Neurofibromatosis Type 1: Dermatologists Should Take an Active Role

Sirkku Peltonen
Department of Dermatology, University of Turku, PO Box 52, 20521 Turku, Finland
E-mail: sirkku.peltonen@tyks.fi

Neurofibromatosis is a disease that affects several organ systems. Patients should be evaluated and offered counselling if needed. This is one of the actions the author is asking for from every dermatologist.

The diagnosis of neurofibromatosis type 1 (NF1) should be straightforward for a dermatologist. In addition to stigmata in skin, NF1 is a highly variable disease with symptoms and complications from several organ systems. NF1 is also the most common cancer predisposition syndrome. The diagnosis is often made by dermatologists who also operate on cutaneous neurofibroma tumours. However, the task of a doctor does not end here, since a patient with NF1 should never be left with only a diagnosis. It is the responsibility of the dermatologist to ensure that the NF1 patient is evaluated for the need for genetic counselling and gets adequate referrals to, for example paediatric neurologist, neuro-ophthalmologist, or surgical specialties. Because NF1 is a potentially fatal syndrome, every patient should be provided with the opportunity for regular follow-up visits or consultations with a doctor who is familiar with the syndrome.

Type 1 neurofibromatosis (NF1) was first described by Friedrich von Recklinghausen in 1882. Synonyms for NF1 disease include von Recklinghausen's disease and peripheral neurofibromatosis. NF1 is a genetically different disease from NF2 or central neurofibromatosis, which classically causes bilateral acoustic schwannomas and few skin symptoms.

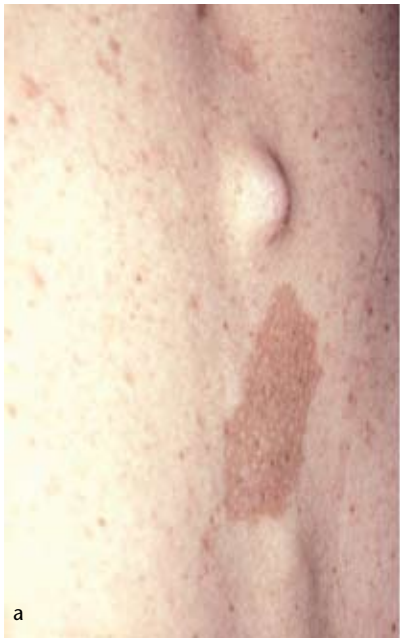
NF1 is an autosomal dominantly inherited disease with a worldwide birth incidence of 1 in 2500–3300 (1–5). Thus, it is one of the most common genetic diseases caused by a mutation in a single gene. NF1 results from mutations in the NF1 gene located in chromosome 17, band q11.2. The NF1 gene was cloned in 1990 (6, 7). The gene is complex and large, spanning more than 350 kb of genomic DNA and contains 61 exons. The gene encodes a protein called neurofibromin, which acts as a GTPase-activating protein (GAP). The GAPs accelerate the switch of active Ras-GTP to inactive Ras-GDP, thus participating in cell regulation. Neurofibromin is considered to be a tumour suppressor protein (8).

All affected individuals are heterozygous for a mutation in the NF1 gene. NF1 has full penetrance, meaning that a mutation in the NF1 gene always causes NF1 syndrome. Half of cases are, however, caused by a new, sporadic germline mutation, which implicates no other affected individuals in the family. At present, hundreds of different mutations and several different mutation types have been reported in the NF1 gene. Thus, taking the size of the gene and the variable mutation types and locations into account, molecular diagnostics is not straightforward. NF1 mutation analyses are available in selected laboratories in Belgium, UK, Austria, Germany and USA, but the cost of the analyses restricts their use in most cases. NF1 diagnosis is thus still based on the clinical signs. The most important stigmata of NF1, café-au-lait macules, axillar and inguinal freckles and neurofibromas, can be recognized readily by a dermatologist. The diagnostic criteria of NF1 were defined in 1987 in a consensus meeting by National Institutes of Health (NIH) and are shown in Table I. Based on these criteria, the penetrance of the NF mutation is virtually 100% by the age of 10 years. Indeed, NF1 can, in over 90% of cases, be diagnosed by the age of 6 years on routine clinical examination (5).

The first sign of NF1 is usually the café-au-lait macules (Fig. 1). The typical café-au-lait spot is 10–30 mm in diameter, ovoid in shape, and uniform in colour. The macules are sharply demar-

Table I. *National Institutes of Health (NIH) diagnostic criteria for neurofibromatosis 1 (NF1). Two or more criteria must be fulfilled for a diagnosis of NF1.*

1. Six or more café-au-lait macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients.
2. Two or more neurofibromas of any type, or one plexiform neurofibroma.
3. Axillary or inguinal freckling.
4. Optic glioma.
5. Two or more Lisch nodules.
6. A distinctive osseus lesion, such as sphenoid dysplasia or pseudarthrosis.
7. A first-degree relative with NF1 according to the preceding criteria.



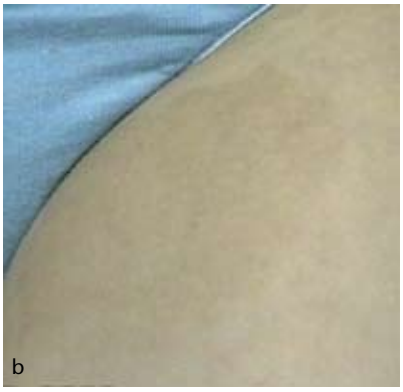


Fig. 1. (a) Café-au-lait macule, freckles and a neurofibroma. *(b)* Café-au-lait macules may be very light brown in the skin of blond Scandinavian children.

cated and slightly darker than the apparently normal skin of the patient. Café-au-lait macules may be visible in a newborn or may appear during the first year. Almost every affected 5- or 6-year-old child has six or more macules. In most cases no other dermatological signs are visible before the age of 4–5 years. Thus a toddler with four or more café-au-lait macules should be examined by a paediatric neurologist and followed up like an NF patient. Individuals with NF2 may have one to four café-au-lait macules and some cutaneous neurofibromas, but the symptoms from the central nervous system tumors are usually dominating over skin signs.

The appearance of the café-au-lait spots is followed by freckles in the flexural areas (Fig. 2). The freckles may be present at birth but usually appear by the age of 6 years. Approximately 90% of adult NF1 patients show freckling, and the typical sites are in axillary, inguinal and neck region, and the upper eyelids. Examination of the underarms is very unusual in

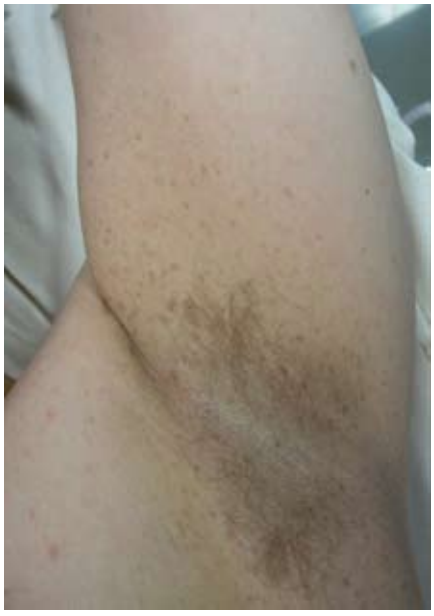


Fig. 2. Freckles in the underarm.

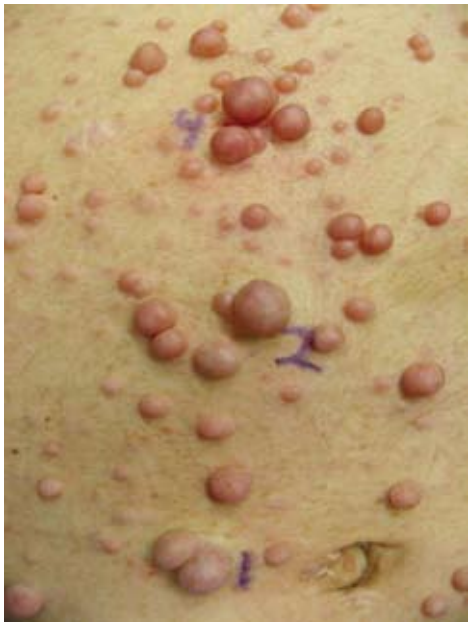


Fig. 3. The number and size of neurofibromas varies between patients and skin areas.

Fig. 4. Protruding cutaneous neurofibromas can be removed by carbon dioxide (CO_2) laser. Cutting a "buttonhole" allows the tumour to bulge out.

general practice and this sign is thus easily ignored. The third hallmark to appear during childhood is Lisch nodules, which are asymptomatic and non-precancerous hamartomas of the iris. Investigation by an ophthalmologist is required to make a distinction between a Lisch nodule and naevus of the iris.

Cutaneous neurofibromas (Fig. 3) typically appear during or shortly after puberty and their number increases during pregnancy. Cutaneous neurofibromas are benign tumours that never undergo malignant transformation. The number and the size of these tumours vary between adult individuals with NF1: there may be only a limited number of tumours with a diameter of few millimetres, while the tumour burden in some individuals may reach thousands. Cutaneous neurofibromas may project out of the skin surface, or reside within the skin. In the latter case the overlying skin may have a purple hue. Cutaneous neurofibromas are usually painless but may periodically be painful or itchy. Cutaneous neurofibromas are ball-shaped and can be safely removed by a traditional surgery or carbon dioxide laser (Fig. 4). The more the tumour protrudes the less is situated under the skin surface, thus removal with a laser will leave a smaller scar (Fig. 5). However, somewhat deeper tumours in hands and feet are safer to be left for hand or plastic surgeons because of the risk of nerve damage.

Neurofibromas may also grow along peripheral nerve trunks and extend to smaller nerve branches and surrounding tissue. These tumours are called plexiform neurofibromas (Fig. 6). Plexiform neurofibromas infiltrate surrounding tissues and are poorly demarcated. Approximately 25% of NF1 patients have at least one plexiform neurofibroma (1, 4). They are considered to be congenital tumours and are often visible at birth. Plexiform neurofibromas may eventually form large and disfiguring tumour masses in the craniofacial region, trunk and extremities. Plexiform neurofibromas are associated with an increased risk of transformation to malignant peripheral nerve sheath tumour (MPNST), formerly known as a malignant schwannoma. NF1 patients have an estimated lifetime risk of about 10% of developing an MPNST. Patients with a plexiform neurofibroma have a higher risk and it has been estimated that approximately 2–5% of plexiform neurofibromas undergo

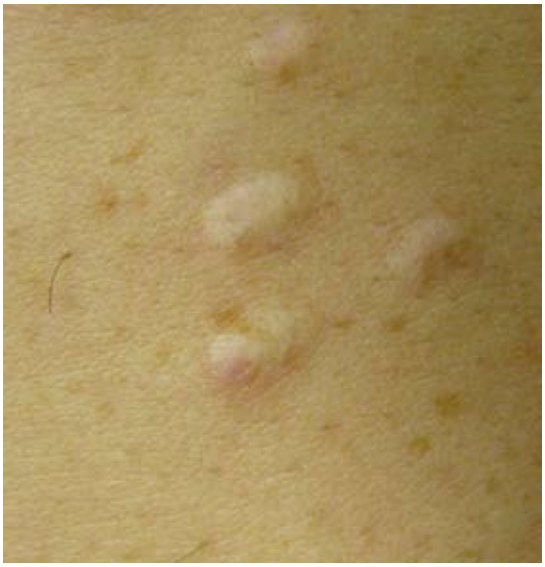


Fig. 5. Scars 1 year after of removal neurofibromas with a carbon dioxide (CO_2) laser. The wounds generally heal very well.

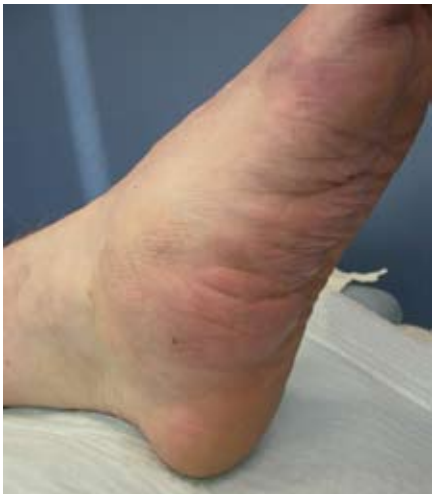


Fig. 6. Plexiform neurofibromas are masses which may deform the face, trunk or extremities. These tumours have a risk of malignant transformation.

malignant change (4). MPNSTs in NF1 patients usually occur at a young age, in contrast to approximately 60 years in patients without NF1. The MPNST is an aggressive tumour with 5-year life expectancy of 20–40%, or median survival of 17 months. The only way to increase the survival is to make an early diagnosis, thus providing the possibility of a radical operation. In addition to MPNSTs, NF1 patients have an increased risk of developing brain tumours, especially during childhood. MRI scanning reveals optic gliomas in approximately 15% of NF1 patients. Most of these tumours, however, remain indolent. Taken together, these make NF1 the most common cancer predisposition syndrome.

In addition to cutaneous and neural involvement, the spectrum of NF1-related manifestations includes skeletal dysplasias, such as pseudarthrosis of tibia and sphenoidal dysplasia (2). Severe dystrophic scoliosis may develop in a few weeks during early childhood. Attention-deficit hyperactivity disorder (ADHD), mild cognitive impairment, and various problems in speech are common, and learning disabilities are present in more than half of NF1 patients. Vascular stenosis caused by the proliferation of the intimal cells most commonly manifests itself as high blood pressure, or strokes (9).

Thus, NF1 is a multi-organ syndrome with readily visible stigmata in skin. A dermatologist may feel that there is not much more to do after giving a diagnosis or removing disturbing neurofibromas. In past decades it was common for a patient to be given the diagnosis von Recklinghausen's disease by a dermatologist, who then bid goodbye to the patient. Nowadays, as the whole spectrum of the features and complications of the disease are known, the role of a dermatologist cannot be that of a bystander. First, every child with NF1 should get a diagnosis at least by pre-school age in order to be evaluated for learning difficulties. This implies that if a dermatologist makes a diagnosis of NF1 for a child, the patient should be referred to a paediatric neurologist for evaluation. If there is hesitation in diagnosis, a neuro-ophthalmologist could provide help by identifying Lisch nodules. The family needs plenty of information. Genetic counselling should not be attempted by a dermatologist, and it is best to offer the patient or the family a referral to a medical geneticist. If an adult with NF1 attends for an appointment, whether or not the reason is NF1-related, the dermatologist should ask whether the patient needs more information on NF1. Many patients are surprisingly ignorant when it comes to the different signs, symptoms and risks of NF1. In addition, asking about the aesthetic burden caused by cutaneous neurofibromas, or chronic pain by spinal or deep tumours may open the door to discussion and sometimes reveals a great need for surgery. Approximately 50% of NF1 patients have cognitive and speech impairments, and may not be able to express their worries and needs to a doctor. Patient organizations for NF provide valuable support for patients, parents and children with NF. All patients should at least be given information about patient support groups. The NF Europe website: http://www.nfeurope.org provides information on NF clinics and doctors in European countries. Patient support groups in Scandinavian countries have published information on NF in their own languages, and the contact information for each country can be found on the following websites:

- Finland: http://www.snf.fi/
- Denmark: http://www.nfrecklinghausen.dk
- Norway: http://www.ffo.no/no/Medlemsorganisasjoner/Norsk-Forening-for-Nevrofibromatose/
- Sweden: http://www.nfforeningen.com

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