Birthmarks of Potential Medical Significance

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Objectives  After completing this article, readers should be able to:

1. Describe the clinical manifestations of neurofibromatosis type 1.
2. List conditions associated with café au lait macules.
3. Explain the clinical significance of congenital melanocytic nevi.
5. List the two syndromes associated with port-wine stains and extracutaneous abnormalities.
6. Categorize and describe the three types of hemangiomas.

Introduction

Birthmarks are common (~8% to 10%) in newborns. Most birthmarks represent vascular and pigmentary lesions. The natural history of these lesions varies from being transient phenomena and essentially normal variants of no clinical significance to permanent cutaneous abnormalities that may be associated with significant systemic complications or diseases. Table 1 lists some neonatal skin lesions that should be recognized by the clinician as clues to more serious disorders.

This review describes some of the most commonly encountered, clinically significant birthmarks, emphasizing those findings that should prompt early assessment, diagnosis, and appropriate treatment and counseling.

Hyperpigmented Birthmarks

Hyperpigmented lesions are common at birth and in the first few postnatal weeks. They may be macular, papular, plaquelike, evenly colored, or speckled.

Café Au Lait Macules

Café au lait macules (CALMs) are localized epidermal melanocytic flat lesions that usually are round or oval, evenly colored with light brown pigmentation, have distinct margins, and range in size from a few millimeters to 15 to 20 cm in diameter. They can occur anywhere on the body, most often on the buttocks in newborns (Fig 1). Most CALMs are present at birth or develop in the first few postnatal months. They are seen in 0.3% to 18% of neonates and usually are not associated with specific abnormalities, although they can be markers for some genetic diseases, such as neurofibromatosis type 1 (NF-1). Neonates who have multiple CALMs should be evaluated carefully for stigmata of NF-1, including measuring and counting of lesions. Although solitary lesions are common or nonspecific, more than three CALMs in Caucasian infants and more than five CALMS in infants of other races are uncommon at any age. Six or more CALMs greater than 5 mm in diameter are presumptive evidence of NF-1. The presence of axillary or inguinal freckling in addition to multiple CALMs enhances the possibility of NF-1. Other signs of NF-1 in neonates are extremely rare (eg, Lisch nodules, optic gliomas, osseous lesions, other neural tumors). The clinical manifestations of NF-1 may evolve over time, and neonates at risk or in whom evidence of disease is presumed should be monitored closely. Approximately 75% of infants who have six or more CALMs and are followed for 2 years develop signs of NF-1.

Diagnosis is based on the clinical experience. A family history of NF or other syndromes should be investigated, and parents examined when possible. The differential diagnosis of...
conditions associated with CALMs is extensive (Table 2). Watson syndrome presents with multiple CALMs, intertriginous freckling, short stature, pulmonary stenosis, and low intelligence and is believed to be a subset or allelic form of NF-1. NF-2 is a genetically distinct autosomal dominant disorder characterized by CALMs and acoustic or central nervous system schwannomas.

The McCune-Albright syndrome refers to the triad of CALMs, polyostotic fibrous dysplasia, and endocrine dysfunction. CALMs in this syndrome are usually large, linear or segmental, unilateral or bilateral, can follow Blaschko lines, and may have an irregular jagged margin said to resemble the “coast of Maine” (Fig 2). Polyostotic fibrous dysplasia is a disorder in which bone is replaced by fibrous tissue, resulting in asymmetry, bony growth, and pathologic fractures. These bony lesions generally develop in the first decade of life and usually are on the same side as unilateral CALMs, consistent with the syndrome being a mosaic disorder. Multiple associated endocrine abnormalities include precocious puberty, hyperthyroidism, Cushing syndrome, hypertopomatropism, hyperprolactinemia, and hyperparathyroidism. This syndrome is more common in females than in males and most likely is caused by an autosomal dominant lethal mutation with resulting mosaicism. The responsible defect has been mapped to the alpha subunit of the GNAS-1 gene. Close observation and follow-up for endocrine abnormalities and referral for orthopedic evaluation are appropriate.

**Congenital Melanocytic Nevi**

Congenital melanocytic nevi (CMN) are collections of melanocytes in the skin present at birth or appearing in the first few months after birth. They are macular, papular, or plaquelike pigmented lesions in different shades of brown, with black or blue foci. Their texture may be smooth, nodular, verrucous, or rough cobblestonelike, with or without hair. Lesions typically grow proportionally with the individual and typically are classified based on the assumed adult size. Small CMN measure 1.5 cm or less, intermediate CMN range between 1.5 cm and 20 cm, and large CMN (LCMN), also called “garment or bathing trunk nevi,” are more than 20 cm in diameter (Figs. 3 and 4). In the neonate, any lesions on the head that are approximately 9 cm in diameter or on the body that are 6 cm qualify as LCMN or giant.

CMN are clinically significant because of their association with malignant melanoma. Small nevi are seen in 1% to 2% of newborns, intermediate-size lesions in 0.6%, and LCMN in no more than 0.02%. The risk of malignant melanoma arising within small and intermediate CMN is very small, usually 2% or less. Consequently, the clinical management of these patients remains controversial. Most require only clinical follow-up. The decision to excise the lesions is individualized. Large CMN are most common on the posterior trunk, but also may be seen on the anterior and lateral trunk, head, neck, or extremities. Multiple small satellite CMN are seen in most patients who have LCMN. Although the estimated lifetime risk for melanoma in patients who have LCMN ranges between 6% and 8%, the associated death rate is less than 1%. Approximately 50% of melanomas occur by 3 to 5 years of age; the greatest risk for malignant transformation appears to be in the prepubertal years. LCMN of the scalp and dorsal axis have been associated with neurocutaneous melanosis. Large CMN in the lumbosacral area may be associated with spinal dysraphism, myelomenin-

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**Table 1. Neonatal Skin Lesions That Are Clues to More Serious Disorders**

<table>
<thead>
<tr>
<th>Hyperpigmented Birthmarks</th>
<th>Hypopigmented Birthmarks (“white spots”)</th>
</tr>
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<tbody>
<tr>
<td>Coffee au lait macules (CALMs)</td>
<td>Cafe au lait macules (CALMs)</td>
</tr>
<tr>
<td>Congenital melanocytic nevi (CMN)</td>
<td>Congenital melanocytic nevi (CMN)</td>
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</tbody>
</table>

**Vascular Birthmarks**
- Vascular Malformations
  - Port-wine stains (PWS)
  - Lymphatic malformations
- Vascular Tumors
  - Hemangiomas

**Nevus Sebaceous**

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**Table 2. Other Syndromes Definitely Linked to Multiple CALMs**

<table>
<thead>
<tr>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Watson syndrome</td>
</tr>
<tr>
<td>Neurofibromatosis type 2 (NF-2)</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
</tr>
<tr>
<td>Tuberous sclerosis complex (TSC)</td>
</tr>
<tr>
<td>Ring chromosome syndromes</td>
</tr>
<tr>
<td>Less consistently:</td>
</tr>
</tbody>
</table>
  - Bloom syndrome |
  - Leopard syndrome |
  - Silver-Russell syndrome |
Vascular Malformations

<table>
<thead>
<tr>
<th>Flow Type</th>
<th>Tissue Type</th>
<th>Disease Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow flow</td>
<td>Capillary</td>
<td>Port-wine stain (PWS)</td>
</tr>
<tr>
<td></td>
<td>Venous</td>
<td>Klippel-Trenaunay syndrome</td>
</tr>
<tr>
<td></td>
<td>Lymphatic</td>
<td>Cystic hygroma</td>
</tr>
<tr>
<td>Fast flow</td>
<td>Arterial</td>
<td>Aneurysm and stenosis</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous</td>
<td>Arteriovenous malformations</td>
</tr>
<tr>
<td>Complex</td>
<td>Mixed tissues</td>
<td>Hemolymphatic angiodysplasia</td>
</tr>
</tbody>
</table>

Hypopigmented Birthmarks

Localized forms of hypopigmentation (“white spots”) are relatively common and may be present at birth or manifest later in infancy or early childhood (Fig. 5). These hypopigmented macules are the result of impaired melanocyte function. Because infants have lighter skin color at birth than later in life, focal forms of hypopigmentation may be less obvious or completely missed at birth. Examination under a Wood lamp may be necessary to detect subtle lesions in fair-skinned infants.

The clinical significance of these localized forms of hypopigmentation is their potential association with the tuberous sclerosis complex (TSC). Although isolated hypopigmented macules may be a variant of normal in neonates, the presence of three or more white spots or isolated hypopigmented macules in the setting of suspicious signs or symptoms or a family history should prompt evaluation for TSC. Examination of the parents and other family members may be indicated.

TSC, an autosomal dominant disorder that is characterized by cutaneous and neurologic abnormalities as well as multiple visceral hamartomas. The classic triad for TSC consists of multiple angiofibromas, seizures, and mental retardation. Estimates of the prevalence of TSC range from 1:10,000 to 1:40,000, and spontaneous mutations account for 50% to 75% of cases. Hypomelanotic macules can be one of the earliest indicators of the disease. They occur in approximately 80% of patients who have TSC and generally are present at birth. These hypopigmented macules appear polygonal (“thumbprint”), lance-ovate (“ash leaf spot”), and guttate-like (“confetti”). The margins may be regular or irregular, and size ranges from 1 to several centimeters. Poliosis on the scalp (white patches of the hair) or in the eyebrows and eyelashes also can be seen. It is rare for newborns to have other cutaneous signs of TSC. Shagreen patches (sometimes present at birth) and angiofibromas usually become apparent in early childhood, and periungual fibromas tend to occur in adulthood.

Lesions that should be distinguished from the cutaneous hypopigmented macules of TSC include nevus anemicus, nevus depigmentosus, postinflammatory hypopigmentation, piebaldism, and vitiligo. Criteria for the diagnosis of TSC are very well defined in the standard textbooks of pediatrics and dermatology.

Vascular Birthmarks

Vascular birthmarks are cutaneous anomalies of angiogenesis and vasculogenesis resulting in various clinical presentations and often heralding other disease states or anomalies. Two major groups of vascular birthmarks are recognized: vascular malformations, which are composed of dysplastic vessels, and vascular tumors that demonstrate cellular hyperplasia (hemangiomas).

Vascular Malformations

Vascular malformations are errors in morphogenesis that may affect any branch of the neonatal vasculature. They are subcategorized according to flow characteristics and predominant anomalous channels (Table 3). Capillary, venous, lymphatic, arterial, and arteriovenous malformations occur either alone or in combination. They are present at birth and often are localized and circumscribed, although they can present in a segmental, systematized pattern or in a diffuse, disseminated form. Some are part of a more complex syndrome pathology. Although they grow proportionately with affected children’s development, they do not have a proliferative phase or tendency to spontaneous involution. This review focuses only on the clinical significance of the capillary malformations.

Salmon patch is the most common capillary malformation. It is present at birth as a pink blanching patch most commonly located on the forehead (“angel kiss”) and nape (“stork bite”). Other involved sites include the glabella, nose, upper eyelids, and upper lip, where the lesions simply are referred to as vascular stains or nevus simplex. Salmon patches occur in nearly 50% of newborns and affect males and females equally. They are
asymptomatic, pose minimal cosmetic problems, and usually disappear within 2 years, although nape lesions usually persist. Port-wine stains (PWSs) are slow-flow capillary malformations that may occur anywhere on the body and almost always are present at birth. These pink or red patches grow proportionately with the child and persist throughout life. Usually, PWSs, like hemangiomas, do not involute (Fig. 6). They have been associated with other cutaneous lesions and with extracutaneous abnormalities. When associated with a pigmented lesion, such as mongolian spot, nevus spilus, or hyperpigmented nevi, the condition is known as phakomatosis pigmentovascularis. If a PWS is found midline over the spine or scalp, it may be a marker for an occult spinal or cranial dysraphism. Two syndromes associated with PWSs and extracutaneous abnormalities are Sturge-Weber syndrome (SWS) and Klippel-Trenaunay syndrome (KTS).

Also known as encephalotrigeminal angiomatosis, SWS occurs sporadically in the general population and is characterized by the classic triad of facial PWS in the ophthalmic (V1) distribution of the trigeminal nerve, eye abnormalities, and leptomeningeal and brain abnormalities. Facial PWS associated with SWS may involve the maxillary (V2) or mandibular (V3) distribution of the trigeminal nerve. Patients who have V2 and V3 PWS alone without involvement of V1 are not at risk for SWS. Eye abnormalities include choroidal vascular anomalies and glaucoma in about 30% of cases with secondary buphthalmus and visual loss. Among the brain abnormalities are leptomeningeal vascular abnormalities, calcifications, enlarged choroidal plexus, cerebral atrophy, and developmental venous anomalies, resulting in seizures, mental retardation, and sometimes hemiparesis. SWS occurs in 10% of neonates who have V1 PWS and can pose significant medical and ophthalmologic problems. Imaging of the central nervous system is best performed after 6 months of age, with magnetic resonance imaging (MRI) used to find vascular anomaly and atrophic changes.

KTS also is known as angio-osteohypertrophy syndrome and is a complex-combined vascular malformation of the limbs that is visible at birth and grows significantly. It is characterized by a capillary malformation (PWS) associated with limb hypertrophy (overgrowth of the soft tissue and bone), varicose veins, lymphedema, and phleboliths (Fig. 7). Sometimes a significant lymphatic or venous malformation may be present. The limb hypertrophy often increases progressively and disproportionately to the child’s growth, but in some cases the soft-tissue hypertrophy shows proportionate growth, representing a milder form of the disease. KTS is commonly unilateral (95%) and usually involves the lower extremity (95%), upper extremity (5%), or both. When the predominant vascular malformation is multiple arteriovenous shunts, the syndrome is called Parkes-Weber syndrome; when the limb abnormality is undergrowth, the syndrome is Servelle-Martorell syndrome. The diagnosis usually is made clinically, but modern vascular imaging techniques help delineate the vascular defect. MRI angiography and Doppler ultrasonography are necessary to evaluate flow characteristics and rule out an arteriovenous fistula.

**Vascular Tumors (Hemangiomas)**

Hemangiomas represent the most common vascular tumor encountered during the neonatal period, occurring in 1.0% to 2.6% of newborns. Approximately 25% of the tumors are present at birth; the remainder develop in the first few postnatal weeks. Rarely, they appear as fully grown tumors at birth (congenital hemangioma) that resolve rapidly, often leaving pronounced atrophic skin changes. True hemangiomas are benign vascular tumors produced by proliferation of endothelial cells that undergo a phase of rapid growth followed by spontaneous slow involution. Approximately 30% of hemangiomas spontaneously involute by age 3 years, 50% by age 5 years, and 80% to 90% by age 9 to 10 years. Hemangiomas are clinically heterogeneous, with their appearance dictated by the depth, location, and stage of evolution. They are classified as superficial hemangiomas (~60%), deep hemangiomas (~15%), and mixed-type hemangiomas (~25%), which have features of both. Superficial hemangiomas (strawberry hemangioma) are usually present at birth or develop within the next few weeks. In the newborn, a pale macule that has threadlike telangiectases and a bruiselike macule represent a common precursor lesion. As the tumor proliferates, it assumes its most recognizable form: a bright red, slightly elevated, noncompressible plaque. Its surface texture is finely lobulated, resembling strawberries (Fig. 8). Hemangiomas that lie deeper in the skin are soft, warm masses that have a slightly bluish discoloration. They range from a few millimeters to several centimeters in diameter and usually are solitary, although up to 20% of infants have multiple lesions. A female predominance (3:1) and an increased incidence among preterm infants have been documented. Generally, superficial hemangiomas reach their maximal size by 6 to 8 months of age, but deep hemangiomas may proliferate for 12 to 14 months or longer. The involuting phase begins with changes in the surface color and texture, usually in the center of the
hemangiomas. It is important to realize that not all hemangiomas look like strawberries, and not all strawberry-like lesions are hemangiomas.

Despite the benign nature of most cutaneous hemangiomas, a significant number cause functional compromise, residual skin changes, or permanent disfigurement. Ulceration, the most frequent complication, can be excruciatingly painful and carries the risk of infection, hemorrhage, and scarring. In addition, hemangiomas may be associated with extracutaneous abnormalities and dysmorphogenesis. Periorbital hemangiomas pose considerable risk to vision and should be monitored carefully. Infants who have extensive facial hemangiomas, particularly those in the “beard distribution,” may have associated subglottic hemangiomas (~60%) and warrant direct visualization of the airway. Lumbosacral hemangiomas may be markers for occult spinal dysraphism and anorectal and urogenital anomalies. Imaging of the spine is indicated in all patients who have midline hemangiomas in this region.

PHACE(S) syndrome applies to the association of large facial hemangiomas with multiple extracutaneous structural abnormalities, such as cardiovascular, neurologic, and ophthalmologic anomalies (Fig. 9). The term PHACE(S) refers to: Posterior fossa brain malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac anomalies, Eye abnormalities (and sometimes Sternal clefting/supraumbilical raphe). This syndrome has a marked female predominance (9:1) and is believed to represent a developmental defect that occurs during the 8th to 10th week of gestation.

Management and treatment of hemangiomas must be approached on a case-by-case basis according to the number of lesions, their location and size, and the presence of any associated clinical abnormalities. Most hemangiomas involute spontaneously, requiring no treatment. Early treatment of superficial hemangiomas with flash lamp-pulsed dye laser therapy may reduce the extent of vascular proliferation and induce earlier involution. If complications arise and treatment is warranted, oral systemic corticosteroids are the mainstay of therapy. Recombinant interferon-alpha, an inhibitor of angiogenesis, has been used successfully in treating life-threatening hemangiomas. However, because 10% of treated patients develop spastic diplegia, it should not be a primary therapy. Overly aggressive surgical procedures generally should be avoided, but sometimes they are the last alternative.

Neonatal hemangiomatosis (NH) refers to the presence of numerous small, superficial hemangiomas scattered across the skin surface (Fig. 10). Its clinical significance is the potential association with visceral hemangiomatosis. If these lesions are limited only to the skin, the entity is termed benign neonatal hemangiomatosis. If evidence shows systemic visceral involvement, the term diffuse neonatal hemangiomatosis (DNH) is used. NH appears early in the neonatal period, and girls are affected more commonly. The cutaneous lesions may range from a few millimeters to more than several centimeters in diameter. There is no consensus regarding the number of cutaneous hemangiomas and the risk of visceral involvement. The gastrointestinal tract (bowel and liver), lungs, and central nervous system are involved in more than 50% of cases of DNH. The oral mucosa and eyes also commonly are affected. Additional complications include high-output congestive heart failure, visceral hemorrhage, hydrocephalus, and ocular abnormalities. Untreated patients have a high mortality rate (>80%). With current treatment regimens, the mortality rate can be as low as 29%. Serial physical examinations, visceral ultrasonography, and MRI should be performed in neonates who have DNH.

Kasabach-Merritt syndrome (KMS) refers to the consumption (trapping) of platelets and coagulation factors within a congenital or neonatal vascular neoplasm, resulting in thrombocytopenia, microangiopathic hemolytic anemia, hemorrhage, and purpura from disseminated intravascular coagulation (Fig. 11). KMS most commonly occurs with tumors such as kaposiform hemangioendotheliomas and tufted angiomias. KMS is a rare and distinctive syndrome or phenomenon that has no gender predilection and presents at birth as a tumoral mass of variable size and location that subsequently develops a deep red or purple mass that grows rapidly. This syndrome is a medical/dermatologic emergency that requires aggressive, often multimodality treatment by a team of specialists and carries a significant mortality rate (20% to 30%). Thrombocytopenia may persist for a few years, but more commonly resolves with treatment by 12 to 18 months. Current therapies of reported success include corticosteroids, interferon-alpha, vincristine, and ticlopidine plus aspirin. Surgical excision and arterial embolization may also benefit some patients.

Suggested Reading
Frieden IJ. Which hemangiomas to treat and how? Arch Dermatol. 1997;133:1593–1595
Paller AS. The Sturge-Weber syndrome. Dermatology. 1987;4:300–304
1. Café au lait macules (CALMs) are localized epidermal melanocytic flat lesions that have a light brown pigment. Six or more CALMs that are greater than 5 mm in diameter each are markers for certain genetic diseases. Of the following, the finding of pulmonary stenosis in addition to multiple CALMs is most consistent with the diagnosis of:

   A. Leopard syndrome.
   B. McCune-Albright syndrome.
   C. Neurofibromatosis type 2.
   D. Tuberous sclerosis complex.
   E. Watson syndrome.

2. Hypopigmented macules resulting from impaired melanocyte development are significant because of their potential association with the tuberous sclerosis complex (TSC). Of the following, the clinical sign of TSC that is most likely to be present at birth is:

   A. Adenoma sebaceum.
   B. Ash leaf spot.
   C. Periungual fibroma.
   D. Scalp poliosis.
   E. Shagreen patch.

3. Port-wine stains (PWSs) are slow-flow capillary malformations that often are associated with other cutaneous lesions and extracutaneous abnormalities. Of the following, the finding of limb undergrowth in association with PWSs is most consistent with the syndrome of:

   A. Klippel-Trenaunay.
   B. Parkes-Weber.
   C. Servelle-Martorell.
   D. Silver-Russell.
   E. Sturge-Weber.

4. Strawberry hemangiomas are benign vascular tumors produced by proliferation of endothelial cells. They undergo an initial phase of rapid growth followed by a phase of spontaneous involution. Of the following, strawberry hemangiomas are most likely to:

   A. Be solitary.
   B. Have a reduced incidence among preterm infants.
   C. Involute in most infants by age 3 years.
   D. Involve both superficial and deep tissues.
   E. Show male predominance.