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Café-Au-Lait Spots

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Café-au-lait spots (CALS) are common in children. They often represent benign birthmarks; however, they may also be markers of systemic disease. Establishing an early diagnosis of neurofibromatosis type 1 (NF1), the most common disorder evident with multiple CALS is important; these children have an increased risk of malignant disease including malignant schwannoma, rhabdomyosarcoma, Wilms' tumor, and myeloid disorders.[1]

Incidence

Numerous studies on infants, children, and adults have focused on prevalence rates of CALS in the general population.[2-10] In newborn infants, CALS were found in 0.4%[2] to 2.7%.[3] Whitehouse[4] studied children younger than 5 years old and found 24% had one or more CALS. Four large-population studies of school-age children ranging in ages from 4 to 18 years old found CALS in 25%,[5] 28%,[6] 32.7%,[7] and 36.3%.[8] Studies in adults found CALS ranging in incidence from 10%[9] to 13.8%.[10] In all of these studies of the normal population, the incidence sharply decreased with increasing number of lesions. Generally, it was demonstrated that one or two lesions are quite common, found in up to 36% of children without associated disease, but the incidence of more than five with no other sign of NF1 was rare, ranging from 0.003%[5] to 1%.[7] Multiple CALS, although infrequent, were found in a significantly higher incidence in black than in white children.[3,4]

Clinical Description

CALS appear as sharply defined, round to oval, homogenous macules or patches varying in size from 2 mm to 20 cm (Figure 1). Most are under 2 cm in diameter. In children, CALS should be distinguished from ephilides (freckles), nevus spilus, giant congenital melanocytic nevus, and Becker's melanosis. CALS typically demonstrate the milky-brown coloration implied by their name. Each is uniform in color, but may vary from tan to dark brown. They may occur on any area of the body, although individual CALS are more prevalent on unexposed skin in contrast to ephilides.[5,9] In general, more lesions are found on the trunk, buttocks, and lower limbs, and tend to spare the head, neck, and upper extremities.[5]

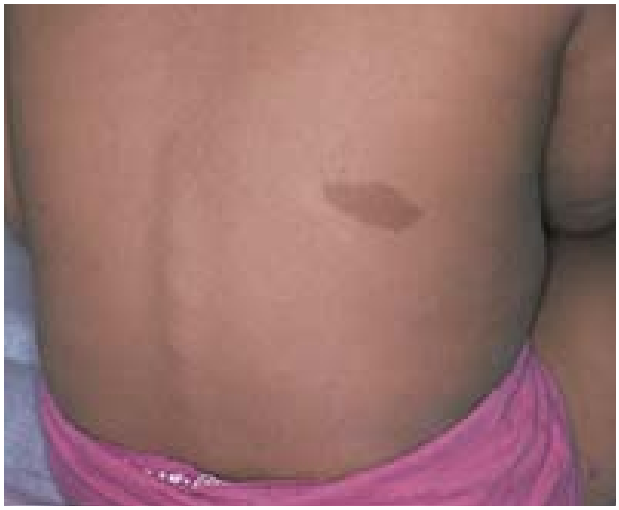

FIGURE 1. Café-au-lait spot on the back of a young child.

When multiple lesions are evident, careful clinical examination may help in differentiating CALS of NF1 and those of McCune-Albright syndrome, the latter having a predilection for the posterior neck, thorax, sacrum, and buttocks as well as the tendency to remain unilateral and to cover large anatomic regions.[11] Those of NF1 tend to be randomly and widely distributed, often with localized or generalized freckle-like macular CALS in addition to the larger more typical appearing CALS. In addition, those found in McCune-Albright syndrome often have a characteristic, irregular border with jagged or serrated edges, resembling, in outline, the coast of Maine; whereas the CALS of NF1 tend to have smooth mar-

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gins, likened to the coast of California. It has generally been recognized that these differences alone are not enough to distinguish these two diagnoses.[11]

Histopathology

Microscopically, CALS demonstrate an increase in DOPA-positive melanocytes.[12] Increased melanin is seen either free or in melanocytes and keratinocytes in the basal cells of the epidermis. CALS in patients with NF1 may have increased production of melanin by those melanocytes affected by defective alleles of the NF1 gene.[13] The melanocytes within CALS produce increased concentrations of melanosomes, which may be enlarged or may aggregate into macromelanosomes. Macromelanosomes are a common feature of NF1 both in the CALS and in the normal skin of these patients,[12] although they are not specific for this disease. They may be demonstrated in patients without NF, and may be seen in other conditions, but are demonstrated only rarely in McCune-Albright syndrome.[11]

Neurofibromatosis

The incidence of CALS in patients with NF1 is significantly increased, with almost all patients having at least one spot. In fact, it has been demonstrated that up to 97% of children with proven NF1 may have five or more spots.[14]

Clinical criteria for the diagnosis of NF1 include more than five CALS each exceeding 0.5 cm in diameter in prepubertal children, neurofibromas, intertriginous freckling, optic gliomas, Lisch nodules, and a first-degree relative with NF1. Two or more are needed for a definite diagnosis, while one criterion is sufficient for a presumptive diagnosis. However, many of these features may not become evident before the onset of puberty. CALS, usually greater than five seen on a patient, tend to be the first sign and are often used to establish a presumptive diagnosis.[4] Multiple smaller "freckle-like" CALS in the axillary or inguinal region may also be evident, known as Crowe's sign (Figure 2). Likewise, multiple small CALS in the perioral region, Török's sign, may be observed, although less frequently.[15,16] These may be generalized.

If a child has between one and five CALS, but no other signs of NF1, a question often raised is the likelihood of having NF. If the child has a sibling or parent with proven NF, the pattern of spots between the two should be compared since it has been shown that a positive correlation exists.[9] The degree of similarity is linked with the likelihood of NF, with sibling-to-sibling comparison being preferable to that of parent to offspring. Often, no family history exists. In this case, the number of CALS should be compared with the incidence in the normal population to determine the likelihood of disease.[9]

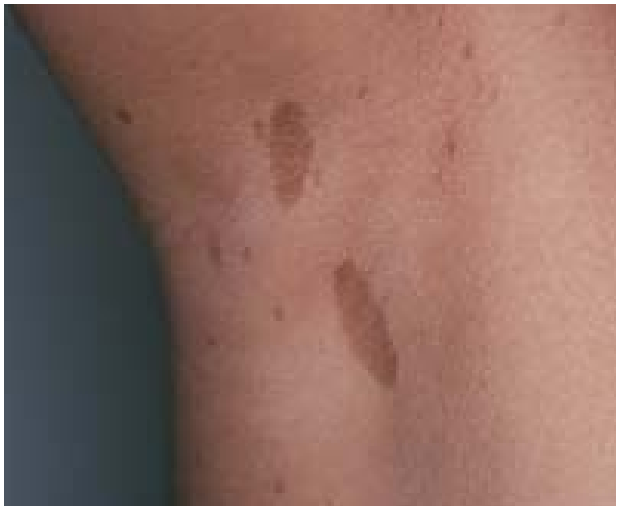

FIGURE 2. Café-au-lait spots and axillary freckling on a child with NF1.

When examining a child with more than five CALS, each exceeding 0.5 cm in diameter, the major diagnostic concern should be NF1. Familial multiple CALS with no other features of NF, a rare disorder, should also be considered, and is classified by some as NF type 6.[17] It should be remembered that a diagnosis of neurofibromatosis cannot be ruled out by the absence of skin lesions; NF type 2 is associated with few CALS. Furthermore, NF type 5 (segmental NF), marked central nervous system involvement, and late-age onset are more frequently associated with NF patients having three or less CALS.

When other clinical features are evident, especially if no other signs of NF1 have developed, other syndromes associated with CALS must be considered. The most common, with a significantly increased incidence of CALS, include McCune-Albright syndrome, Silver-Russell dwarfism, Watson's syndrome, and multiple lentigines syndrome.[1,9,11,17,18] These should be distinguished from NF1 on the basis of their distinct clinical features. When considering the differential diagnosis, it is important to remember that CALS are quite common in the normal population. In fact, the association of CALS with certain disorders, such as tuberous sclerosis, may be solely due to the high incidence of these lesions in the normal population.[19]

Treatment

Therapy is not usually indicated. However, a variety of options are available, including laser surgery.[20]

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