The Diagnostic and Clinical Significance of Café-au-lait Macules

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KEYWORDS

• Café-au-lait • Neurofibromatosis • NF-1

DEFINITION

Café-au-lait, also referred to as café-au-lait spots or café-au-lait macules, present as well-circumscribed, evenly pigmented macules and patches that range in size from 1 to 2 mm to greater than 20 cm in greatest diameter (**Fig. 1**). In light-skinned persons, the color appears light brown, or "coffee with milk," whereas in darker-skinned patients the color may appear as a medium to dark brown hue. Morphologically, café-au-lait have often been described as appearing either oval and smooth-bordered, resembling the "coast of California," or with jagged contours resembling the "coast of Maine." Although it has been suggested that the smooth-bordered, "coast of California" café-au-lait are more typical of the café-au-lait seen in neurofibromatosis type 1 (NF-1) whereas those with the more jagged "coast of California" are more indicative of the café-au-lait seen in McCune-Albright syndrome, in clinical practice there appears to be a wide variability in morphology, such that this generalization is not diagnostically significant. Isolated, large café-au-lait may be seen on the torso or extremities (**Fig. 2**).

Histologically, café-au-lait demonstrate an increase in melanin content of both melanocytes and basal keratinocytes.[1] Giant melanosomes (macromelanosomes) may be seen. Both an increase in the number of melanocytes and an increase in the concentration of melanin and macromelanosomes has been reported in the

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Pediatr Clin N Am 57 (2010) 1131–1153
doi:10.1016/j.pcl.2010.07.002 **pediatric.theclinics.com**
0031-3955/10/$ – see front matter

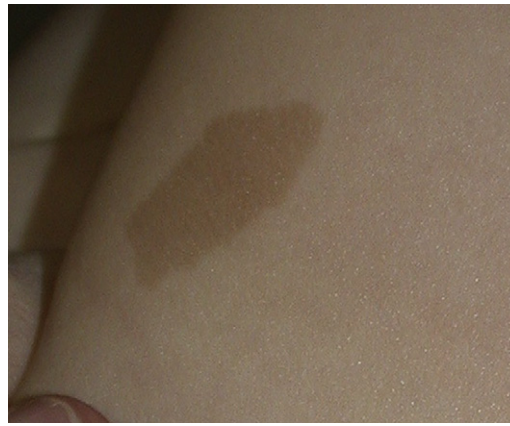

Fig. 1. Café-au-lait. Characteristic features include even pigmentation and smooth, well-defined borders.

café-au-lait associated with NF-1 as opposed to sporadic café-au-lait.[2,3] Proliferation of melanocytes is not seen.

EPIDEMIOLOGY AND NATURAL HISTORY

Solitary café-au-lait are common birthmarks. The presence of more than one café-au-lait, however, is less common. The frequency of multiple lesions, which has significance regarding the requirement for additional evaluation, has been examined in several population-based studies. Overall, the presence of one or more café-au-lait appears more common in African Americans than in Caucasians. The overall prevalence of at least one café-au-lait was noted to be present in 2.5% of neonates among 18,155 newborns of Caucasian, African American, Latino, and mixed-race ethnicity.[4] In this same study, one café-au-lait was noted in 0.3% of Caucasian newborns and 12% of African American newborns; 3 or more café-au-lait were seen in 1.8% of African American newborns but not in any Caucasian newborns. In a heterogeneous population of 4641 neonates in Boston, the overall prevalence of café-au-lait was noted to be 2.7% with at least one café-au-lait noted in 0.3% of Caucasian newborns and 18.3% of black newborns; none of the Caucasian infants was noted to have more than one café-au-lait, although in black infants 4.4% were noted to have 2 and 1.8%

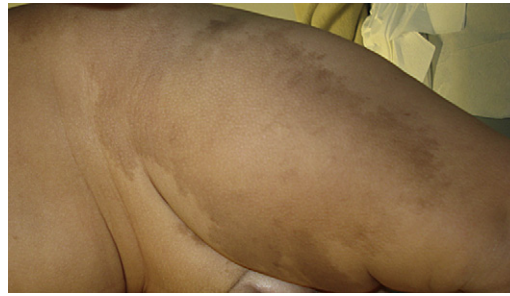

Fig. 2. Segmental café-au-lait. Characteristic features include even pigmentation with well-demarcated but "ragged" borders.

had 3 or more café-au-lait.[5] In infants and preschool-aged children, the prevalence of at least one café-au-lait increases to 25% of children as determined from a Baltimore cohort of 365 children aged 1 month through 5 years.[6] Whereas one café-au-lait was noted in 18.9% of children, the presence of 3 or more café-au-lait were seen in only 1.1% of children, and overall only 0.7% of otherwise normal children had 2 or more café-au-lait. In school-aged children, at least one café-au-lait has been noted in 22% to 36% of children.[7–10] Overall, the presence of 2 café-au-lait was reported to occur in 4.1% of a cohort of 732 Caucasian children from Nottingham, United Kingdom, and 3 café-au-lait were reported to occur in only 1.2% of children; the presence of 5 or more café-au-lait were seen in only 0.7% of children, and 60% of these children, all of whom had 6 or more café-au-lait, were presumed to have NF-1.[6] In a population of 1123 white Australian children aged 6 to 15 years, 26.1% were noted to have one café-au-lait, 6.9% to have 2 café-au-lait, and 3.3% to have 3 or more café-au-lait.[9]

Although many café-au-lait are present at birth, they may also manifest within the first few years of life. In fair-skinned infants they may be difficult to perceive on routine physical examination, but may be accentuated with examination under a Wood lamp. In general, it is unusual for additional sporadic café-au-lait to develop after the age of 6 years; in syndromes such as NF-1, however, new café-au-lait may continue to develop throughout childhood and adulthood. Sporadic café-au-lait often have been noted to fade in adulthood, whereas those associated with syndromes such as NF-1 do not.[11] Café-au-lait may develop anywhere on the body, although they more commonly occur on the torso, buttocks, and lower extremities and are uncommon on the face. During childhood they increase in size proportionate to the growth of the child. There does not appear to be any significant risk of malignant melanoma arising in a café-au-lait; only 2 case reports have been presented in the literature and likely occurred in combination by chance alone.[12,13]

PATHOGENESIS

Although café-au-lait may be seen anywhere on the body, they appear to be most common on the torso and occur rarely on the face, suggesting that sunlight exposure is not involved in the pathogenesis. An increase in the secretion of hepatocyte growth factor (HGF) and stem cell factor (SCF) by dermal fibroblasts has been reported in café-au-lait associated with NF-1, suggesting that these growth factors may be associated with the increased epidermal melanization observed in at least some café-au-lait.

DIFFERENTIAL DIAGNOSIS

Although café-au-lait are usually readily diagnosed on examination, occasionally they may be difficult to differentiate from other pigmented lesions (**Table 1**). At times, café-au-lait may be difficult to distinguish from other pigmented birthmarks, including congenital melanocytic nevi, speckled lentiginous nevus, Becker nevus, and forms of pigmentary mosaicism such as nevoid hypermelanosisand segmental pigmentation disorder. Acquired pigmentary lesions, including ephelides (freckles), lentigo, and postinflammatory hyperpigmentation may also be mistaken for café-au-lait. The lesions of urticaria pigmentosa or solitary mastocytomas, which are benign manifestations of cutaneous mastocytosis, are often mistaken for café-au-lait as they are usually noted during infancy as acquired, light-brown macules scattered on the torso, buttocks, and extremities. They may be easily distinguished in most children by eliciting Darier's sign, or the development of urticaria with firm stroking, which triggers mast cell degranulation. Blistering may sometimes occur, most commonly during infancy.

Table 1
Differential diagnosis of café-au-lait

Diagnosis	Clinical Features
Ephelides	"Freckles"; 1–2-mm light brown macules on sun-exposed areas; darken with sun exposure and fade in winter
Lentigenes	Darkly pigmented, well-circumscribed 1–2-mm macules; usually solitary but may be more numerous; commonly associated with sun exposure
Congenital melanocytic nevus	Light-brown to dark-brown, usually well-circumscribed macules, patches or plaques; may be associated with hypertrichosis; although many are uniform in color, areas of darker pigmentation may be noted
Becker nevus	Acquired light brown patch that usually develops during adolescence; more common in males; usually seen on the shoulder upper chest or upper back; associated with hypertrichosis
Pigmentary mosaicism	Irregular, light-brown to medium-brown patches, often with jagged borders, that typically present at birth or in early infancy; may be referred to as nevoid hypermelanosis. Larger patches, referred to as segmental pigmentary disorder, may be seen on the torso and demonstrate a well-defined midline border and less well-defined lateral border represent a form of cutaneous mosaicism
Postinflammatory hyperpigmentation	Poorly defined hyperpigmented macules and patches that develop at sites of prior trauma or inflammation; there may be associated atrophic or hypertrophic scarring; usually fade over time
Speckled lentiginous nevus	Congenital light-brown patch that develops acquired pigmented lesions within, usually junctional or compound melanocytic nevi
Urticaria pigmentosa, mastocytoma	Light brown to medium brown, relatively well-circumscribed congenital or acquired macules, papules, and plaques composed of increased numbers of cutaneous mast cells; often urticate when stroked or in response to heat, friction, or other exposures that trigger mast cell degranulation

EVALUATION

Presentation of a child with café-au-lait macules to the primary care provider, geneticist, or dermatologist is a common scenario. Two prospective cohort studies have attempted to define the predictive value of the number and morphology of café-au-lait macules in children with regard to eventual diagnosis of NF-1 or other disorders associated with café-au-lait. In one study, a cohort of 41 children with 6 or more café-au-lait greater than 5 mm in diameter was followed prospectively.[14] The children ranged in age from 1 month to 10 years at initial evaluation and were followed clinically over a period of at least 2 years. Fifty-eight percent of children were eventually diagnosed with NF-1 using established clinical criteria, predominantly based on the presence of axillary and/or inguinal freckling, with Lisch nodules and cutaneous neurofibromas developing in only a few patients each. The mean age at diagnosis of skin-fold freckling was 4.4 years, with a range of 18 months to 11.6 years. Lisch nodules were noted at a mean age of 3.7 years, with a range of 1.2 to 7.5 years. Six children were noted to have features of segmental neurofibromatosis with

café-au-lait and skin-fold freckling only without other manifestations of NF-1. When those patients who were diagnosed with segmental neurofibromatosis or another disorder were excluded, NF-1 was diagnosed in 75% of children. Seventy-five percent of children were diagnosed with NF-1 on the basis of consensus criteria by 6 years of age, and the majority by 10 years. Of note, 8 children were diagnosed with multiple café-au-lait only without any other stigmata of NF-1; one of these children was also noted to have severe developmental delay but no other unifying diagnosis. One patient each was diagnosed with Banayan-Riley-Ruvalcalba syndrome, LEOPARD/multiple lentigenes syndrome, and McCune-Albright/polyostotic fibrous dysplasia, respectively. In a smaller cohort of 21 patients with 6 or more café-au-lait 5 mm or larger, 8 of 14 children with "typical" café-au-lait were diagnosed with NF-1; in the remaining 6 patients with NF-1, the diagnosis was suspected on the basis of nondiagnostic clinical features but was unconfirmed. Only 1 patient of 5 with "atypical" café-au-lait was suspected of having NF-1.[15]

More recently, a cohort of 110 children aged 1 to 206 months referred for evaluation to a single NF-1 center on the basis of the presence of one or more café-au-lait was followed for a period of 4 years.[16] Thirty-one percent of children met clinical criteria for NF-1 during the study period. Of the children with 6 or more café-au-lait at presentation, 77% were eventually diagnosed with NF-1. No child with less than 6 café-au-lait was diagnosed with NF-1. The children eventually diagnosed with NF-1 had a mean of 11.8 café-au-lait (ranging from 6 to more than 20). In patients with "typical" café-au-lait (those with even pigmentation and smooth, distinct borders, usually round or oval in shape), 32 of 68 (47%) eventually met criteria for NF-1 compared with 2 of 42 (4.7%) of those patients with "atypical" café-au-lait (those with irregular or smudgy borders or nonhomogeneous pigmentation), both of whom had greater than 6 café-au-lait. The mean age at diagnosis of NF-1 was 33.5 months; 76% met criteria for diagnosis by 4 years of age, 94% met criteria for diagnosis at 6 years of age, and all were diagnosed by 8 years of age. The most common diagnostic feature in addition to café-au-lait was axillary or inguinal freckling, which was observed in 77% of patients.

CLINICAL PRESENTATIONS

Although neurofibromatosis-1 is the most common and well-recognized syndrome associated with café-au-lait, they have been associated with several other syndromes, including neurofibromatosis-2 (NF-2), McCune-Albright syndrome, and Noonan syndrome. A review of the features of many of the syndromes associated with café-au-lait is presented in **Table 2**. Although comprehensive, this list is not exhaustive, and for many of these syndromes the evidence that café-au-lait occur with more frequency than in the general population is weak because overall, the presence of 1 to 2 café-au-lait is relatively common.

Neurofibromatosis Type 1

Although von Recklinghausen is generally credited with the earliest systematic description of the clinical features of neurofibromatosis-1, which was previously known as von Recklinghausen disease, café-au-lait macules were not initially recognized as a prominent feature of this disease. Crowe published the first association of café-au-lait with neurofibromatosis in the English literature, and although the cohort of 98 institutionalized patients he described likely was composed not only of patients with what we now recognize as NF-1 but also with patients with other forms of neurofibromatosis, including familial spinal neurofibromatosis and segmental neurofibromatosis, he noted that "not a single adult was found with 6 or more café-au-lait spots who

Table 2
Syndromes associated with café-au-lait macules

Strength of Association	Syndrome	Clinical Features	Gene or Locus
Strong	Neurofibromatosis type 1	Multiple café-au-lait, skin-fold freckling, Lisch nodules, optic pathway glioma, skeletal dysplasia, cutaneous and plexiform neurofibromas, neurocognitive deficits, macrocephaly	NF-1
	Neurofibromatosis type 2	Acoustic neuromas, schwannomas, neurofibromas, meningiomas, juvenile posterior subcapsular lenticular opacity; café-au-lait seen but not a criterion for diagnosis	NF-2
	Multiple familial café-au-lait	Multiple café-au-lait without other stigmata of NF-1	?
	Legius (NF-1–like) syndrome	Multiple café-au-lait and skin-fold freckling without other stigmata of NF-1	SPRED1
	McCune-Albright syndrome	Segmental café-au-lait, precocious puberty, other endocrinopathies, polyostotic fibrous dysplasia	GNAS1
	Constitutional mismatch repair deficiency syndrome	Multiple café-au-lait, adenomatous colonic polyps, multiple malignancies, including colonic adenocarcinoma, glioblastoma, medulloblastoma, and lymphoma	MLH1, MSH2, MSH6, PMS2
	Ring chromosome syndromes	Multiple café-au-lait, microcephaly, mental retardation, short stature, skeletal anomalies	Chromosomes 7, 11, 12, 15, 17
	LEOPARD/multiple lentigenes syndrome	Café-au-lait, café-noir, lentigenes, cardiac conduction defects, ocular hypertelorism, pulmonary stenosis, genitourinary anomalies, growth retardation, hearing loss	PTPN11
	Cowden syndrome (multiple hamartoma syndrome)	Facial trichilemmomas, cobblestoning of the oral mucosa, predisposition to soft tissue tumors (lipomas, neuromas), gastrointestinal polyps, fibrocystic breast disease and breast carcinoma, thyroid adenoma and thyroid cancer	PTEN
	Banayan-Riley-Ruvalcalba syndrome	Facial trichilemmomas, oral papillomas, pigmented genital macules, gastrointestinal polyps, macrocephaly, vascular anomalies, mental retardation	PTEN
Weak	Ataxia-telangiectasia	Cerebellar ataxia, cutaneous and ocular telangiectasias, immunodeficiency, hypogonadism, predisposition to lymphoreticular malignancy	ATM
	Bloom syndrome	Photosensitivity, immunodeficiency, chronic lung disease, cryptorchidism, syndactyly, short stature, susceptibility to malignancy	RECQL3

Fanconi anemia	Bone marrow failure, multiple congenital anomalies, predisposition to malignancy, mental retardation, microcephaly	FANCA, FANCB (putative), FANCC, FANCD locus on chromosome 3, FANCE locus on chromosome 6, FANCF, FANCG, FANCH (putative)
Russell-Silver syndrome	Short stature, craniofacial and body asymmetry, low birth weight, microcephaly, triangular facies, fifth finger clinodactyly, congenital cardiac defects	?
Tuberous sclerosis	Facial angiofibromas, cutaneous collagenomas, seizures, mental retardation, hypomelanotic macules, periungual fibromas, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, pulmonary lymphangiomyomatosis renal angiomyolipoma, retinal hamartomas	TSC1, TSC2
Turner syndrome	Short stature, lymphedema, congenital heart disease, valgus deformity	X-chromosomal anomalies (XO karyotype or Xp deletion)
Noonan syndrome	Facial dysmorphism, pulmonary valve stenosis, webbed neck, pectus excavatum, mental retardation, short stature, cryptorchidism, hematologic malignancies	PTPN11, SOS1, RAF1, KRAS
Multiple mucosal neuroma (MEN) syndrome 1	Parathyroid adenoma, pituitary adenoma, pancreatic islet adenoma, lipoma, gingival papules, facial angiofibromas, collagenomas	MENIN
MEN syndrome 2B	Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma, parathyroid adenoma, marfanoid habitus	RET
Johanson-Blizzard syndrome	Short stature, failure to thrive, microcephaly, sensorineural hearing loss, dental anomalies, congenital heart disease, exocrine pancreatic insufficiency, imperforate anus, genitourinary anomalies, mental retardation, hypothyroidism	UBR1
Microcephalic osteodysplastic primordial dwarfism, type II	Short stature, microcephaly, intrauterine growth retardation, dysmorphic facies, skeletal anomalies, developmental delay, premature puberty	PCNT2
Nijmegen breakage syndrome	Short stature, growth retardation, microcephaly, cleft lip/palate, dysmorphic facies, bronchiectasis, sinusitis, dysgammaglobulinemia with recurrent urinary tract and gastrointestinal infections, mental retardation, spontaneous chromosomal instability, predisposition to malignancy	NBS1
Rubinstein-Taybi syndrome	Short stature, microcephaly, dysmorphic facies, congenital cardiac disease, sternal anomalies, skeletal anomalies, mental retardation	CREBBP, EP300
Kabuki syndrome	Postnatal growth retardation, microcephaly, dysmorphic facies, congenital cardiac defects, malabsorption, anal stenosis, genitourinary anomalies, congenital hip dysplasia, hirsutism, mental retardation	?

did not also have neurofibromata" and "the fewer the number of café-au-lait spots the more marked was the central involvement, as characterized by central nervous system, intrathoracic, or retroperitoneal tumors."[17] Of note, in Crowe's original study of neurofibromatosis patients (likely representing a mixed population of patients with NF-1, NF-2, schwannomatosis, and segmental neurofibromatosis), 22% had less than 6 café-au-lait and 5% had none.

The majority of children with NF-1 have multiple café-au-lait scattered predominantly on the torso, buttocks, and legs, although they may occur anywhere (**Fig. 3**). The macules are classically described as having a smooth, "coast of California" border, although it is well known that café-au-lait with a less typical morphology also occur in NF-1. Café-au-lait are usually the first presenting sign of NF-1, although in young children they may be overlooked or, in fair-skinned infants, difficult to appreciate on physical examination. The spots are often present at birth, and frequently increase in number during the first 6 to 10 years of life; they increase in size proportionate to the growth of the child and darken with sun exposure. There is no association between number of café-au-lait and severity of NF-1.

Diagnostic criteria for NF-1 were established in 1988 by a National Institutes of Health Consensus Conference and revised in 1997.[18,19] The presence of 2 or more of the following criteria is required to establish the diagnosis.

- Six or more café-au-lait $\geq$5 mm in prepubertal individual or $\geq$15 mm in a postpubertal individual
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Axillary and/or inguinal freckling
- Optic pathway glioma
- Two or more Lisch nodules
- A distinctive osseous lesion, including sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudarthrosis
- A first-degree relative (parent, sibling, offspring) with confirmed NF-1.

Lisch nodules are benign, asymptomatic iris hamartomas that are pathognomonic for NF-1. These nodules are typically only visualized under slit-lamp examination and usually develop during childhood. Optic pathway gliomas (OPG) are present in about 15% of patients with NF-1, but are considered indolent tumors with a low incidence of progression to symptomatic presentation, with only about 30% becoming symptomatic. These gliomas may be noted on fundoscopic examination, incidentally

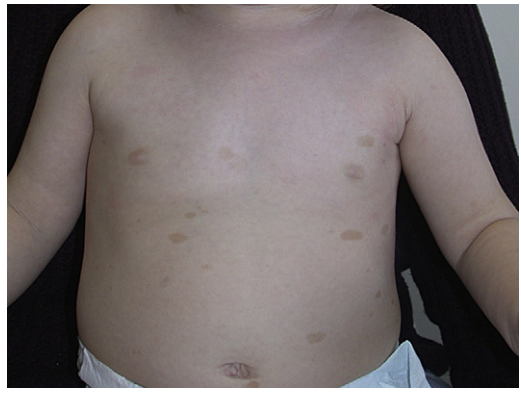

Fig. 3. Multiple café-au-lait in a child with neurofibromatosis type 1.

on radiologic examination, or may present with proptosis, decreased visual acuity, visual field defects, headache, or precocious puberty; most are diagnosed by 3 years of age.[20,21] Current recommendations for screening for OPG in children with NF-1 do not include the routine use of magnetic resonance imaging but do include annual full ophthalmologic evaluation through age 6 years with less frequent evaluation after age 6 years.[20,21] Sphenoid wing dysplasia and cortical thinning and dysplasia of the long bones are peculiar osseous malformations seen in NF-1 that represent congenital mesodermal dysplasias. Sphenoid wing dysplasia may be noted on careful physical examination or on radiologic imaging of the facial bones. Cortical thinning and dysplasia of the long bones are usually congenital in origin and may present with anterolateral bowing of the tibia and subsequent pathologic fractures during the first year of life with resultant pseudoarthoses; any long bone may be involved, but the tibia, humerus, and femur are the most commonly affected sites.

Use of the diagnostic criteria for NF-1 has been validated in the diagnosis of NF-1 in children. In a large cohort of 1402 patients younger than 21 years who were diagnosed with NF-1 after evaluation at a neurofibromatosis clinic, 97% met 2 or more criteria by 8 years of age, and all met criteria by 20 years of age.[22] However, 30% of infants diagnosed with NF-1 before 1 year of age presented with only one criterion in addition to an affected first-degree relative, and overall 46% of sporadic cases did not meet criteria at 1 year of age, suggesting that diagnosis in infants for whom there is no family history is difficult if they are younger than 1 year. Ninety-nine percent of NF-1 patients presented with 6 of more café-au-lait 5 mm or larger by 1 year of age. Inguinal and/or axillary freckling was noted in 90% of patients by 7 years of age, and Lisch nodules were seen on slit-lamp examination in more than 70% of affected children by 10 years of age. In contrast, neurofibromas were seen in only 48% of children by 10 years of age and 84% of patients by 20 years of age. Osseous lesions are usually noted within the first year of life and were noted in 14% of patients. Symptomatic optic pathway glioma was noted in 1% of patients by 1 year of age and in 4% by 3 years of age. Excellent reviews of the clinical features of NF-1, including both the cutaneous and extracutaneous manifestations, have been published recently.[23–25]

Skin-fold freckling, also known as Crowe's sign, presents as multiple 1- to 3-mm pigmented macules resembling small café-au-lait and is reportedly the most specific of the NF-1 criteria; it is considered pathognomonic for NF-1[23] (**Fig. 4**). Skin-fold freckling often arises around 3 to 5 years of age, although it may be noted earlier and occasionally at birth.[26] In addition to the axillary and inguinal areas, skin-fold freckling may also involve the posterior neck, inframammary region, and perioral area.

Neurofibromas are benign nerve sheath tumors composed of Schwann cells, fibroblasts, mast cells, nerve axons, and perineural cells, and although not specific for NF-1, they are a cardinal feature. Neurofibromas are further characterized as cutaneous (dermal), subcutaneous, and plexiform. Cutaneous neurofibromas appear as rubbery, exophytic soft papules and nodules in the skin and may occur anywhere on the body. These lesions usually present during adolescence and increase in number during adulthood; they may eventually number in the hundreds.[27] Neurofibromas may cause significant disfigurement and pruritus. Cutaneous neurofibromas are not considered to have the potential for malignant degeneration. Subcutaneous neurofibromas appear as rubbery subcutaneous masses; they are often painful, and those that involve the dorsal root ganglia may cause symptoms of spinal cord compression. Malignant degeneration is uncommon. Plexiform neurofibromas are usually present at birth, although they may not become clinically apparent until later in childhood or in adulthood. Plexiform neurofibromas are clinically apparent in 27% of patients, although about 50% of adult NF-1 patients show evidence of plexiform

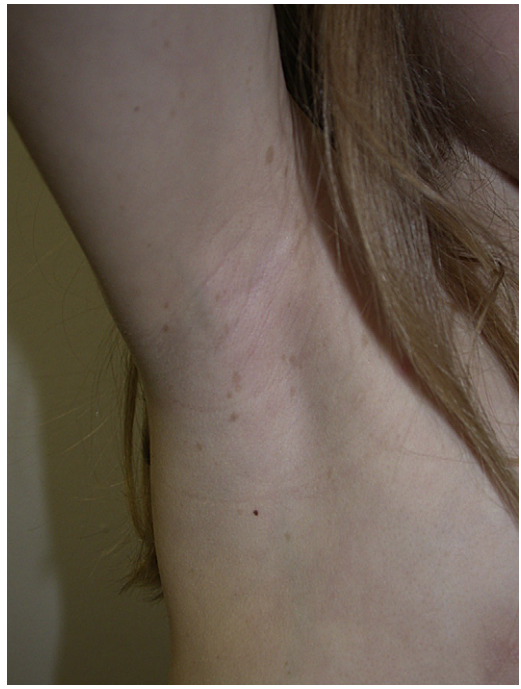

Fig. 4. Axillary freckling in a child with neurofibromatosis type 1.

neurofibromas on computed tomography imaging.[28] These lesions are typically large nodular tumors that develop along nerves. On examination, they feel like a "bag of worms." Associated overlying café-au-lait and/or hypertrichosis may be evident. Large, diffuse plexiform neurofibromas may cause significant pain, disfigurement, and compression of the skin, subcutis, and associated viscera. Plexiform neurofibromas are associated with the development of malignant peripheral nerve sheath tumors (MPNST), which are reported to occur in 8% to 12% of NF-1 patients.[29] Although plexiform neurofibromas are often noted to grow during childhood, the development of sudden, rapid growth, associated pain, or neurologic deficit should alert the clinician as to the possibility of malignant transformation. MPNST carry a poor prognosis; metastasis is common, and many are resistant to chemotherapy.

In addition to café-au-lait, skin-fold freckling, and cutaneous and plexiform neurofibromas, other cutaneous findings in NF-1 include generalized hyperpigmentation, blue-red macules, and pseudoatrophic macules; the latter 2 entities are believed to represent unusual variants of cutaneous neurofibromas. Juvenile xanthogranulomas, which are non-Langerhans cell histiocytic proliferations that most commonly involve the skin, have also been reported to occur more frequently in NF-1 than in the general population and to possibly indicate an increased risk of juvenile myelomonocytic leukemia, although these associations are questionable.[30,31] Other clinical features of NF-1 include relative macrocephaly (45%), short stature (30%), scoliosis (10%), pectus excavatum, cognitive deficits (including attention deficit hyperactivity disorder, learning disabilities, below average intelligence) (30%–60%), hypertension, vascular dysplasia, precocious puberty, and unidentified bright objects on brain magnetic resonance imaging.[32] Vascular dysplasia, including pulmonary stenosis, renal artery stenosis, and stenosis or occlusion of the internal carotid and cerebral arteries occurs

in about 2% of children with NF-1.[33] In addition to MPNST, other malignancies reported to occur in association with NF-1 include pheochromocytoma, rhabdomyosarcomas, gastrointestinal stromal tumors, intracranial neoplasms, and juvenile myelomonocytic leukemia.[34–40] Neurofibromatous neuropathy is a symmetric, predominantly sensory polyneuropathy that may develop in NF-1 patients and is associated with the development of large numbers of cutaneous and subcutaneous neurofibromas.[41] Vitamin D deficiency, osteopenia, and osteoporosis have been reported to occur in adults and children with NF-1, and may be a predisposing factor in skeletal anomalies, including scoliosis.[42–44]

The prevalence of NF-1 is estimated to be between 1 in 2000 and 1 in 4500 persons.[45] NF-1 is an autosomal dominant disorder with 100% penetrance but broad variability in clinical manifestations.[46,47] The gene responsible for NF-1 was discovered in 1990, is localized on chromosome 17q11.2, and encodes the protein neurofibromin, a tumor suppressor involved in the intracellular Ras-guanosine triphosphate pathway, which regulates cell proliferation and differentiation.[48–50] Wild-type neurofibromin inhibits Ras-guanosine triphosphatase (GTPase) activity; when the NF1 gene is mutated, activation of Ras occurs and results in increased signaling through downstream effectors such as Raf and mitogen-activated protein kinase (MAPK).[51]

The NF1 gene has one of the highest spontaneous mutation rates among known human genes; approximately 50% of patients present with de novo mutations and therefore no family history of NF-1. Eighty to ninety percent of new mutations are paternally derived.[52,53] In addition, a wide variety of mutations have been described, including gene deletions, insertions, amino acid substitutions, chromosomal rearrangements, and splicing mutations.[54,55] There appears to be little genotype-phenotype correlation with the exception of patients with deletion of the entire NF1 gene as part of a contiguous gene deletion syndrome, which occurs in about 5% of all NF-1 patients; deletion of the entire NF1 gene is associated with a tendency to develop large number of neurofibromas, more severe cognitive deficits, and greater risk of developing MPNST.[56–59] Many of the known mutations in the NF1 gene are predicted to result in premature truncation of the neurofibromin protein. The NF1 gene is quite large, encompassing 60 exons and more than 300 kilobases of DNA; therefore detection of NF1 mutations is a difficult and time-consuming endeavor. A comprehensive mutation analysis of the NF1 gene now allows for identification of NF1 mutations in 95% of patients who meet clinical criteria for the diagnosis of NF-1.[60] Although penetrance appears to be nearly 100%, there is a significant degree of variability in expressivity, even among family members carrying the same NF1 mutation.[61] Genetic analysis of a panel of melanocyte-derived primary cell cultures from café-au-lait from 5 patients with NF-1 demonstrated not only the germline NF1 mutation but also a second mutation in the other NF1 gene.[62] Neurofibromas from patients with NF-1 have also been shown to possess not only the germline NF1 gene mutation but also a second-hit mutation in the NF1 gene.[63]

Segmental NF-1 is a variant of NF-1 that results from somatic mosaicism arising from postzygotic mutations in the NF1 gene, such that the clinical manifestations of NF-1 are present only in a localized body segment.[64–68] Mutations in NF1 have been demonstrated in café-au-lait and neurofibromas in these patients.[62,68] Bilateral presentations of segmental NF-1 have been reported.[69–74] Another variant of NF-1 is hereditary spinal neurofibromatosis, a rare disorder that generally presents with multiple café-au-lait and multiple, symmetric spinal root neurofibromas; skin-fold freckling may be present but other stigmata of NF-1 are typically absent.[75,76]

A subset of patients with NF-1 appears to manifest overlap in clinical features with Noonan syndrome, including pulmonary valve stenosis, “Noonan” facies, and pectus

excavatum; these patients have been shown to manifest NF1 mutations.[77–80] Of note, both NF-1 and Noonan syndrome, in addition to several other genetic syndromes, display a remarkable overlap in clinical features, including pigmentary skin anomalies, facial dysmorphism, short stature, congenital heart defects, neurocognitive defects, and a predisposition to malignancy. Related disorders include Costello syndrome, cardiofaciocutaneous syndrome, and LEOPARD syndrome. These disorders have been collectively referred to as the neuro-cardio-facial-cutaneous syndromes, and they have all been shown to result from mutations in one or more of several genes involved in the Ras/Mitogen-activated protein kinase (RAS/MAPK) signaling pathway, which regulates cell proliferation and differentiation through several downstream effectors, including ERK (extracellular signal-regulated kinase).[51,81–83]

Familial Multiple Café-au-lait

Several reports have identified families in which multiple café-au-lait are present without any other stigmata of NF-1 and no evidence of mutation in the NF1 gene. Familial multiple café-au-lait appears to be transmitted as an autosomal dominant disorder; its relationship to NF-1 remains unclear and awaits further characterization at the genetic level.[84–87] This diagnosis should only be made in an older child when other features of NF-1 are absent and there is a clear family history of multiple café-au-lait without other stigmata of NF-1.

Legius Syndrome

The presence of familial café-au-lait in association with axillary and/or inguinal freckling but without the presence of Lisch nodules, neurofibromas, or other stigmata of NF-1 was recently demonstrated to be associated with mutations in the gene SPRED1 (Sprouty-related, EVH1 domain containing 1) in several families in whom no NF1 gene mutations were identified.[88] SPRED1 is a negative regulator of ERK, and SPRED1 specifically inhibits MAPK signaling by suppressing activation of Raf.[89] Previously known as NF-1–like syndrome, Legius syndrome is indistinguishable from NF-1 regarding number and pattern of distribution of café-au-lait and skin-fold freckling.[90] In the original cohort of 44 patients from 5 families, multiple café-au-lait were noted in each patient with a variable number manifesting skin-fold freckling, which was described as “mild”; other reported features included macrocephaly 97% or greater (29.5%), cutaneous lipomas (32%), Noonan-like facial dysmorphism (9%), attention-deficit/hyperactivity disorder (ADHD) and/or learning disability (9%), pectus excavatum (7%) and supravalvular pulmonic stenosis (2%). No Lisch nodules, neurofibromas, OPG, or distinctive osseous lesions were noted.[88] A cohort of 42 patients with documented SPRED1 mutations, including 23 probands and 19 relatives, were screened for the presence of café-au-lait, skin-fold freckling, and macrocephaly.[91] Twenty of these patients (47.6%) met clinical criteria for NF-1 based on 6 or more café-au-lait and skin-fold freckling. Skin-fold freckling, however, was reported as “mild or faint” in half of the affected patients. In addition, 34 of 1318 (2.6%) of patients from an anonymous cohort referred for NF1 genetic testing demonstrated a SPRED1 mutation. The majority of mutations were predicted to result in premature SPRED1 protein translation. Overall, from the anonymous cohort, 1086 patients met clinical criteria for NF-1; 76% demonstrated an NF1 mutation, 1.9% demonstrated a SPRED1 mutation, and 22% failed to demonstrate either an NF1 or SPRED1 mutation. In the patients with documented SPRED1 mutations, there were no patients with Lisch nodules, neurofibromas, OPG, or the typical osseous lesions of NF-1. Several children with ADHD and/or abnormal language and speech development were noted.

Neurofibromatosis Type 2

In contrast to NF-1, NF-2 is significantly less common, with a prevalence of about 1:25,000 based on epidemiologic studies in England.[92] Penetrance approaches 100%.[92,93] Café-au-lait, although not a diagnostic criterion for NF-2, are present in 33% to 43% of patients; other cutaneous manifestations are seen in 59% to 68% of patients and include cutaneous schwannomas, which present as pigmented plaques and intradermal tumors, and cutaneous neurofibromas.[93–95] Although vestibular schwannomas, previously known as acoustic neuromas, are the most recognizable feature of this disorder, other diagnostic criteria include spinal schwannomas, neurofibromas, meningiomas, and gliomas.[92] The Manchester diagnostic criteria comprise the diagnostic standard for NF-2. Any one of the following sets of clinical manifestations is required for the diagnosis of NF-1[96]:

- Bilateral vestibular schwannomas
- First-degree relative with NF-2 plus unilateral vestibular schwannoma or two of meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lenticular opacity
- Unilateral vestibular schwannoma plus two of meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lenticular opacity
- Multiple meningiomas plus unilateral vestibular schwannoma or two of schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacity.

Schwannomas are benign, encapsulated tumors arising from the Schwann cells of cranial nerves 3 to 12, spinal nerves, and peripheral nerves; malignant degeneration is rare. The clinical and genetic features of NF-2 have recently been reviewed.[97] Although most patients present in early adulthood with hearing loss secondary to a vestibular schwannoma, often with associated tinnitus, dizziness, and vertigo, presentation during childhood may occur.[96,98] In children the most common presenting signs and symptoms include deafness, meningiomas, spinal schwannomas, cutaneous schwannomas, café-au-lait, early-onset lens opacities, visual abnormalities, and peripheral neuropathy.[99–101]

The gene for NF-2 is located on chromosome 22q11.2 and encompasses 17 coding exons. NF2 encodes the protein merlin (also known as schwannomin), which is believed to function as a tumor suppressor, and loss of merlin expression has been documented in NF-2–associated tumors.[102,103] There is a high rate of de novo mutations, with about 50% of patients lacking a family history of NF-2.[96] Somatic mosaicism has been reported with evidence for gonadal mosaicism and transmission of the mutated NF2 gene to offspring.[104] Genetic testing is available and can detect mutations in NF2 in 95% of patients who meet diagnostic criteria. Genotype-phenotype correlations exist.[105]

McCune-Albright Syndrome

McCune-Albright syndrome (MAS) is a rare, sporadic disorder; the incidence is unknown. The cardinal features include polyostotic fibrous dysplasia, precocious puberty and other endocrinopathies, and large, irregular segmental café-au-lait that typically involve the torso or buttocks. The differential diagnosis for the large café-au-lait that occurs in MAS includes segmental pigmentation disorder and segmental NF-1.[106–108] Diagnosis of MAS requires the presence of at least 2 of the 3 cardinal clinical features. Fibrous dysplasia is most commonly polyostotic, although monostotic presentation may be seen, and typically involves the long bones and base of the skull. Although these anomalies may be asymptomatic, pain, fracture and skeletal

asymmetry may develop. Fibrous dysplasia has been reported in 46% to 98% of patients with MAS.[109,110] Severely affected persons may present at birth; although most children are diagnosed with MAS within the first few years of life with a mean age at diagnosis of 4.9 years. Precocious puberty is the most common presentation and is significantly more common in girls, which may account for the preponderance of this disorder in girls. MAS is frequently characterized by alternating progression and regression of pubertal development with atypical pubertal development. Precocious puberty has been reported in 64 to 94% of girls with MAS but in only 15% of boys.[110–113] Other endocrinologic abnormalities include hyperthyroidism, hyperparathyroidism, and acromegaly. Cardiac disease, hepatobiliary disease, nephrocalcinosis, renal phosphate wasting, and platelet dysfunction have also been reported in patients with MAS.[114–116]

The café-au-lait associated with MAS generally are large, unilateral, and often occur on the buttocks, chest, and posterior neck. Although clinically the café-au-lait of MAS are indistinguishable from those seen in NF-1, macromelanosomes are reportedly absent in the café-au-lait associated with MAS.[117] The café-au-lait seen in association with MAS are usually noted at birth or within the first few years of life, and are seen in 53% to 95% of patients with MAS.[109,112] Once present, they do not increase in number but do increase in size proportionate to the growth of the child. Accentuation with sun exposure occurs. The macules are commonly described as having a jagged, "coast of Maine" border, although this morphology is not uniformly present. The café-au-lait are distributed along the lines of Blaschko, which represent ectodermal migration patterns during embryogenesis and thus are a manifestation of the somatic mosaicism that underlies MAS.[118] Pigmentation of oral mucosa manifesting as melanotic macules has also been reported in MAS.[119,120]

MAS is caused by postzygotic mutations in the gene GNAS1, which encodes the α subunit of stimulatory G protein.[121,122] Only 4 missense mutations have been described in MAS; all of these mutations have been documented to involve arginine 201, which is critical for modulation of GTPase activity. Through their interaction with numerous G-protein–coupled receptors, G proteins regulate a variety of signal transduction pathways; in MAS, dysregulation of GTPase activity results in constitutive activation of adenylyl cyclase activity and increased intracellular cyclic adenosine monophosphate (AMP) levels.[123] Autonomous endocrine hyperfunction, increased melanogenesis, and dysregulation of cell proliferation all result from increased cyclic AMP–mediated intracellular signaling. Germline mutations in GNAS1 are proposed to be lethal, thus only embryos with somatic mutations survive; the resultant genetic mosaicism results in marked phenotypic variability.[124] Family history, therefore, is routinely negative. Within the skin, melanocytes derived from areas of café-au-lait have been shown to manifest activating mutations in GNAS1 with resultant increased cyclic AMP activity and increased tyrosinase activity.[125] Overall, however, genetic testing of skin from café-au-lait in patients with MAS for the presence of GNAS1 mutations yields an identifiable mutation in only 27% of affected patients, compared with 21% from peripheral blood, 82% from affected bone, and 100% from thyroid tissue as demonstrated in an analysis of 113 affected patients.[113] This finding has been attributed to the low proportion of melanocytes in affected skin, which renders detection of GNAS1 mutations difficult, even despite use of highly sensitive polymerase chain reaction–based analysis.

Constitutional Mismatch Repair Deficiency Syndrome

Recently, an association between the presence of multiple café-au-lait and skin-fold freckling without other stigmata of NF-1, adenomatous colonic polyps with

early-onset colorectal carcinoma, and a predisposition to a variety of pediatric malignancies has emerged.[126] This syndrome has been variably termed constitutional mismatch repair deficiency (CMMR-D), Lynch III syndrome, and CoLoN (colon tumors and/or leukemia/lymphoma and/or neurofibromatosis features). Homozygous or compound heterozygous germline mutations in one of several genes involved in DNA mismatch repair have been identified in affected children, including MLH1, MSH2, MSH6, and PMS2. These genes have all been previously associated with hereditary nonpolyposis colorectal cancer, also referred to as Lynch syndrome.[127] The malignancies associated with CMMR-D include hematological malignancies, including non-Hodgkin lymphoma and acute lymphoblastic lymphoma; brain tumors, including glioblastoma multiforme, primitive neuroectodermal tumor, medulloblastoma, and astrocytoma; Lynch syndrome–associated tumors, including colorectal carcinoma; and other tumors, which have included neuroblastoma and rhabdomyosarcoma.[126]

In several reports, the café-au-lait observed in children with CMMR-D have been described as having a "ragged-edge, slightly diffuse appearance," with irregular borders.[128–131] Axillary freckling has been described in some patients.[128,132–135] Skin-fold freckling has been noted in some affected children, and isolated patients with plexiform neurofibroma, cutaneous neurofibroma, Lisch nodules, and pseudarthrosis of the tibia have been reported.[132,136–138] NF1 gene evaluation for patients with CMMR-D has been negative.[133,134,139,140] In addition, 3 siblings with CMMR-D and biallelic MSH2 germline mutations and a single patient with biallelic MSH6 mutations who manifested both hyperpigmented and hypopigmented cutaneous macules and patches have been reported.[130,141]

Somatic inactivation of the NF1 gene through mismatch repair defects has been proposed to explain the occurrence of café-au-lait, skin-fold freckling, and other features of NF-1 in affected patients. The NF1 gene has been shown to be a mutational target in mismatch repair–deficient cells.[142]

Ring Chromosome Syndromes

Multiple café-au-lait have been reported in patients with ring chromosome syndromes involving chromosomes 7, 11, 12, 15, and 17.[143–150] These children tend to present with a variety of other congenital anomalies including facial dysmorphism, microcephaly, and clinodactyly, as well as with short stature and neurocognitive deficits.

TREATMENT

Treatment of café-au-lait is not required for medical reasons, but is often requested by patients and caregivers for cosmetic concerns, in particular with large, segmental café-au-lait or when café-au-lait are present on the face. There is no uniformly successful treatment modality for removing café-au-lait. Several medical lasers have been used for the treatment of café-au-lait, all with variable clinical results. Complications of laser surgery include discoloration of the skin and scarring, and recurrence after treatment is common. The Q-switched ruby laser, erbium:YAG laser, 1064-nm frequency-doubled Q-switched Nd:YAG laser, copper vapor laser, and 510 nm pulsed-dye laser have all been used.[151–160]

SUMMARY

Café-au-lait are common pigmented skin lesions in children. Although most café-au-lait present as 1 or 2 hyperpigmented macules or patches in an otherwise healthy child, the presence of multiple café-au-lait, large segmental café-au-lait, associated facial dysmorphism, other cutaneous anomalies, or unusual findings on physical examination

should suggest the possibility of an associated syndrome. While NF-1 is the most common syndrome seen in children with multiple café-au-lait, other syndromes associated with one or more café-au-lait include McCune-Albright syndrome, Legius syndrome, Noonan syndrome, and other neuro-cardio-facial-cutaneous syndromes.

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