Café au Lait Spots: The Pediatrician's Perspective

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The Pediatrician's Perspective

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Additional media illustrating features of the disease processes discussed are available in the online version of this article at www.pedsinreview.org.

Objectives

After completing this article, readers should be able to:

1. Define café au lait spots typical of neurofibromatosis type 1 (NF1) and describe their frequency and variability in the normal population.
2. List three or more genetic disorders other than NF1 that are associated with café au lait spots.
3. Summarize three or more clinical manifestations and molecular bases of NF1 and NF2.
4. List the diagnostic criteria for NF1.
5. Summarize clinical findings of genetic disorders other than NF1 associated with café au lait spots.

Introduction and Epidemiology

Every pediatrician faces the challenge of deciding if a patient who has café au lait (CAL) spots has an underlying genetic condition. CAL spots typical of neurofibromatosis type 1 (NF1) are discrete, round or oval, uniformly hyperpigmented skin patches. Their color varies from light to dark brown, and the border may be smooth or irregular. They usually are smaller in newborns, enlarge as children get older, and are less prominent in adults. The histologic basis of CAL spots is increased melanin content, with the presence of giant melanosomes in both melanocytes and basal keratinocytes and no melanocytic proliferation. The giant melanosomes in CAL spots are not unique to NF1; they can be seen in unaffected skin of adults who have NF1 and occasionally in normal skin of healthy individuals. Therefore, the presence of giant melanosomes is not helpful for diagnosing NF1.

The frequency and number of CAL spots vary in the general population according to ethnic background and age. Sometimes otherwise healthy children who have red hair and often are of Irish or Welsh background have multiple areas of patchy hyperpigmentation. Similarly, multiple patchy areas of hyperpigmentation can occur in healthy children who have mixed ethnic backgrounds in which two parents have very different skin colors. CAL spots were noted in 0.3% of Caucasians and 18% of African-Americans in a study that included more than 4,000 newborns. Interestingly, none of the 2,682 Caucasian newborns had more than one CAL spot, although two or more spots were noted in 31 of 492 African-Americans. The frequency of having at least one CAL spot has been reported as 3% in Hispanic, 0.5% in Arab, 0.4% in Chinese, and 0.1% in Jewish newborns. CAL spots are often more discernable in older children. The frequency of having at least one CAL spot has been reported to be 13% in Caucasians and 27% in African-Americans who were younger than 10 years of age. Approximately 25% of Caucasian children between 6 to 15 years of age have at least one CAL spot.

Although solitary CAL spots are common in the general population, multiple spots may indicate an underlying genetic disorder. More than three CAL spots have been noted in only 0.2% to 0.3% of schoolchildren who have no known evidence of a multisystemic genetic disorder. Although data are not robust, more African-Americans than Caucasians appear to have multiple CAL spots without evidence of an underlying disorder. Because previous studies have shown that the frequency of having more than six CAL spots in

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Table 1. Some Mendelian Disorders In Which CAL Spots Have Been Reported Clinically

Disorder	Mode of Inheritance	Chromosome Location/ Defective Gene/ Protein Product	Clinical Summary
McCune Albright syndrome	Sporadic, rarely AD*	20q13.2/GNAS1	CAL spots, multiple osseous fibromas, precocious puberty, multiple endocrine problems
Tuberous sclerosis	AD*	9q34/TSC1/hamartin; 16p13.3/ TSC2/tuberin	See Table 3
Fanconi anemia	AR†	16q24.3/FANCA; 9q22.3/FANCC; 3p26–p22/FANCD; 6p22–21/FANCE; 11p15/FANCF; 9p13FANCG	Aplastic anemia, mental retardation, generalized hyperpigmentation, physical abnormalities (see Table 4), increased risk for malignancy
Bloom syndrome	AR†	15q26.1/BLM	Prenatal-onset short stature, malar hypoplasia, telangiectatic erythema of the face, increased risk for malignancy
Ataxia telangiectasia	AR†	11q22.3/ATM	Bulbar telangiectasia, progressive ataxia, immune deficiency, increased risk for malignancy
Russell-Silver syndrome	Mostly sporadic, rarely AD*	7; 17q25?	Prenatal-onset short stature, body asymmetry, fifth finger clinodactyly, small and triangular face
Multiple lentigines (LEOPARD) syndrome	AD*	?	Multiple small lentigines (occasionally CAL spots), mild pulmonary stenosis and electrocardiographic changes, hypertelorism, sensorineural deafness
Multiple endocrine neoplasia type 2b	AD*	10q11.2/RET	Mucosal neuromas, medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma, marfanoid habitus
Bannayan-Riley-Ruvalcaba syndrome	AD*	10q23.3/PTEN	Increased birthweight, developmental delay and growth retardation, macrocephaly, downslanting palpebral fissures, polyposis of colon, subcutaneous lipomas and hemangiomas, tan spots on glans penis, myotonia

*AD: Autosomal dominant
†AR: Autosomal recessive

normal individuals is less than 0.1%, this number of spots that are larger than 0.5 cm at prepubertal ages and 1.5 cm at postpubertal ages is considered as the cut-off for diagnosing NF1.

There are a few reports of children who had multiple CAL spots at a young age and were followed prospectively with evaluations for the development of multisystemic disorders. Korf reported on 41 children referred to an NF clinic whose ages ranged from 1 month to 14 years when they were noted to have six or more CAL spots and who were followed subsequently for at least 2 years. Twenty-four developed other findings of NF1. Six had a segmental distribution of CAL spots that suggested segmental type of NF. Bannayan-Riley-Ruvalcaba syndrome (Table 1), multiple lentigines (LEOPARD) syndrome (Table 1), and McCune Albright syndrome (Table 1) were diagnosed in three other children. The remaining eight children were followed for 2 to 5 years between 2 and 18 years of age and did not develop any additional manifestations.

Table 2. A Summary of Clinical and Genetic Features of NF1 and NF2

Disorder	Inheritance	Locus/Gene/Protein	Diagnostic Criteria
NF1	AD*	17q11.2/NF1/neurofibromin	Two or more of the following: 1. Six or more CAL spots • ≥1.5 cm in postpubertal individuals • ≥0.5 cm in prepubertal individuals 2. Two or more neurofibromas of any type or one or more plexiform neurofibromas 3. Freckling in the axillary or inguinal region 4. Optic glioma 5. Two or more Lisch nodules 6. A distinctive osseous lesion: • Dysplasia of the sphenoid bone • Dysplasia or thinning of long bone cortex 7. A first-degree relative who has NF1 according to the preceding criteria
NF2	AD*	22q12.2/NF2/merlin	Bilateral vestibular schwannomas visualized by magnetic resonance imaging or a parent, sibling, or child who has NF2 in addition to unilateral vestibular schwannoma detected before 30 years of age or any of the following: meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity

*AD: Autosomal dominant

A few CAL spots can be relatively common at any age or in any ethnic background, but more than three is uncommon in Caucasians and should prompt evaluation for the association of other findings of the syndromes. Relatives also should be investigated for multiple CAL spots. There have been several examples of families in which at least two generations that had more than six CAL spots exhibited no other manifestations of multisystemic genetic disorders. Interestingly, linkage to the NF1 gene was established in one family, but not in the others. This suggests that although inheritance of CAL spots is autosomal dominant, multiple CAL spots as a solitary finding is genetically heterogeneous.

Some skin markings have similar appearances to CAL spots and should be distinguished. In nevus spilus, multiple small, dark nevi are spread out on a lightly hyperpigmented patch. Lentigines are darkly pigmented multiple macules that measure a few millimeters in diameter.

The clinical importance of CAL spots is related to their potential associations with multisystemic genetic disorders. Table 1 lists some of the important mendelian disorders in which CAL spots are present.

Neurofibromatosis Type 1 (NF1)

The most frequent disorder seen in association with multiple CAL spots is NF1. The estimated population frequency of NF1 is approximately 1 in 3,500. It occurs with equal frequency in males and females and has been identified in all ethnic groups. The disorder is associated with a wide variety of complications. The diagnosis is based on the presence of two or more of the seven clinical criteria (Table 2).

CAL spots are the hallmark of NF1 and are seen in almost all affected patients. They often become obvious during infancy, although they can be noticed at birth in most patients. The typical CAL spots in NF1 are 1 to 3 cm in diameter (ranging from 0.5 to 30 cm), ovoid, and uniformly colored and have sharp, well-defined borders. Color intensity depends on the background cutaneous pigmentation, which means that they are darker in darkly pigmented individuals (Fig. 1). Color variations and border irregularities may occur.

Axillary or groin freckling present at birth in association with CAL spots is diagnostic for NF1. Freckling in this area and elsewhere usually becomes apparent in childhood. The overall frequency of freckling in axillary or groin regions is approximately 85% at 10 years of age.

Cutaneous neurofibromas usually do not develop until preadolescence, with their number often increasing during adolescence and young adulthood. Their frequency is approximately 20% at 10 years of age and more than 90% in adults. Although cutaneous neurofibromas

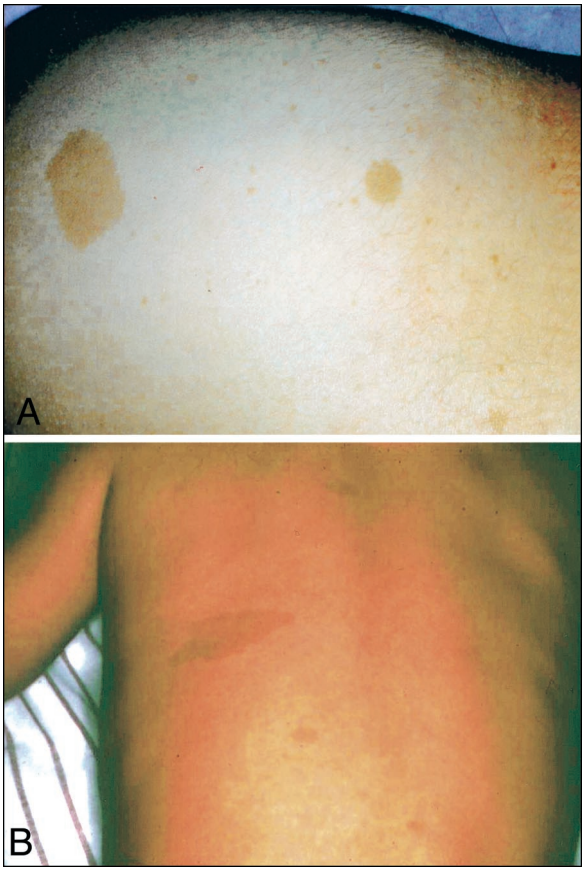

Figure 1. A. CAL spots on the buttocks of a 7-year-old Caucasian child who has NF1. Note freckling spreading from the inguinal region. B. CAL spots in an African-American infant who has NF1.

may become a major cosmetic problem, they are not premalignant lesions. Cutaneous neurofibromas can be defined clinically because they move with the skin when it is moved. In contrast, the skin can be moved over subcutaneous neurofibromas. Subcutaneous neurofibromas usually are spherical or ovoid, are firm or rubbery, and may be painful. Plexiform neurofibromas occur in approximately 15% of patients who have NF1. They are significant because of the potential for cosmetic disfigurement and malignant transformation. They almost always are present at birth, although they are not always diagnosed at that time. The frequency of large lesions of the head and neck is about 5%. Diffuse plexiform neurofibromas often extend deeply to involve all levels of skin, fascia, muscle, bone, and even viscera. They may cause compression, distortion, or overgrowth of adjacent structures. Lesions that lie superficially in the skin tend to become obvious at later ages and cause fewer clinical problems. When a diffuse plexiform neurofibroma affects the skin, overlying hyperpigmentation or hypertrichosis is frequent. These hyperpigmented areas sometimes resemble CAL spots and should be distinguished by the presence of a tumor under the hyperpigmented area. Other clinically important lesions are paraspinal neurofibromas, which occur throughout the spine and can cause significant spinal damage. Occasionally an aberrant whorl may be seen over the spine where these tumors are present.

Lisch nodules are hamartomas of the iris. Careful slitlamp examination is necessary to determine the presence of Lisch nodules when only a few are present or the patient is very young. By the age of 5 years, 25% of children who have NF1 develop Lisch nodules. The frequency increases to about 50% by 10 years of age and more than 95% by age 20 years.

Optic pathway gliomas are the most common central nervous system tumors in patients who have NF1. When all patients are evaluated with imaging studies, the frequency is approximately 15%. However, only one third of these children develop symptoms. Common symptoms are decreased visual acuity, visual field defects, proptosis, strabismus, optic atrophy, headache, nausea, anorexia, hypothalamic dysfunction, and precocious puberty. Optic pathway tumors rarely progress following diagnosis, and the utility of screening symptom-free children may be limited. Although not the view of the NF1 Optic Glioma Task Force of the National NF Foundation (as of 1997), a number of high-level clinical specialists do recommend routine (ie, presymptomatic) neuroradiologic screening for optic pathway gliomas among patients who have NF1 and are 5 years of age or younger. Almost all symptomatic children are younger than 6 years of age. Current recommendations for detection of optic glioma in children who have NF1 include: 1) full ophthalmologic examinations for all newly diagnosed patients; 2) follow-up with annual full ophthalmologic examinations up to 6 years of age; 3) abbreviated examinations with visual acuity, color vision, and slitlamp evaluations at 8, 13, and 20 years of age; and 4) full eye examinations at 10, 16, and 25 years of age. Once a tumor is suspected, definitive diagnosis should be made by radiologic studies. An asymptomatic optic pathway tumor that shows evidence of clinical or radiologic progression may require surgical, medical, or radiation therapy.

Mental retardation is not a common finding in NF1; the frequency is less than 5%. Specific learning disabilities are much more common, with a frequency of 30% to 60%.

Although not specific, short stature is seen in 33% and macrocephaly in 50% of individuals who have NF1. Skeletal problems may include scoliosis, long bone dysplasia, and sphenoid bone dysplasia. Bowing of the long bones is a congenital lesion and may lead to pseudoarthritis. Other manifestations of NF1 are renal artery stenosis and hypertension, increased signal intensity on T2-weighted magnetic resonance imaging studies, and peripheral nerve sheath malignant tumors in 1% to 2% of patients.

NF1 is inherited as an autosomal dominant trait. Approximately 50% of index patients have a family history of NF1. The NF1 gene is on chromosome 17 and is comprised of 60 exons. Most NF1 mutations are unique to a single family; there is no clear phenotype-genotype correlation, except for 3% to 4% of individuals in whom large deletions cause mental retardation and distinct facial features. Current commercial testing investigates premature truncation of the NF1 gene and detects 50% to 70% of mutations. Therefore, clinical diagnosis remains important.

... more than six café au lait spots ... that are larger than 0.5 cm at prepubertal ages and 1.5 cm at postpubertal ages is considered to be the cutoff for diagnosing neurofibromatosis type 1.

Other Genetic Disorders Associated With Café Au Lait Spots

Neurofibromatosis Type 2 (NF2)

NF2 is a completely different disorder both clinically and genetically. Its frequency is approximately 1 in 40,000 births. Although a single or a few CAL spots might be noted in patients who have NF2, they are not essential for the diagnosis. At the time of presentation, more than 50% of affected children have small cutaneous schwannomas. Sometimes hypertrichosis is noted over these small skin tumors. Clinical criteria for the diagnosis of NF2 are shown in Table 2. Vestibular schwannoma usually presents with hearing and vestibular problems after 20 years of age. Approximately 10% of individuals manifest NF2 in childhood. Although hearing loss may be the presenting finding, children are much more likely to have neurologic symptoms other than eighth nerve dysfunction. Spinal cord compression due to meningiomas or gliomas and visual impairment due to eye problems, including cataract, strabismus, or amblyopia, are common. The gene for NF2 is located on chromosome 22. It is a large gene similar to that of NF1, and mutations also are heterogeneous.

McCune Albright Syndrome

CAL spots are typical in this sporadic genetic condition. The spots usually have irregular borders and are larger than in other conditions. They occur most commonly over the sacrum, buttocks, and upper spine. In 50% of patients they are unilateral, and their pattern usually follows Blaschko lines. Multiple areas of fibrous dysplasia of bones are typical, occurring in long bones and the pelvis and occasionally in the cranium, facial bones, ribs, and spine. Endocrine abnormalities include precocious puberty, hyperthyroidism, hyperparathyroidism, and pituitary adenomas.

The CAL spots usually are evident in infancy, and the bone dysplasia may progress during childhood, resulting in deformity and fracture, most commonly in the upper femur. Thickening of the bone in the calvarium can lead to cranial nerve compression with consequences such as blindness or deafness. McCune Albright syndrome is due to mutations of a gene encoding the alpha subunit of a G protein (GNAS1). G proteins are involved in signal transduction pathways that affect the production of cyclic adenosine monophosphate (cAMP). Mutations in GNAS1 result in overproduction of cAMP, and an overactive cAMP pathway stimulates the growth and function of the gonads, adrenal cortex, specific pituitary cell populations, osteoblasts, and melanocytes.

Tuberous Sclerosis (TS)

Although CAL spots are noted in some patients who have TS, they are not as common as hypopigmented macules. TS is a neurocutaneous disorder that may involve multiple systems, including the kidneys and heart. Its prevalence is approximately 1 in 6,000. Ash leaf-shaped hypopigmented macules occur in 90% of patients. They may be present at birth or develop during the first 2 years of life. Raindrop or guttate hypopigmented macules distributed in a confetti-like configuration also are

Table 3. Revised Diagnostic Criteria for Tuberous Sclerosis*

Major Features

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibroma
- Hypomelanotic macules (three or more)
- Shagreen patch
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor Features

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- Confetti skin lesions
- Multiple renal cysts

Definitive TSC

- Either two major features or one major plus two minor features

Probable TSC

- One major plus one minor feature

Possible TSC

- Either one major feature or two or more minor features

* From Roach ES, et al. Tuberous Sclerosis Complex Consensus Conference: revised clinical diagnostic criteria. *J Child Neurol.* 1998;13:624–628.

Table 4. Clinical Manifestations of Fanconi Anemia*

Abnormality	%
Hyperpigmented skin	51
Radial ray defect (hypoplastic/supernumerary thumb, hypoplastic radii)	50
Eye anomalies (microphthalmus, ptosis, strabismus, nystagmus)	40
Renal and urinary tract	34
Short stature, frequently prenatal onset	30 to 50
Mental retardation	25
CAL spots	25
Other skeletal	22
Microcephaly	20
Gastrointestinal	14
Cardiac	13
Central nervous system	8

*Adapted from Auerbach AD. Fanconi anemia. *Dermatol Clin.* 1995; 13:41–49 and Alter BP. Fanconi's anaemia and its variability. *Br J Haematol.* 1993;85:9–14.

seen. Table 3 describes the current diagnostic criteria for TS.

Facial angiofibromas are small, discrete papules that can become confluent and fungating. They tend to cluster on the cheeks, nose, and around the mouth. They develop in midchildhood or later. Periungual fibromas similarly develop later in childhood, at puberty, or in adulthood. Shagreen patches or collagenomas are raised, firm plaques that usually are located on the forehead or the sacrum.

Cortical or subcortical white matter tubers that are composed of abnormal giant astrocytes are found in 90% of individuals who have TS. Subependymal glial nodules that calcify are typical. Seizures develop in many patients. They usually begin in infancy, and the classic pattern is hypsarrhythmia and infantile spasms. Mild-to-severe mental retardation is seen in about one third to two thirds of patients. Cardiac rhabdomyomas are congenital lesions that may be detectable by prenatal ultrasonography and can be symptomatic in utero. Renal involvement includes angiomyolipomas that are multiple, bilateral, and usually asymptomatic.

TS is an autosomal dominant disorder that has variable expression. The spontaneous mutation rate is approximately 60%. If parents are unaffected, the risk of a second affected child is approximately 1% to 4%. Germline mosaicism and nonpenetrance underlie this in-

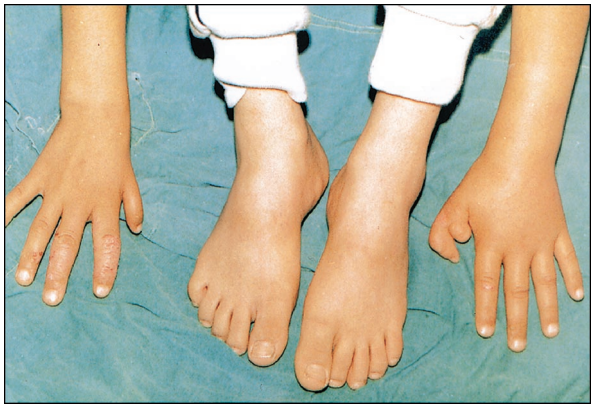

Figure 2. Bifid left thumb and proximally placed right thumb with normal feet in a patient who has Fanconi anemia. (Courtesy of Drs Sevgi Gozdasoglu and Nejat Akar, Ankara University Medical School, Ankara, Turkey.)

creased risk. The two known TS genes, TSC1 and TSC2, are involved in cell cycle, cell proliferation, and differentiation. Each is responsible for approximately 50% of affected patients. Most of the described mutations in the TSC1 gene result in a truncated protein. Many mutations in the TSC2 gene are large deletions. Others are similar to the TSC1 gene in that they cause truncation of the protein. Large deletions in the TSC2 gene involving the pkD1 gene may cause the polycystic kidney disease phenotype. Clinical diagnosis remains important in TS.

Fanconi Anemia (FA)

FA is a genetically heterogeneous autosomal recessive syndrome. Its frequency is approximately 1 in 60,000 to 300,000 births. The cardinal features are chromosomal breakage, pancytopenia, and congenital abnormalities. Approximately 50% to 65% of patients have generalized hyperpigmentation. CAL spots are noted in approximately 25% of patients. Hypopigmentation also may be seen. Table 4 lists frequent physical abnormalities associated with FA. Figure 2 illustrates the hand abnormalities in FA. Approximately 25% of individuals who have FA do not exhibit any structural abnormalities. Chromosomal breakage is evaluated in a clinically available test that investigates the degree of sensitivity of chromosomes to cross-linking agents, such as diepoxybutane. Children who have FA have an increased risk for malignancies, especially acute myelogenous leukemia. Most children develop bone marrow failure by 7 years of age, and chromosomal studies are necessary for diagnosis.

At least eight genetically distinct FA groups have been described. This indicates that the disease may be caused by a defect in at least eight different genes, which have been denoted FANCA through FANCH. The FANCA, FANCC, FANCF, and FANCG genes have been cloned recently, and the FANCD and FANCE genes have been mapped to chromosomes 3 and 6, respectively. In general, FANCA accounts for 60% to 65% of FA patients. However, mutation screening is difficult because the gene is very large, and mutations are very heterogeneous. One exception is the limited number of mutations in the FANCC gene seen in most Ashkenazi Jewish FA patients.

Bloom Syndrome (BS)

BS is another autosomal recessive chromosomal instability syndrome. Small and large areas of hypo- and hyperpigmentation are noted in most patients. Although CAL spots have been reported, their frequency has not been well established, and it has not been compared with the frequency in the normal population in a large series. BS originally was described in Ashkenazi Jews, and its highest prevalence is in this ethnic group. Nevertheless, all races may be affected. The frequency in Ashkenazi Jews is at least 1 in 10,000.

The principal clinical features of BS are prenatal and postnatal growth retardation, a thin triangular face, and telangiectatic rash in sun-exposed areas, particularly on the cheeks. The major complication of the syndrome is an increased incidence of malignancies. Leukemia and breast and gastrointestinal cancers are the most common types of malignancies. The diagnostic cytogenetic finding is a markedly increased level of spontaneous sister chromatid exchange. The gene for BS, BLM, is a member of the RecQ helicase protein family, which is capable of unwinding DNA and RNA, and mutations in the gene probably cause an impairment in DNA repair ability.

Ataxia Telangiectasia (AT)

AT is an autosomal recessively inherited condition that causes an increased susceptibility to malignancies and immunodeficiency. The frequency is approximately 1 in 30,000 births. The principal clinical features are progressive complex neurodegeneration, bulbar conjunctival telangiectasia, variable immunodeficiency, and increased predisposition for lymphoreticular malignancies. Pigmentary disturbances are common in AT, with a mottled pattern of hyper- and hypopigmentation. Excessive numbers of CAL spots have been reported in AT in small series, but several other observations have not supported these reports. The majority of children present in the first 5 years of life with motor delay. Eye movements are usually abnormal by the age of 3 years and involve a dyspraxia of rapid saccadic eye movements, both in the

vertical and horizontal fields of vision. Approximately 25% of individuals have clinically significant immunodeficiency, and 10% eventually develop a malignancy.

Patients who have AT have an increased sensitivity to chromosome breakage, especially after ionizing radiation. There also is an increased incidence of spontaneous chromosome breakage and translocations involving the T-cell receptor genes on chromosomes 7 and 14. However, these findings are not specific. More than 250 mutations have been described in the ATM gene, causing the AT phenotype. Most of them result in truncation of the protein or are large deletions.

Russell–Silver Syndrome

This is a prenatal-onset growth retardation syndrome that also has distinct physical findings. Affected children have delayed osseous development and delayed closure of the fontanelles. They usually have asymmetric extremities, with short and incurved fifth fingers. A small triangular face with frontal prominence and normal head circumference is an important physical finding. The actual frequency of CAL spots in this syndrome is unknown. In a retrospective review, only 10% of individuals who had Russell-Silver syndrome were noted to have CAL spots, which is in the range of the general population frequency.

The genetic basis of this syndrome appears to be heterogeneous. Approximately 7% of patients show maternal uniparental disomy of chromosome 7, which suggests that at least one gene on chromosome 7 is imprinted and involved in the pathogenesis of Russell-Silver syndrome. Based on case reports of balanced chromosomal translocations involving chromosome 17q25, the presence of another locus on this chromosomal region has been suggested.

Suggested Reading

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PIR Quiz

Quiz also available online at *www.pedsinreview.org.*

6. A 5-year-old boy presents with recently noted pubic hair growth. The parents state that he had bilateral bowed tibia at birth and underwent two orthopedic surgeries in the first year of life. During physical examination, you note six small, oval, uniformly hyperpigmented macules and ptosis of the right eyelid. Of the following, the *most* likely diagnosis is:

   A. Bloom syndrome.
   B. Fanconi anemia.
   C. McCune Albright syndrome.
   D. Neurofibromatosis type 1.
   E. Neurofibromatosis type 2.

7. Which of the following is the *most* common genetic disorder associated with café au lait spots?

   A. Fanconi anemia.
   B. McCune Albright syndrome.
   C. Neurofibromatosis type 1.
   D. Neurofibromatosis type 2.
   E. Segmental neurofibromatosis.

8. Which of the following is the *most* appropriate initial step for evaluating a child who has seven uniformly pigmented, well-demarcated café au lait spots at 10 years of age?

   A. Complete blood count.
   B. Hearing evaluation.
   C. Molecular testing for neurofibromatosis type 1.
   D. Ophthalmologic examination.
   E. Skin biopsy and chromosomal studies in fibroblasts.

9. The frequency of café au lait spots in normal children varies by all of the following factors *except*:

   A. Age.
   B. Degree of skin pigmentation.
   C. Ethnic background.
   D. Family history.
   E. Gender.

10. A 6-year-old girl presents with microcephaly, generalized hyperpigmentation with three café au lait spots over the trunk, and a proximally placed thumb in the right hand. The family history reveals that a paternal cousin died from acute leukemia at 25 years of age. Which of the following would be the *most* appropriate diagnostic test?

    A. Audiologic examination for hearing loss that may be associated with acoustic neuroma.
    B. Blood chromosome analysis for evaluation of chromosomal rearrangements related to ataxia telangiectasia.
    C. Brain computed tomography for evaluation of intracranial tumors associated with neurofibromatosis type 1.
    D. Peripheral blood chromosome analysis with diepoxybutane induction.
    E. Wood lamp examination for findings of tuberous sclerosis.