Neurofibromatosis type 1

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Neurofibromatosis type 1 (NF1) is an autosomal dominant, multisystem disorder affecting approximately 1 in 3500 people. Significant advances in the understanding of the pathophysiology of NF1 have been made in the last decade. While no medical therapies for NF1 are currently available, trials are ongoing to discover and test medical treatments for the various manifestations of NF1, primarily plexiform neurofibromas, learning disabilities, and optic pathway gliomas. In addition, mutational analysis has become available on a clinical basis and is useful for diagnostic confirmation in individuals who do not fulfill diagnostic criteria or when a prenatal diagnosis is desired. There are several disorders that may share overlapping features with NF1; in 2007, a disorder with cutaneous findings similar to NF1 was described. This paper addresses the dermatologist's role in diagnosis and management of NF1 and describes the variety of cutaneous and extracutaneous findings in NF1 to which the dermatologist may be exposed. (J Am Acad Dermatol 2009;61:1-14.)

Learning objectives: After completing this learning activity, participants should be able to discuss the indications and limitations of genetic testing in neurofibromatosis type 1, distinguish common and uncommon cutaneous findings, and recognize the dermatologist's role in diagnosis and management.

Key points

- **Not all café-au-lait macules are neurofibromatosis type 1.**
- **Comprehensive mutational testing is available to aid in diagnosis.**
- **Dermatologists have a role in diagnosis and recognition of common and uncommon cutaneous findings.**

Neurofibromatosis type 1 (NF1) is an autosomal dominant, multisystem disorder affecting approximately 1 in 3500 people. The earliest historical evidence first appeared in the 13th century, but it was not until Friedrich Daniel von Recklinghausen published his landmark paper (in German) "On the multiple fibromas of the skin and their relationship to the multiple neuromas" in 1882 that neurofibromatosis began gaining recognition as a distinct disorder. More recently, in 1956, Crowe et al[1] published a milestone manuscript detailing the numerous manifestations of this disorder.

Abbreviations used:

BRM:	blue-red macule
CALM:	café-au-lait macule
FCALS:	familial café-au-lait spots
JMML:	juvenile myelomonocytic leukemia
JXG:	juvenile xanthogranuloma
MRI:	magnetic resonance imaging
NF1:	neurofibromatosis type 1
NIH:	National Institutes of Health
PAM:	pseudoatrophic macule
PN:	plexiform neurofibroma

In 1982, Riccardi[2] classified the heterogeneous neurofibromatosis disorders into eight categories. These have not been universally accepted, although several persist to this day. NF1 and NF2 have remained as originally classified. NF2 results from a mutation in the *NF2* gene and is characterized by bilateral vestibular schwannomas and various other tumors. NF7 is now referred to as schwannomatosis and is distinguished by the late onset of multiple schwannomas and the absence of features of classic NF1 or NF2. These tumors cause significant pain for the patient and can occur on the spinal, cranial, or peripheral nerves. Segmental NF1 and familial café-au-lait spots have replaced NF5 and NF6, respectively, and are discussed in more detail below. NF3, NF4, and NF8 are described as variant, atypical, and "not otherwise specified" forms; these are not routinely used in clinical practice.

Significant advances in the understanding of the pathophysiology of NF1 have been made in the last decade, and this article will highlight those advances

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that affect our care of patients with NF1. Since the *NF1* gene was discovered, in 1990,[3] mutational analysis has become available on a clinical basis and is useful for diagnostic confirmation in individuals who do not fulfill diagnostic criteria or when a prenatal diagnosis is desired. While no medical therapies are currently available, trials are ongoing to discover and test medical treatments for the various manifestations of NF1, primarily plexiform neurofibromas, learning disabilities, and optic pathway gliomas, which are a significant cause of morbidity in these patients. In 2007, a disorder with cutaneous findings (multiple café-au-lait macules [CALMs] and axillary freckling) similar to NF1 was described,[4] although the causative gene (*SPRED1*) was different.

CAPSULE SUMMARY

- Many advances have increased our ability to understand and diagnose neurofibromatosis type 1
- This paper will review the current thinking on the pathogenesis of, discuss the visible manifestations of, and describe a methodical approach to the diagnosis of neurofibromatosis type 1

GENETICS OF NEUROFIBROMATOSIS TYPE 1

Key points

- **NF1 is an autosomal dominant disorder, with a nearly even split between spontaneous and inherited mutations.**
- **Segmental NF1 represents mosaicism.**

Inheritance

NF1 is an autosomal dominant disorder, with a nearly even split between spontaneous and inherited mutations. Penetrance approaches 100% by age 20; if the patient has the mutation, he or she will exhibit manifestations, although expressivity is highly variable, even among family members with the same mutation.[5,6] This point is important for genetic counseling, because an individual with mild clinical findings can have a child with a more severe phenotype, or vice versa.

Neurofibromatosis type 1 gene

The *NF1* gene is located on chromosome 17q11.2 and encodes for the protein neurofibromin. This large gene (60 exons and >300 kilobases of genomic DNA) has one of the highest rates of spontaneous mutations in the entire human genome.[7] Accordingly, the types of mutations that cause the NF1 phenotype vary from complete gene deletions, insertions, stop, and splicing mutations. Other variations include amino acid substitutions and chromosomal rearrangements.[8] In a study of 189 patients with known germline mutations, 85 had a recurrent mutation[9]; another study found that most lead to premature termination of translation of the gene product.[10]

Mosaicism

Mosaicism describes an individual with two genetically distinct cell lines as a result of a postzygotic gene mutation. NF1 occurs in mosaic forms that are classified as segmental, generalized, or gonadal.[11] Individuals with segmental involvement may have regions of pigmentary alterations, tumor growths, or both manifestations that are restricted to one or more body segments. Generalized mosaics appear clinically similar to nonmosaic cases but have little to no evidence of the disorder when the blood leukocytes are screened for the *NF1* gene mutation. Gonadal is the rarest type and occurs when only the ova or sperm are affected. This is suspected if two or more children of otherwise unaffected parents develop the disorder.[12]

The risk of transmission of NF1 from patients with segmental involvement is unknown, but case reports of such transmission exist; the parents presumably have involvement of the gonadal tissue. Consoli et al[13] confirmed a case of gonadal mosaicism in a previously presented patient.[14-17] The visibly affected areas in segmental patients need not cover the genitalia to confer risk of transmission, a fact that is important for counseling.[11] There are even some cases of segmental NF1 apparently being "transmitted" to offspring; the mechanism behind this (if one exists) is unclear.[16,18] One case report addresses a 29-year-old man with clear evidence of segmental NF1 whose parents and siblings exhibited no evidence of NF1 but whose maternal aunt, cousin, and second cousin had classic NF1.[19] It is possible that this represents two independent *NF1* mutations in the two branches of the family, but that was not tested in the published data.

PATHOGENESIS OF NEUROFIBROMATOSIS TYPE 1

Key point

- **The NF1 gene codes for neurofibromin, a tumor suppressor protein.**

Neurofibromin, the *NF1* gene protein product, is a tumor suppressor expressed in many cells,

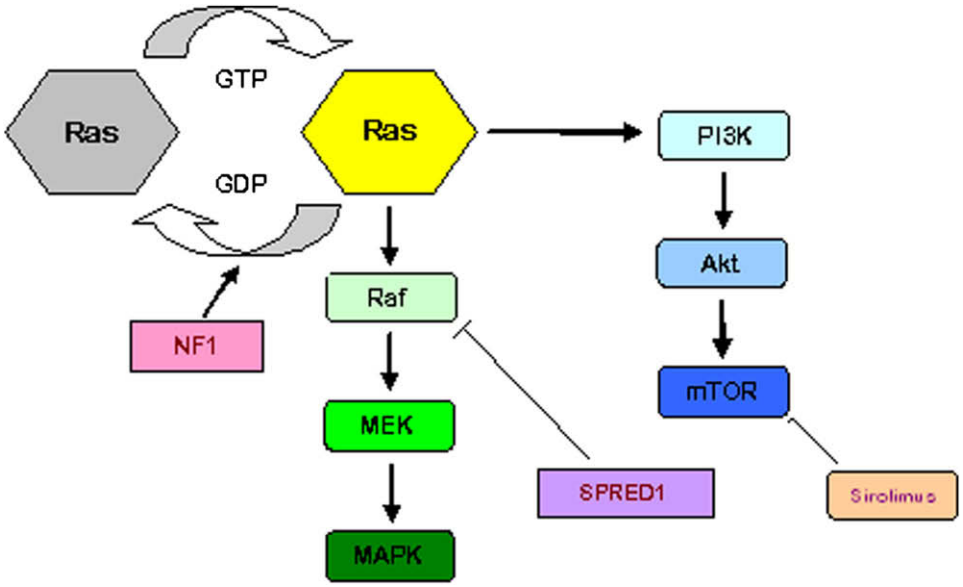

Fig 1. Interactions of key proteins and genes involved in the pathogenesis of neurofibromatosis type 1 (NF1). The mitogen-activated protein kinase/extracellular signal-regulated kinase pathway is a complex series of signals and interactions involved in cell growth and proliferation. Under normal conditions, the *NF1* gene product neurofibromin promotes the conversion of Ras into its inactive form, thereby suppressing cell growth. In NF1, there is a loss of or diminished function of the *NF1* gene and the process is left unhindered. *SPRED1* inhibits Raf and is the implicated gene/protein in NF1-like syndrome. mTOR has a key role in an additional pathway leading to cell growth and proliferation. Sirolimus inhibits it by binding to an intracellular receptor, FKBP12 (not shown), the complex of which then binds directly to mTOR. *ERK*, Extracellular signal-regulated kinase; *MAPK*, mitogen-activated protein kinase; *MEK*, MAPK/ERK kinase; *PI3K*, phosphoinositide 3-kinase.

primarily in neurons, glial, Schwann cells, and early in melanocyte development.[20] This protein is a regulator of Ras guanosine triphosphatase activity (GTPase-activating protein) and as such serves as a regulator of the signals for cell proliferation and differentiation[5] (Fig 1). The loss of function of neurofibromin may therefore remove this regulation and lead to uncontrolled cell proliferation. Schwann cells in neurofibromas and melanocytes in CALMs have a mutation in both *NF1* alleles, including a germline and an acquired somatic mutation, and are considered the primary tumor cell in their respective cutaneous manifestation. Based on these findings, it is likely that NF1 functions as a tumor suppressor gene.[21,22] Both of these cell types are descendants of the neural crest. The exact timing of the acquired mutation is unknown but is crucial in the development of the various manifestations; experiments have shown that *NF1* gene inactivation at the neural crest stage and mature Schwann cell stage do not lead to tumor formation. However, in a progenitor intermediate step between these two stages, tumor formation occurs with *NF1* gene inactivation.[23]

DIAGNOSIS

Key points

- **Some diagnostic criteria may not manifest until later in life.**
- **Clinical diagnostic criteria are not as sensitive in very young children.**

Diagnostic criteria

In 1987, seven cardinal diagnostic criteria for NF1 were established, two of which must be met in order to diagnose an individual with NF1 (Fig 2). These diagnostic criteria have been shown to be both highly specific and sensitive for adults with NF1.[24] Because some of the criteria may not manifest until later in life, they are not as sensitive in children, especially those under 8 years of age. A 2000 retrospective review of nearly 1900 cases of NF1 found that 46% of sporadic cases did not meet criteria by 1 year of age; however, 97% met criteria by 8 years of age, and all fulfilled them by 20 years of age.[25]

The diagnosis of NF1 is generally straightforward when one follows the National Institutes of Health (NIH) guidelines; however, patients with these classic

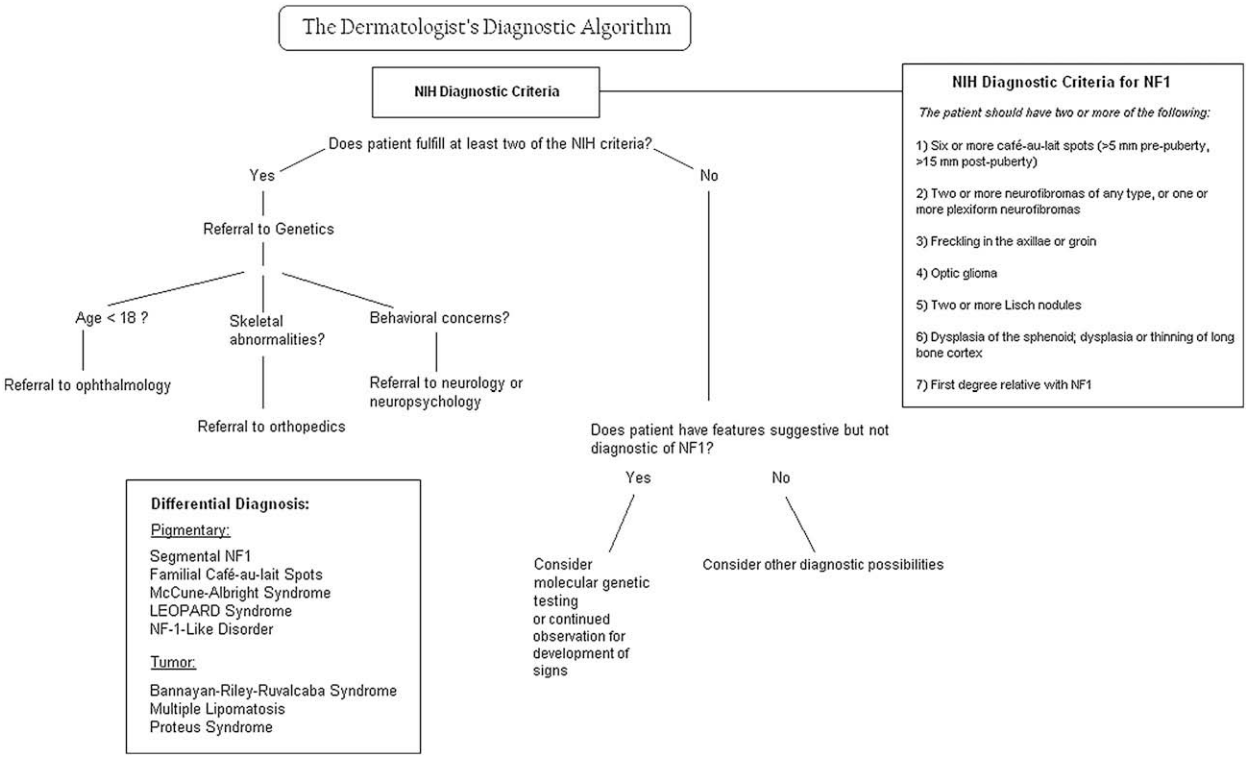

Fig 2. Diagnostic algorithm of neurofibromatosis type 1 geared towards the dermatologist.

findings may not first present to a dermatologist. Of particular interest to dermatologists is the approach to diagnosis of a patient who has some features of NF1 but fails to fully meet the diagnostic criteria. A diagnostic algorithm geared towards the dermatologist is provided in Fig 2. Further, it is important to recognize key historical or physical findings that may require—beyond a referral to the genetics department—a timely consultation with varying specialties, including orthopedics, ophthalmology, or neurology.

Genetic testing

Key point

- **Molecular testing for NF1 is now available.**

Molecular testing for NF1 has recently become clinically available. Because of the large size of the *NF1* gene and the lack of mutation hotspots, a multistep detection protocol is preferred. A comprehensive screening approach to the *NF1* gene found mutations in >95% of tested subjects (including both spontaneous and inherited mutations) fulfilling the NIH diagnostic criteria.[8] This comprehensive approach begins with an optimized protein truncation test, followed by fluorescent in situ hybridization analysis, direct sequencing, long-range reverse transcriptase polymerase chain reaction with Southern blot analysis, and/or cytogenetic analysis, if necessary, and is used in only a select few laboratories (http://www.genetests.org; August 13, 2008). Molecular testing is not indicated for the routine clinical care of patients with NF1, but can be helpful in individuals suspected of having NF1 (eg, a young child with multiple café-au-lait spots and unaffected parents or a patient with a single criterion) or when prenatal or preimplantation genetic diagnosis is desired (Table I). Some experts are calling for a revision of the 1987 criteria to include a positive molecular test as a definitive, standalone diagnostic criterion.

A limitation of genetic testing is the lack of genotype–phenotype correlations. Therefore, while useful for diagnostic confirmation, a positive test will not predict disease severity or outcome. However, there are two exceptions. The first results from complete loss of the *NF1* gene along with multiple contiguous genes and occurs in 4% to 5% of patients with NF1.[26] Patients with whole gene deletion present with a very large neurofibroma burden, more severe cognitive impairment, large hands and feet, dysmorphic facial features, and have a higher lifetime risk of developing malignant peripheral nerve sheath tumors (MPNST).[27,28] A three-base pair inframe deletion in exon 17 of the *NF1* gene is the second exception. Patients with this genetic mutation have

Table I. Indications for genetic testing

Individuals at 50% risk
Patients with a single sign
Individuals with variant disorders
Prenatal testing
Preimplantation genetic diagnosis

an absence of cutaneous neurofibromas and appear to have a lower incidence of serious complications.[29]

Differential diagnosis

Key points

- **Not all children with CALMs have NF1.**
- **The recently described NF1-like syndrome includes multiple CALMs, axillary freckling, and macrocephaly.**

NF1-like syndrome. An important disorder to distinguish from NF1 is NF1-like syndrome. This disorder, first described in 2007, consists primarily of multiple CALMs, axillary freckling, and macrocephaly.[4] Comprehensive mutational analysis for the *NF1* gene was performed on affected individuals from five families; all were negative. Through genome linkage studies, they localized the disorder to chromosome 15 and, based on disease distribution within the families, determined that it was autosomal dominant. The responsible gene is *SPRED1,* which is involved in Ras mitogen-activated protein kinase regulation, similar to neurofibromin (Fig 1). Lipomas, Noonan-like facies, and learning and behavioral problems were present in some of the families; however, it was uncertain how these findings were related to the genetic alteration.[4] This disorder warrants further study to better characterize its phenotype and distinguish it from NF1. At the time that this article was published, clinical testing for this disorder was available only at two laboratories in the United States (http://www.genetests.org; October 20, 2008). NF1-like syndrome should be suspected in families in which individuals present with multiple CALMs, but without Lisch nodules, neurofibromas, and *NF1* gene abnormalities.

Familial café-au-lait spots. Familial café-au-lait spots have an uncertain relationship to NF1. Riccardi[2] described two families whose affected members had only multiple CALMs and felt that they represented a disorder that was separate from the classic form.[30] Affected individuals do not develop other manifestations of NF1. It segregates as an autosomal dominant disorder, and there are conflicting results on whether familial café-au-lait spots are linked to NF1.[31,32] Charrow et al[32] contended that it was a separate entity and should be treated as such. It does not appear to confer any increased risk of developing classical NF1.

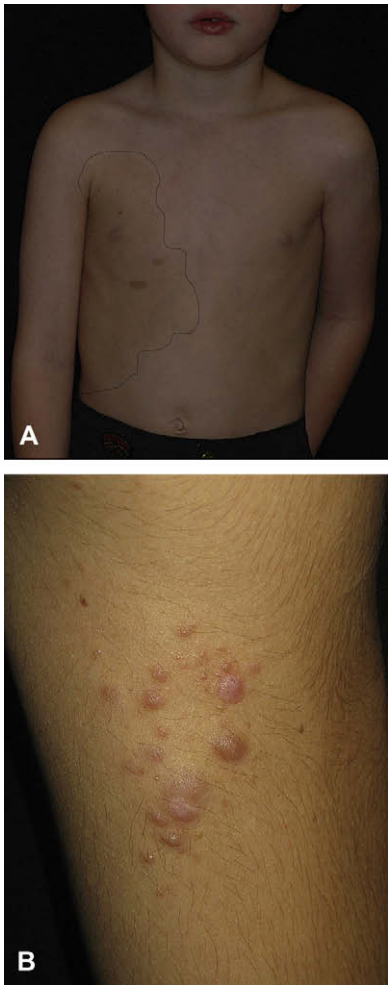

Fig 3. Pictures of segmental neurofibromatosis type 1 showing patients with (**A**) pigmentary and (**B**) tumor manifestations.

Segmental NF1. As mentioned previously, NF1 can manifest as a mosaic (segmental) disorder in both localized and generalized forms. Localized, segmental neurofibromatosis should be considered when skin findings are localized to a particular area of the skin and there is no family history (Fig 3). This is in contrast to familial café-au-lait spots, wherein there is often a family history of "multiple birthmarks" and the sole finding is that of CALMs. Testing of lesional tissue (neurofibromas and CALMs) is available and is of particular use in these patients. Maertens et al[21] tested lesional tissue in three patients with segmental NF1, each of whom had different skin manifestations (pigmentary alone, tumor alone, and a combination of both). Through comprehensive testing, mutations were found in all affected cells; biallelic inactivation was found in either the Schwann cells of

Table II. Cutaneous findings in neurofibromatosis type 1

Common	Uncommon or reported associations
Café-au-lait macules*	Juvenile xanthogranuloma
Axillary/inguinal freckling (Crowe sign)*	Glomus tumor
Neurofibromas (dermal or plexiform)*	Melanoma
Increased base pigmentation	Blue-red macules
	Pseudoatrophic macules
	Nevus anemicus

*Diagnostic criterion for neurofibromatosis type 1.

neurofibromas or in the melanocytes of CALMs.[21] These three cases illustrate not only the variability of the phenotypic expression of NF1 but also the ability to reliably test lesional tissue for the *NF1* mutation if the diagnosis is uncertain. In 2001, Ruggieri and Huson[11] classified the various types of mosaic NF1 into pigmentary changes alone (background hyperpigmentation, CALMs, and freckling), neurofibromas alone, both pigmentary and neurofibromas, and isolated plexiform neurofibromas.[11]

Other diagnostic considerations are given in Fig 2 and will not be discussed in detail here.

CUTANEOUS MANIFESTATIONS

Key point

- **Patients with NF1 may develop a variety of skin findings.**

Dermatologists should quickly recognize not only the salient skin features but also the less common cutaneous findings, because these latter aspects may be the source of a referral. The common and uncommon cutaneous features are provided in Table II. The following is a brief explanation of these findings. Additional details are provided on the more rare skin manifestations and noncutaneous findings that are easy to detect on physical examination or history.

Pigmentary

Café-au-lait macules. The CALM is one of the seven cardinal diagnostic criteria of NF1 (Fig 4). The classic lesion is well demarcated with smooth borders ("coast of California") and homogeneous in appearance. Generally, the color is close to that of its namesake, but can range from tan to dark brown. To fulfill this requirement, patients need six or more >5 mm (prepuberty) or >15 mm (postpuberty) macules. Less than 1% of children under 5 years of age without NF1 have more than two; when multiple macules are present, this is highly suggestive of NF1.[33] The prevalence of CALMs in the general population has varied between 3% and 36%—depending on the population studied—but the presence of multiple CALMs in an otherwise normal population is generally <1%.[34] The CALM is frequently the first sign, occurring in 99% of NF1 patients within the first year of life.[25] Patients continue to accrue them throughout childhood, but they often fade in adulthood.

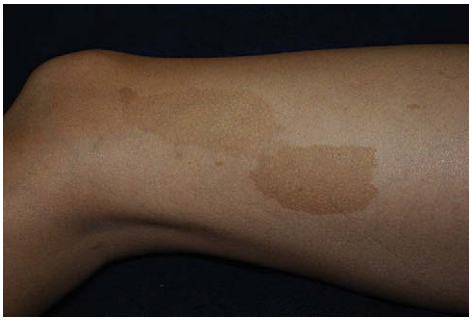

Fig 4. Café-au-lait macules on the thigh of a child.

CALMs get their pigment from the melanocyte, which has been shown to have an increased concentration of melanin and giant melanosomes (macromelanosomes or melanin macroglobules); however, the absolute number of melanocytes in a non-NF1 CALM relative to the surrounding normal skin is not greater.[35] In NF1 patients, it has been shown that their CALMs have an increased number of melanocytes, although there is still some debate on this issue.[36] Others have shown an even greater concentration of melanin and macromelanosomes at the organelle level, in both CALM and non-CALM skin when compared to non-NF1 skin controls.[37] Recent investigations have found that the melanocyte in the CALM has a mutation in both copies of the *NF1* gene and that the melanocytes of non-CALM NF1 skin show the germline mutation only.[22]

Skin fold freckling. Skin fold freckling (Crowe sign) is the most specific of the cardinal criteria for NF1 (Fig 5). It is considered nearly pathognomonic. It is second only to CALMs in terms of age-related frequency[24] and generally occurs between 3 and 5 years of age in either the axillae and/or groin[38]; a majority of adults have the freckling (~90%).[39] Other sites include under the neck and breasts, around the lips, and even the trunk in adults; however, none of these fulfill the NIH diagnostic criterion. Their appearance is similar to that of solar-induced freckling but, notably, these occur almost exclusively in areas

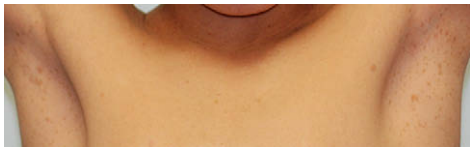

Fig 5. Bilateral axillary freckling in a child.

with minimal to no sun exposure. Their size ranges from 1 to 3 mm, distinguishing them from CALMs. The cause of these lesions is unknown, but it has been suggested that they might be caused by the increased friction, temperature, and/or moisture inherent to these areas.[40,41]

Generalized hyperpigmentation. Also noted (although not extensively studied) is a generalized hyperpigmentation in NF1 patients when compared to their unaffected parents or siblings. Interestingly, the involved body regions of patients with segmental NF1 often have a background of hyperpigmentation that is sharply demarcated from the uninvolved skin (Fig 3, *A*). Melanocytes from the hyperpigmented skin have a one-hit mutation, whereas those from the overlying CALMS have two hits.[21] This strongly suggests that in the patient with nonsegmental NF1, the observed globally-increased pigmentation is likely caused by the one-hit mutation in the melanocytes.

Tumor

Cutaneous neurofibromas. The neurofibroma is considered another one of the hallmark signs of NF1 (Fig 6). Neurofibromas can occur anywhere on the body and there is a wide variation in their shape and size. Terminology has varied and, at times, been somewhat confusing. Generally, the "cutaneous" or "dermal" tumors are dome-shaped, soft, fleshy, and skin colored to slightly hyperpigmented, and the "subcutaneous" tumors are of the firm, nodular variety. Cutaneous neurofibromas usually do not become apparent until puberty and may continue to increase in size and number throughout adulthood. Outside of puberty, pregnancy is the other major time associated with increased growth. The neurofibroma is a major source of morbidity in these patients because of the sheer number, visibility, and size of these tumors.[42]

The tumors themselves are comprised of Schwann cells, fibroblasts, mast cells, and perineural cells. There is also an admixture of collagen and extracellular matrix. Analogous to melanocytes, the neurofibroma-derived Schwann cell—believed to be the primary tumor cell in neurofibromas—has been shown to have both a germline and second-hit mutation in the *NF1* gene, the latter of these differing in each tumor in a patient.[43] Both Schwann cells and melanocytes share a common heritage in the neural

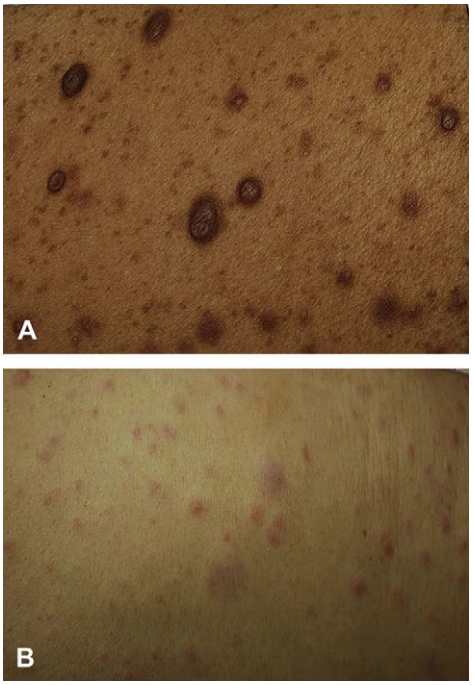

Fig 6. A and **B**, Various morphologies of cutaneous neurofibromas.

crest and may be derived from a bipotent glial-melanocytic precursor.[21]

Blue-red and pseudoatrophic macules. The blue-red macule (BRM) and pseudoatrophic macule (PAM) may represent unusual variants of cutaneous neurofibromas. In one case report, the BRM was described as soft to palpation, ill-defined, and appearing primarily on the trunk.[44] They appeared before or during puberty and became slightly elevated or dome-shaped with time. Histopathologic examination reveals an increased number of thickened blood vessel walls with widened lumina and tumor-like neurogenic tissue in the papillary and reticular dermis. The source of their red color is clear; when hemostasis occurs in these lesions, they develop a bluish tint. A more recent report noted the presence of BRMs in 44 of 583 patients, primarily on the trunk. Histologically, the thickened vessel walls were attributed to neurofibromatous tissue infiltration. They proposed that the BRM may be considered an unusual variety of neurofibroma and, therefore, sufficient for meeting a diagnostic criterion of NF1.[45]

In the same 1982 report,[44] PAMs were described as oval, slightly depressed lesions ranging in size from 5 to 10 cm. Skin texture and color were similar relative to surrounding skin, although upon palpation the lesions were "softer" and showed a loss of underlying subcutaneous tissue. Histologic examination showed a reduction in collagen in the reticular dermis and increased perivascularly situated neuroid

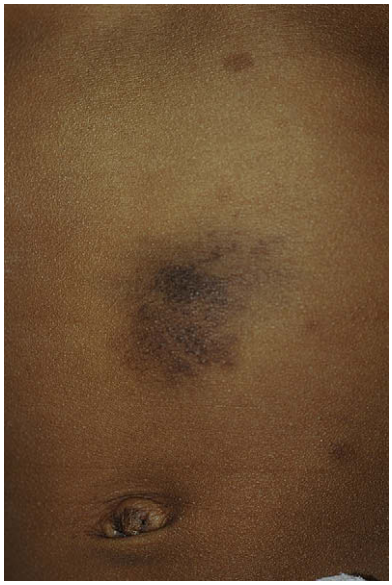

Fig 7. Plexiform neurofibroma on the abdomen of a child.

tissue with Schwann cells and fibroblasts. Another case report from 1996 had similar clinical features; histologic examination revealed the replacement of collagen bundles with neuroid tissue, consisting of neoplastic cells with oval/spindle nuclei.[46] Norris et al[47] examined the ultrastructure of biopsies of these lesions (they referred to them as neurofibromatous dermal hypoplasia [NDH]) and the response to several vasodilators and a vasoconstrictor. Histologic examination showed loose whorls of neurofibromatous tissue intermingled with collagen fibers surrounding both nerve trunks and small blood vessels; the primary cell type was the perineurial cell. Further, the authors postulated that the cuff of cells surrounding the vessels acted as both a physical splint and diffusion barrier because the PAMs did not respond with a wheal-and-flare reaction to vasodilators.[47] It is interesting to note that in both the BRMs and PAMs there is a similarity in that neurofibromatous tissue surrounds (PAMs) or infiltrates (BRMs) vascular structures, leading to their unique clinical appearances.

Plexiform neurofibroma. The plexiform neurofibroma (PN) is distinct from the cutaneous neurofibroma in that it is usually congenital. Superficial PNs are often associated with overlying hyperpigmentation and/or hypertrichosis and may be easily confused with a congenital melanocytic nevus (Fig 7). The affected skin may also appear thickened. These tumors are diffuse, growing along the length of a nerve, and feel like a "bag of worms." PN can be quite disfiguring and may interfere with both growth and function of the affected area. Eight percent to 12% of NF1 patients will develop a malignant peripheral nerve sheath tumor, and usually these arise from preexisting plexiform neurofibromas.[48,49] A warning sign is the development of persistent pain or rapid growth in an otherwise stable PN.

Other cutaneous findings

Juvenile xanthogranuloma. The purported triple association of juvenile xanthogranuloma (JXG), NF1, and juvenile myelomonocytic leukemia (JMML) is often reported and is the source of frequent debate. In 1990, Morier et al[50] reported on their own case and reviewed the literature, finding an additional 23 cases. An analysis in 1995 found that the risk of JMML in patients with NF1 and JXG was 20 to 32 times higher than in other patients with NF1, although the methodology of this analysis has been called into question.[51,52] In their commentary, Burgdorf and Zelger[53] analyzed the literature and all available information pertaining to the association and found that patients with NF1 are, indeed, at an increased risk of developing JMML and JXG, but that the triple association of these findings (assuming the worst odds) is <1% per year; however, regardless of the presence of JXGs, children with NF1 are at a 200- to 500-fold greater risk of this hematologic malignancy.[53] Their conclusion was that physicians should be aware of presenting features of JMML (hepatosplenomegaly, lymphadenopathy, pallor, and petechiae), but routine screening in patients with NF1 is of no benefit. JXGs in children with JMML most often present as multiple papules or nodules no larger than 1 cm or as confluent papular lesions.[54]

Glomus tumor. The glomus tumor is derived from the glomus body, which is a specialized vascular structure involved in thermoregulation. Clinically, the tumor appears as a small blue-red papule or nodule, is characterized by marked pain and cold intolerance, and is most commonly seen in the subungual region of the finger.[55] The finding of multiple glomus tumors in one individual is rare in the general population, but seven case reports exist in NF1 patients.[56-58] De Smet et al[56] postulate that the glomus cell is of neural crest origin and, much like the Schwann cell in neurofibromas, is the tumor cell in glomus tumors. A similar two-hit mechanism that has been described in both neurofibroma-derived Schwann cells and CALM-derived melanocytes could explain the increased frequency of these tumors in NF1 patients.[22,43,56] It is important to recognize the increased, albeit low, risk of glomus tumors in NF1 patients, because surgical removal of the tumor eliminates the pain.

Melanoma. The first report of concurrent NF1 and melanoma dates to the 1930s.[59] Its relationship to NF1 is controversial; a variety of reports have been published in cutaneous[60,61] and extracutaneous[62]

melanoma, but no true incidence has been established. Frequencies vary between 0.1% and 5.4%.[41] This association is not completely implausible, however, given the aberrations of the melanocyte in NF1. One review examined 11 cases of cutaneous melanoma in NF1 patients and found that, when compared against controls, patients were predominantly female, younger in age, and had a higher Breslow thickness of their lesions.[63] De Schepper et al[41] noted that this is consistent with reports of ocular melanoma and hypothesized that the increased lesional thickness might be caused by confusion with the multitude of other pigmented lesions in NF1.

Nevus anemicus. Nevus anemicus is a congenital, hypopigmented lesion found most often on the trunk. The pallor of these lesions is caused by the increased sensitivity of blood vessels to catecholamines.[64,65] Most reports of the association of this finding and NF1 appear anecdotal, because as there is scant literature exploring this relationship. In 1969, Fleisher and Zeligmann[66] performed experiments on nevus anemicae of patients with NF1, but the association was not explored. In their paper on NDH, Norris et al[47] drew comparisons to the similarity of diminished vascular reactivity of NDH and nevus anemicus, but the underlying pathophysiologic mechanisms are distinct.[66] It is uncertain whether the finding of nevus anemicus in NF1 is coincidental, because to our knowledge, no studies have attempted to establish a correlation.

Pruritus. Another common manifestation in NF1 is pruritus. Generally, it is a widespread cutaneous phenomenon, but anecdotally, some patients are able to relate that certain tumors itch more than others. The pathogenesis of this finding is uncertain, but may be related to the increased number of mast cells that are found in neurofibromas. These mast cells undergo rapid growth in these tumors and, consequently, release histamine, a substance known to cause itch.[5] Localized pruritus can also be a clue to the presence of an underlying spinal cord or central nervous system tumor.[67]

NONCUTANEOUS MANIFESTATIONS

Key points

- **Dermatologists should screen for bone abnormalities that may require referral to orthopedics.**
- **Learning disabilities are the most common complication in children with NF1.**

NF1 has the ability to affect nearly every organ system. While this paper is focused on the cutaneous manifestations, consideration must also be given to findings that the dermatologist may note on a physical examination or gather from the patient's history so that appropriate steps may be taken. A summary of these findings is provided in Table III.

Table III. Extracutaneous findings in neurofibromatosis type 1

Skeletal	**Cardiovascular**
Scoliosis	Hypertension
Dysplasia of the long bone or sphenoid*	Vascular dysplasia
Macrocephaly	
Prominent brow	**Endocrine**
Short stature	Precocious puberty
Pectus excavatum	Pheochromocytoma
Pseudoarthrosis (especially of the tibia)	
Neurologic/psychologic	**Gastrointestinal**
Headaches	Constipation
Learning disabilities/ADHD	Gastrointestinal stromal tumors
Astrocytoma	
Seizures	
Ophthalmologic	**Associated malignancies**
Lisch nodules*	Juvenile myelomonocytic leukemia
Optic glioma*	Malignant peripheral nerve sheath tumor

ADHD, Attention deficit hyperactivity disorder.
*Diagnostic criterion for neurofibromatosis type 1.

Orthopedic

Bony abnormalities in NF1 are variable and include scoliosis, sphenoid wing or long bone dysplasia, and, more recently, osteopenia/osteoporosis.[68] The underlying pathogenic mechanisms are not fully understood, but experimental evidence suggests that osteoblasts (mediators of bone construction) are deficient and their counterparts (osteoclasts) have increased survival rates, leading to increased degradation of bony tissue.[69]

Scoliosis. Scoliosis (lateral curvature of the spine) is the most common orthopedic finding in NF1, occurring in up to 10% of patients,[49] usually manifesting by 10 years of age.[16] The pathogenesis of this finding in NF1 is unknown but may be related to osteopenia and subsequent dysplastic bony elements.[69] Management varies depending on the degree of curvature, location, rate of progression, and the patient's age.[5] The dermatologist's role is limited, but periodic screening of the young NF1 patient is simple and painless. If evidence of scoliosis is found, referral to the department of orthopedics is warranted.

Dysplasia of a long bone. Dysplasia of a long bone is another common manifestation of NF1, occurring in nearly 14% of patients, and is usually evident within the first year of life.[25] This finding is particularly relevant to dermatology, because young patients typically come to the clinic for the evaluation of "birthmarks" before 1 year of age and can be easily screened for this manifestation. The most commonly affected bone is the tibia, which will bow in an anterolateral direction. Coupled with the appropriate number and size of CALMs, this orthopedic manifestation is sufficient to make the diagnosis of NF1. Other findings may include overgrowth of a limb or congenital pseudoarthrosis (usually of the tibia), in which a fracture heals abnormally. Recently, loss of heterozygosity of the *NF1* gene was shown in osseous tissue from two patients with tibial pseudoarthrosis, suggesting that this mutation has a role in the pathogenesis of these skeletal dysplasias.[70] Again, the dermatologist's role is limited, but the recognition of any of these findings will lead to appropriate management by an orthopedic specialist.

Other. Other features include short stature, relative macrocephaly, and a prominent forehead and brow. Anywhere from 29% to 45% of patients with NF1 have a head circumference greater than or equal to two standard deviations above the mean for sex and age.[39,49,71]

Neurologic/psychiatric

Learning disabilities and attention deficit hyperactivity disorder. In the broadest sense, learning disabilities occur in nearly half of all NF1 patients and are a chief concern of parents. No consistent profile of the specific deficiencies in NF1 exists, but an extensive review in 2006 found that patients have academic deficiencies, particularly in math and reading, slightly lower intelligence quotients, and a high preponderance of attention deficit hyperactivity disorder.[72] These issues are of particular interest to the pediatric practitioner, because early intervention to address these concerns may lead to improved outcomes later in life.

A relationship between unidentified bright objects (UBOs) and cognitive function has been proposed. UBOs are seen in up to 80% of patients with NF1.[73] These hyperintense areas noted on magnetic resonance imaging (MRI) scans are of uncertain clinical significance; studies attempting to correlate them to cognition have had mixed results, but there is some evidence that specific locations (ie, the thalamus) correlate to measured cognitive performance.[74,75] Using MRI scans to screen for the presence of UBOs is not recommended, because they are neither diagnostic nor helpful in management. Regardless, children should be assessed for developmental milestone delays, learning disabilities, and school performance, and appropriate resources, such as neurology and/or neuropsychology, should be used.

Ophthalmologic

The two most common problems in this category are not readily apparent in clinic to the dermatologist but are worth mention.

Lisch nodules. Lisch nodules are small, dome-shaped hyperpigmented macules of the iris that cause no impairment of vision. They are a common finding (by 6 years of age, 15% to 20% of children have them; 95% of adults have them) and are included as one of the cardinal NIH diagnostic criteria.[76-80] Visualization requires slit lamp examination by experienced practitioners. For patients or family members in whom the diagnosis of NF1 is uncertain, referral for a complete eye examination is necessary.

Optic glioma. The optic glioma is a tumor of the optic nerve and is present in 15% to 20% of patients with NF1.[81,82] It is a slow-growing tumor and can present clinically with eye proptosis, decreased visual acuity, or precocious puberty (the latter most commonly after 6 years of age); accelerated linear growth is evidence of early puberty, necessitating the use of growth charts in NF1 patients.[83] Symptomatic optic gliomas typically present before 6 years of age, with most children being diagnosed with an optic glioma by 3 years of age.[25,81,82]

There is considerable controversy over the diagnosis and management and the pros and cons of the various approaches will not be debated here. It is important to the dermatologist who makes the diagnosis in a child to understand how an optic glioma may manifest and that children under 8 years of age should undergo annual evaluation by a skilled ophthalmologist or neuro-ophthalmologist. Less strong (but still graded as "good") evidence suggests that ophthalmologic evaluation should be continued every 2 years until the 18 years of age.[83] According to this same review,[83] there is no strong evidence that routine screening with neuroimaging (MRI) in the asymptomatic individual is of benefit. However, if a reliable eye examination cannot be performed, imaging may be appropriate.[83]

MANAGEMENT AND FUTURE DIRECTIONS

The dermatologist has a primary role in recognizing and differentiating NF1 from other conditions based on a careful skin examination, making appropriate referrals once the diagnosis is made, and

managing symptomatic or disfiguring cutaneous neurofibromas. Currently, neurofibromas are amenable only to surgical removal. Symptomatic (ie, painful and bleeding) neurofibromas are most commonly removed but, depending on the community, this may not be handled by dermatology. Several studies have looked or are looking at testing various agents specifically directed at the plexiform neurofibroma.[84-86] Clinical trials with a variety of pharmacologic agents are ongoing for neurofibromas, primarily progressive or disabling plexiform neurofibromas, and an updated list of trials is available at www.clinicaltrials.gov. One of these agents, sirolimus, targets mTOR (a known regulator of cell growth in the nervous system) and is the focus of a multicenter trial for plexiform neurofibromas. Sirolimus has also shown promise in the treatment of several tumor manifestations of tuberous sclerosis.[87,88] Another pharmacologic agent, imatinib mesylate, was shown to reduce the size of a plexiform neurofibroma compromising the airway of a 3-year-old girl; a phase II clinical trial is currently underway. Imatinib inhibits stem cell factor's growth-potentiating effects by interfering with c-kit receptor activity.[89]

Pigmentary disturbances are generally not treated beyond the recommendation that patients wear sunscreen. CALMs will darken in response to sunlight and tend to fade with time and become less noticeable. While not often located on the face, CALMs may also be amenable to various cover-up products. A study with eight NF1 patients used the combination of intense pulsed-radio frequency and topical vitamin D_3 to treat both freckling and CALMs. Some improvement was noted, primarily in freckling, and no repigmentation of the lesions occurred for at least 6 months.[90] In another study, the same group found that topical vitamin D_3 analogues had measurable clinical and histologic effects: there was notable lightening of the lesions and an increase in melanin incontinence.[91] This was a small study, however, and no large-scale, double-blind studies have been performed to our knowledge. Other studies have examined the effects of lasers on pigmented lesions in the general population, but these will not be discussed in detail here.

A relationship of vitamin D and NF1 has been proposed. Nakayama et al[92] examined the response of xenograft neurofibroma tissue to a vitamin D_3 analogue and found decreased cell density when compared against those treated with growth promoting agents. Lammert et al[93] investigated the relationship of serum 25-OH vitamin D concentrations in patients with NF1 and found a statistically significant inverse relationship between the number of dermal neurofibromas and serum levels of this hormone.

Recently, improved cognition in NF1 was reported in mice following treatment with lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that also inhibits Ras.[94] However, a large, randomized, double-blind, placebo-controlled trial failed to show any significant improvement after 3 months of treatment with simvastatin (another HMG-CoA reductase inhibitor) in the cognitive abilities of children with NF1. This is still an ongoing area of investigation.[95]

SUMMARY

NF1 is a multisystem disorder requiring management by multiple disciplines, often coordinated through a primary care physician or a geneticist. The dermatologist has a role not only in the diagnosis of NF1 and differentiating it from other similar disorders but also in the recognition of rare but associated skin manifestations. Genetic testing has increased our ability to make the diagnosis in uncertain cases, but has not allowed us to predict a particular patient's natural history based on the mutation. Further research into genotype–phenotype correlations is needed before such predictions can be made. There is a paucity of available medical treatments, but ongoing trials hold promise in treating both the cutaneous and noncutaneous manifestations of NF1.

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