Editorial

Update on Hemangioma

Pediatricians are used to diagnosing cutaneous hemangiomas in about 5% to 10% of their tiny patients. Parents recall that their infant was born unblemished. Typically hemangiomas appear about 2 weeks after birth; however, about one-third or more of hemangiomas manifest in the newborn nursery as a premonitory vascular "birthmark"—either a tiny red papule, telangiectasia, pale macule (so called "anemic nevus"), or pseudoecchymosis. A deep or subcutaneous tumor often goes unnoticed until weeks or months after birth. A tumor can also be fully grown at birth—this is designated *congenital hemangioma*. This differs from common postnatally appearing hemangioma for it has completed its growth cycle in utero. Regression is often rapid, leaving behind atrophic skin and subcutis.

Fortunately, most hemangiomas only grow to a small size and do not cause problems. The pediatrician counsels the parents and monitors the tumor in expectation of natural regression. Involution usually begins by 1 year and continues over 4 to 6 years. Only a minor cutaneous blemish will remain. However, there is a small subset of evolving hemangiomas that destroy tissue or endanger the infant's life, either because of the tumor's size, location, multiplicity, or aggressive growth.

In the past few years, there has been increasing discussion about management of hemangiomas that grow in the mid-spectrum between the problematic and tiny tumors. To some degree, this controversy has been fueled by parents, armed with newly acquired (non-peer reviewed) material found on the Internet. They learn that hemangiomas can be "lasered" in the nascent stage. Some parents find information on antiangiogenic therapy. The formation of vascular anomaly teams in university centers has also stimulated debate about treatment of hemangioma.

Pediatricians must be prepared to respond to the anxious parents' questions. Often, the first concern is: what caused the hemangioma in their baby who was perfect at birth. Was it due to something the mother did? Parental anxiety is only made worse by comments from relatives and from insensitive strangers in the supermarket. The second concern is: what can be done about it? There is increasing parental pressure for early intervention.

Unfortunately, there is no answer to the parents' question "why?" They appreciate a brief explanation about what is known of the biology. Hemangiomas are benign tumors composed of rapidly growing endothelial cells; other cell types also play a role. These are unique tumors because they are programmed to grow rapidly and regress slowly. Textbook photographs illustrating the life cycle are helpful to parents. The pediatrician may want to explain, without too much detail, what is known about the cellular events. Immunohistochemical studies show that angiogenic factors, specifically basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), are prominent during the proliferating phase (0-12 months). During the same period, interferon (an inhibitor of endothelial migration) is diminished in the epidermis overlying the tumor. By one year, the involution phase is underway. Levels of angiogenic factors begin to diminish, endothelial inhibitors are upregulated, and epidermal interferon returns to normal levels. Mast cells and fibroblasts appear during regression; they appear to communicate with one another during the deposition of fibrofatty tissue. Gradually, the hyperactive endothelial cells die, leaving behind a few channels that are lined by flat, inactive endothelium. Notwithstanding our knowledge of the cellular and molecular events in hemangioma's natural history, we do not know the switch that activates hemangioma or how the switch is slowly turned off. We do know that regression involves programmed endothelial cell death and that the rate of apoptosis is maximum at age 2 years. This fact is useful information for parents who are trying to decide whether an operation should be done at this stage.

The absolute indications for referring an infant with a proliferative phase hemangioma include ulceration (and bleeding), destruction, distortion, obstruction, and congestive heart failure. Spontaneous ulceration can happen in any superficial hemangioma; the most common locations where this happens are the lower lip and anogenital areas. Secondary infection can occur. An ulcerated hemangioma is painful. The infant is often irritable and eats and sleeps poorly. Ulcerated hemangioma heals slowly. Treatment regimens include topical antibiotic, frequent dressing changes, pharmacologic therapy, and pulsed dye laser application. Unfortunately, there are no controlled prospective studies to compare these treatments. The most rapidly effective therapy is excision. This is sometimes indicated for ulcerated hemangioma of the scalp, thorax, or extremity. Occasionally a superficial hemangioma will suddenly bleed from a tiny punctum. Although this is alarming to parents, the bleeding is usually easily controlled by pressure. Rarely does a suture need to be placed.

For over one-half century, profound thrombocytopenia (Kasabach-Merritt syndrome) was believed to be a complication of "giant hemangioma." Today, this coagulopathy

is attributed to other rare vascular tumors of infancy called kaposiform hemangioendothelioma and congenital tufted angioma. These tumors differ from hemangioma in presentation, anatomic predilection, and natural history. Thus, it is unnecessary to order a platelet count in an infant with banal hemangioma.

Systemic corticosteroid therapy is the first treatment option for problematic hemangiomas. Interferon alfa 2a or 2b given for 2 weeks is the second line therapy for tumors that are unresponsive to corticosteroid trial. Pharmacologic therapy is indicated for tumors that cause obvious distortion or destruction of tissue. Obstructive complications are more insidious. A large periorbital tumor can block the visual axis and cause deprivation amblyopia. Less well-known is the fact that even a small tumor (typically in the upper eyelid) can deform the cornea, causing astigmatic amblyopia. Any infant with a periorbital tumor should be examined promptly by a pediatric ophthalmologist.

Intralesional corticosteroid therapy is as effective as systemic therapy and is often used for small facial hemangiomas. Local steroid treatment for eyelid tumors has fallen from favor in some centers because of fear of embolism to the retinal artery causing blindness. If systemic corticosteroid (and/or interferon) fail to control a periorbital tumor that affects vision, surgical resection is a consideration.

Subglottic hemangioma is another obstructive (and life-threatening) complication for which pediatricians must be alert. Typically the infant presents with hoarseness and biphasic stridor at 6 to 12 weeks. The infant is often mistakenly treated for "croup." Any infant with multiple hemangiomas or hemangioma in the lower cervicofacial area (the "beard distribution") is at risk. Noisy breathing warrants referral for direct laryngoscopy. Approximately one-half of infants with subglottic hemangioma do not have a cutaneous tumor.

High output cardiac failure can occur secondary to either single or multiple hepatic hemangiomas, and less commonly with a large cutaneous hemangioma. These infants present either at birth or several weeks postnatally with the classic triad of heart failure, hepatomegaly, and anemia. The same neonatal presentation occurs with hepatic arteriovenous malformation (AVM). It can be difficult to distinguish solitary hepatic hemangioma from AVM. Any infant with numerous cutaneous hemangiomas should have Doppler ultrasonography of the liver. Not all infants with hepatic hemangiomas have cutaneous lesions or develop congestive heart failure. Other visceral sites for hemangioma are the mesentery and gastrointestinal tract, often manifesting with bleeding. The infant with multiple hemangiomas is also at risk for intracranial tumor.

There are rare instances of extensive cervicofacial hemangioma in association with a malformative (structural) anomaly. These include posterior cerebellar cyst, anomalous intracranial and aortic arch arteries, ocular anomalies, and sternal or abdominal clefting (supraumbilical raphe). Infants with associated arterial abnormalities can develop cerebrovascular occlusive disease. Low lumbar hemangioma can also be a red flag signalling underlying spinal dysraphism and intrathecal hemangioma. Ultrasonography is a useful screening test, but magnetic resonance imaging is more definitive. Banal hemangiomas occur in a female to male ratio of 3:1. Female preponderance is even higher in these infants with hemangioma and associated anomalies.

Parents who have read about the wonders of "laser surgery" often ask their pediatrician to help them decide whether or not their infant with a small (usually facial) hemangioma should be treated. Some laserists recommend immediate treatment during the nascent stage, but flashlamp pulsed dye laser only penetrates 0.75-1 mm into the skin. Thus, only the surface color of the hemangioma will fade with photocoagulation. There is no effect on deep tumor. Furthermore, there is no evidence that laser photocoagulation hastens the onset of involution. Because hemangioma can arise synchronously in a large field or deep in the dermis, most emerging tumors are beyond the laser beam, even when discovered early. If ulceration and crusting occur after laser treatment, shallow pocklike scars or depigmentation can result. Another strategy is to insert a bare laser fiber through a needle and puncture the tumor several times to photocoagulate from within. In experienced hands, this technique produces rapid thermal shrinkage; however, ulceration is not an uncommon complication. The accepted role for flashlamp pulsed dye laser is treatment of persistent telangiectasia and staining, administered during the involuting and involuted stages.

Parents may ask their pediatrician about the possibility of surgical removal as an option during the proliferative phase. There are generally accepted indications for early resection, such as a pedunculated, ulcerated, or bleeding hemangioma. Excision is considered for tumors in which pharmacologic therapy is not indicated or has been tried without response (such as in the upper eyelid). There is always concern about the child's developing facial image prior to entering school. Usually it is best to operate in the involuting or involuted phases; often this is done in stages. The appearance and dimensions of the scar must be weighed against the child's anxiety, not that of the parents.

Excision in early childhood is indicated if: (1) resection is inevitable, for example if there is post-ulcerative scarring or a high probability of fibrofatty residuum; (2) if the scar would be the same in length and appearance if excision were to be done later; or (3) if the scar is easily concealed.

In conclusion, pediatricians continue to play a pivotal role in the management of infantile hemangiomas. They are usually the first to discover the tumor. They must see the infant frequently because it is difficult to predict the

ultimate size and behavior of a particular tumor. Pediatricians are responsible for appropriate referral.

Vascular anomalies teams have been organized in many centers. The members typically include a dermatologist, hematologist, interventional radiologist, pathologist, and surgical specialists. Such an interdisciplinary setting serves as a focus for accurate diagnosis, appropriate therapy, and research in the field of vascular anomalies. The goal is to learn what triggers hemangiogenesis. Then, someday, every neonate with a warning sign of hemangioma will be given a drug that arrests proliferation. Prompt therapy will rely on early recognition by the pediatrician.

References

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