoriasis (3.4%), spilus nevus (3.2%), juvenile xanthogranuloma (3.2%), vitiligo (2.3%), Becker's nevus (1.9%), melanoma (0.7%) and poliosis (0.5%).

Conclusions. Neurofibromatosis type 1 is a multisystem disorder primarily involving the skin and nervous system. The clinical manifestations are extremely variable even within a family. This study was performed to delineate the prevalence of cutaneous manifestations in NF1. *Clin Ter 2020; 171 (5):e371-377. doi: 10.7417/CT.2020.2242*

Key words: Café-au-lait macules, cutaneous manifestations, freckling, neurofibromatosis type 1, neurofibroma, neurofibromin

Introduction

Neurofibromatosis type 1 (NF1), formerly called von Recklinghausen disease, is a rare genetic disorder with an autosomal dominant transmission and an estimated incidence of 1:2500-3000 live birth. In about 50% of individuals, the disease is caused by a spontaneous mutation and in the other 50%, the disease is inherited (1-3).

NF1 gene that maps on chromosome 17q11.2, is characterized by a wide mutational spectrum, with more than 3.000 genomic variants reported so far (4). Approximately 10-15% of patients harbor missense or inframe mutations: in this case validation may be problematic since less functional data are available for this protein. Importantly, a relevant

fraction of exonic point mutations affects splicing, behaving like classical inactivating alleles (5). There are some genotype-phenotype correlations for specific NF1 variants, but much of the variability in phenotype has been attributed to stochastic events, environmental factors or modifier genes. The NF1 gene encodes the protein neurofibromin, a 220 kDa guanosine triphosphate (GTP)ase-activating cytoplasmatic protein that is involved in cell growth regulation mechanisms by regulating the RAS protein, specifically by converting RAS-GTP active form to RAS-GDP inactive form. The consequence of the lack of neurofibromin results in an excess of the RAS-GTP active form, which promotes excessive cell growth, leading to deregulation and tumorigenesis (6-9). Neurofibromin is expressed in Schwann cells, melanocytes, leukocytes, the adrenal gland, and tissues such as the central nervous system (10,11).

The diagnosis of NF1 is based on the clinical criteria recommended by the NIH Consensus Conference which include multiple café-au-lait macules (CALMs), cutaneous or subcutaneous neurofibromas, plexiform neurofibromas, axillary or inguinal freckling, optic gliomas, distinctive osseous lesion and iris Lisch nodules and a first-degree relative with NF1. Two of these criteria must be met in order to diagnose NF1 (12). NF 1 may involve almost every organ system in the body, with considerable inter-familial and intra-familial variation, there may be ophthalmologic, musculoskeletal, cardiovascular, gastrointestinal, autoimmune, endocrine, central and peripheral nervous system, and learning alterations (13-24). Patients with NF1 have an increased susceptibility to develop tumors such as pheochromocytoma, sarcoma, melanoma, breast cancer, leukemia and gastrointestinal stromal tumors (25-28).

To better understand the real prevalence of cutaneous manifestations, we reviewed all clinical charts of 1102 NF1 patients followed by 1983 to 2020 in our Rare Disease Center.

Methods and patients

We reviewed all clinical charts of 1102 NF1 patients followed by February 1983 to February 2020 at the “Sapienza” University of Rome, Italy. NF1 patients in our clinic are seen usually every year by a dermatologist. Diagnosis of NF1 was made according to criteria from the NIH Consensus Conference. Patients were aged 5-85 years, included 583 females and 519 males.

Results

Four hundred ninety-nine (45.3%) had family history of NF1. CALMs were shown in 1063 (96.5%), axillary and inguinal freckling in 991 (90%) while neurofibromas in 861 (78.1%). Other skin manifestations included: lipoma (6.2%), nevus anemicus (3.9%), psoriasis (3.4%), spilus nevus (3.2%), juvenile xanthogranuloma (3.2%), vitiligo (2.3%), Becker’s nevus (1.9%), melanoma (0.7%) and poliosis (0.5%).

Lipoma was present in 69 cases (6.2%): 59 patients had single lipoma, 9 had 2-4 lipomas while one patient had multiple lipomas (>30) of the trunk. Lipoma diameter varied from 1 to 6 cm. Nevus anemicus (NA) was present in 43 cases (3.9%). In patients younger than 16 years (273) NA was present in 20 cases (7.3%) while in patients with NF1 aged over 16 years NA was present in 23 cases (2.7%). Thirty-one patients showed NA as a single lesion, whereas in 12 patients it was present as a multiple lesion; diameter varied from 0.5 to 8 cm. It was located on the back (20 cases), on the chest (9 cases), on the neck (6 cases), on the abdomen (5 cases) and on the limbs (3 cases). Psoriasis was present in 37 cases (3.4%): 19 patients had a psoriasis vulgaris, 15 patients had a psoriasis of the scalp, 2 patients had an inverted psoriasis, while one patient was also diagnosed as psoriatic arthritis. Spilus nevus (SN) was present in 35 cases (3.2%): in 21 patients SN was localized at the level of the trunk while in 14 cases was localized at the level of limbs. SN diameter varied from 3 to 15 cm. Juvenile xanthogranuloma (JXG) was present in 35 cases (3.2%). The number of JXGs varied greatly from patient to patient. Although the JXGs occurred everywhere on the body surface except for the palmoplantar areas, a clear predilection for cephalic skin was observed (86%). Vitiligo was present in 25 cases (2.3%): 7 patients (28%) had a generalized vitiligo while 18 (72%) patients had a localized form of disease. Becker’s nevus (BN) was present in 21 cases (1.9%): in 19 patients, BN was localized at the level of the upper limb while in 2 cases was localized at the level of the lower limb. BN diameter varied from 8 to 23 cm. Melanoma was present in 7 cases (0.7%). The diameter of the melanoma, in terms of major axis, ranged from 0.9 to 4.5 cm. The Breslow thickness of the primary lesion ranged from 0 to 3.5 mm. Poliosis was present in 6 cases (0.5%): in 4 cases the lesion was localized at the level of the parietal area, in two cases at the level of the temporal area.

Discussion

In NF1, cutaneous findings, which are readily apparent on visual inspection, are usually the first sign of the disease. Three of these, CALMs, freckling on flexural areas and neurofibromas are particularly relevant because they comprise 3 of the 7 clinical diagnostic criteria of the NIH.

The largest and best known cutaneous manifestation in NF1 are the CALMs, which are in general typically flat, uniformly hyperpigmented macules with regular, well-defined borders. Atypical CALMs have irregular borders and inhomogeneous pigmentation and are less likely to be associated with NF1 than typical CALMs (Fig. 1). The occurrence of CALMs appears to be stochastically dispersed in the skin (29). CALMs are a hallmark of NF1 but they are also found in other genetic conditions such as Legius syndrome, McCune-Albright syndrome, Watson syndrome, Noonan syndrome, tuberous sclerosis, LEOPARD syndrome, Cowden disease, multiple endocrine neoplasia 1 and 2B, ataxia-telangectasia and Bloom syndrome (30-34). In addition, solitary CALM is a common finding occurring in the general population (0.3-36.3%) (35,36). In NF1, CALMs, are usually present at the time of birth or they become evident shortly afterwards. Their size increases in proportion with the growth of the child, with a diameter of more than 15 mm in adults and 5 mm in children and they take on a darker tone during childhood (37). Histologically, they have increased melanin in melanocytes and basal keratinocytes, but no melanocyte proliferation (38).



Fig. 1. CALMs on the trunk in a patient with NF1.



Fig. 2. Axillary freckling in a patient with NF1.



Fig. 3. Cutaneous and subcutaneous neurofibromas in a patient with NF1.

Freckling, traditionally known as the Crowe sign, are small pigmented lesions (1 or 2 mm) of light brown color that are not usually present at birth but rather develop during childhood, usually from age 2 years onwards (Fig. 2). Their appearance is similar to solar-induced freckling, but in NF1 they occur typically in areas with minimal to none sun exposure; they are located to body regions (axillae, inguinal regions, apposing skin surface below the breasts in women, base of the neck, upper eyelids) where the skin is thought to be influenced by certain physical properties such as increased skin temperature, absence of light exposure and skin secretions like sweat (39). Some patients develop more diffuse freckling. Their incidence is variable, ranging from 21% to 93.7%, even in series that only included pediatric patients (40). The histological and ultrastructural findings are identical to those of the CALMs, and so some authors propose to include freckles and CALMs in the same diagnostic criterion (41). Freckles can appear in other genetic diseases such as Legius syndrome, LEOPARD syndrome, Cowden disease and Peutz Jeghers syndrome.

Neurofibromas, the hallmark tumors of NF1, are benign tumors of the peripheral nerve sheath. They exhibit extensive cellular heterogeneity (Schwann cells, perineural cells, mast cells, fibroblasts and axons in an extracellular matrix) and can be classified into cutaneous, subcutaneous and plexiform neurofibromas. Cutaneous and subcutaneous neurofibromas usually appear in late childhood or early adolescence (57-99% of patients) while plexiform neurofibromas usually occur from birth to 18 years of age (20-30% of patients) (42). Cutaneous neurofibromas are more frequent, and usually increase in number with increasing age. There are 2 critical periods of development, adolescence and pregnancy, for presence of the progesterone receptors (43). In adults

numerous cutaneous neurofibromas are usually present, but the total number varies from a few to many thousands. Their most typical morphology is one of a raised, sessile lesion of soft or elastic consistency, that is depressible on palpation (buttonholing) (Fig. 3). Solitary neurofibromas can be seen healthy individuals. Plexiform neurofibroma is a benign proliferation of the neural element of peripheral nerve that occurs particularly in the head and neck region and in deep body regions. Regardless of location, they can cause significant morbidity because of pain, disfigurement, local compression, and loss of function of nerves, great vessels, and airways. Although these tumors are usually benign, there is a 2-5% chance of malignant transformation in the setting of NF1 (malignant peripheral nerve sheath tumor; MPNST). The natural history of a plexiform neurofibroma varies, as some lesions remain asymptomatic superficial lesions, while others progress into large invasive disfiguring lesions as seen in our case (44-46).

Lipomas are defined as soft masses of adipose (fat) cells which are often encapsulated by a thin layer of fibrous tissue. The association with NF1 has been rarely reported. In our case lipomas were present in 6.2%, a higher incidence than in the general population (0.21%). The development of lipomas could be justified by neurofibromin deficiency as with other tumors in NF1 (47-49).

NA is congenital, nonprogressive skin anomaly that appear as pale spots with sharp margins sometimes surrounded by smaller satellite spots. In general, it tends to appear at birth or in early childhood and is most frequently localized on the trunk. Pathogenesis of NA seem to be due to a local hypersensitivity of cutaneous arteriolar α 1-adrenergic receptors (AR) to catecholamines. It has been proposed that, in NF1, neurofibromin-deficient tissues exhibit an imbalance

between α - and β -adrenergic receptors which leads to increased α -adrenergic stimulation. Some studies assessed the association between NF1 and NA. Tadini we found NA in 8.85% of 565 NF1 patients. Marque, in a multicenter case-control study of 151 patients with NF1 found NA in 51% of the cases (77 patients). In our study, we found NA in 3.9% of all NF1 patients examined (50-52).

Psoriasis is an inflammatory, immune-mediated and genetically determined skin disease characterized by hyperproliferation of keratinocytes, impaired barrier function and pronounced infiltration of inflammatory cells. The association with NF1 has been rarely reported. In our case psoriasis was present in 3.4%. Reduced levels of neurofibromin and an increased activation of Ras, characteristic of the NF1, were also demonstrated in psoriatic lesions, although the primary events leading to these alterations remain to be elucidated. Alterations in activity of Ras causes hyperproliferation, altered cytoskeletal organization and altered cell adhesion. Moreover, Endo found that defects in the regulation of the Hedgehog signaling pathway, due to deficiency of neurofibromin, contributed to the hyperproliferation of lesional keratinocytes in psoriasis (53-56).

NS is a tan to light brown patch of various sizes and sites characterized by multiple small darker brown macules superimposed, which can be flat or raised and irregular in nature (Fig. 4). The association between NF1 and SN has been reported very rarely. In our case, we found NS in 3.2% of the patients. This correlation could be justified by the release of growth factors including nerve growth factor, and stem cell factor by fibroblasts. Moreover, were identified in NS activating HRAS mutations that promotes cell growth predominantly through activation of the mitogen-activated protein kinase (MAPK) signaltransduction pathway (57,58).

Juvenile xanthogranuloma (JXG), the most common non-Langerhans cell histiocytosis, consists of an asymptomatic yellow brown papule or nodule, usually solitary, preferentially localized on the head and neck. It appears in the early years of life and is usually self-healing and rarely associated with systemic manifestations. According to some authors the presence of JXG in patients with NF1 is consi-

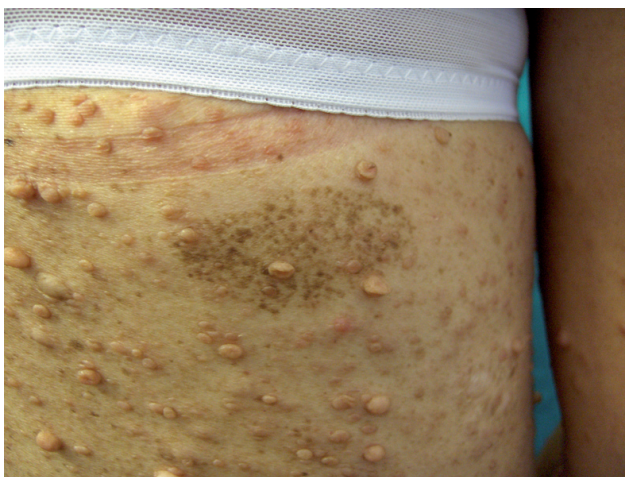


Fig. 4. Spilus nevus and neurofibromas in a patient with NF1.



Fig. 5. Vitiligo and neurofibromas on the trunk in a patient with NF1.

dered awarning sign for juvenile chronic myelomonocytic leukemia (JCMML). Estimated prevalence in patients with NF1 ranges from 0.7% in adults to 37.5% in children. In, our case, JXGs were present in 3.2% of all NF1 patients examined. The presence of a defect in the Ras pathway in JXG has not been investigated, although a recent study found recurrent Ras mutations in Erdheim-Chester disease, which is also a non-Langerhans cell histiocytosis (59-62).

Vitiligo is one of disorders of melanin pigmentation characterized by progressive macular depigmentation of varying sizes or shapes with a tendency to progress (Fig. 5). The association between vitiligo and NF-1 has been rarely reported. Neurofibromin also has an anti-proliferative effect on the immune system. Abnormal production of this protein suppresses expression of FAS-ligand, preventing apoptosis of CD4+ T-cells. Decreased T cell apoptosis may be an important factor for the development of autoimmune diseases. Moreover, vitiligo observed in NF may be a consequence of distinct aberrations in melanosome size and distribution in melanocytes derived from NF-1 patients as reported in the literature. In fact, it was described that neurofibromin is also present on the melanosomal membrane and forms a complex with amyloid precursor protein (APP); the NF-1 gene mutation modifies this interaction influencing the transport of melanosome and it might be relevant on the etiopathogenesis of pigment-cell-related manifestations in NF-1, as café-au-lait macules, hypopigmented macules and also vitiligo (63-65).

BN is a relatively common cutaneous hamartoma which usually affects young males and is characterized by a unilateral hyperpigmented, hypertrichotic patch on the upper trunk or proximal upper extremities. The association with NF1 has been rarely reported. Mahè, in a study involving 614 patients with NF1, observed a patient with BN. In our case BN was presented in 1.9%. Several hypotheses have been suggested such as the production of pro-opiomelanocortin that induces the production of melanocyte-stimulating hormone, tumour-necrosis factor- α and interleukin-8 and the production of growth factors including nerve growth factor, hepatocyte growth factor and stem cell factor by fibroblasts in the dermis of neurofibroma (66-68).



Fig. 6. Poliosis in a patient with NF1.

Melanoma is a malignant tumor that arises from epidermal melanocytes. Its relationship to NF1 is controversial; a variety of reports have been published in cutaneous and extracutaneous melanoma, but no true incidence has been established. Frequencies vary between 0.1% and 5.4%. Seminog found 19 melanoma in 6,739 NF1 patients (0.28%). Uusitalo did not find statistical evidence for an increased incidence of melanoma (0.21%). In a retrospective study, Guillot et al. reported 11 cases of melanoma over a period of 13 years among 671 NF1 patients. Melanoma was found to occur more frequently in women (F:M = 10:1), and young people (median age, 33 years). The mean Breslow depth was 3.2 mm, that is, considerably greater than in other series of patients with melanoma without NF1, perhaps because other pigmented lesions make detection more difficult (69-72).

Poliosis circumscripta is defined as a localized patch of white hair in a group of hair follicles (Fig. 6). The association between poliosis and NF-1 has been reported. Poliosis observed in NF may be a consequence of distinct aberrations in melanosome size and distribution in melanocytes; the NF-1 gene mutation modifies this interaction influencing the transport of melanosome and it might be relevant on the etiopathogenesis of pigment-cell-related manifestations in NF-1, as CALMs and also poliosis (73-76).

Other skin findings in NF1 are pruritus, generalized hyperpigmentation and presence of hypochromic macules (77).

NF1 is a multisystem disorder primarily involving the skin and nervous system. It is characterized by extreme clinical variability, not only among unrelated individuals and among affected individuals within a single family but also even within a single person at different times in life. Cutaneous manifestations are the most frequent alterations in NF1; they are usually the first sign of the disease and their presence is sufficient to make a diagnosis. This study was performed to delineate the prevalence of every cutaneous manifestations in NF1.

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