Infantile Hemangiomas: An Update on Pathogenesis and Therapy

abstract

Infantile hemangiomas (IHs) are the most common vascular tumors of childhood, affecting ∼5% of all infants. Although most lesions proliferate and then involute with minimal consequence, a significant minority can be disfiguring, functionally significant, or, rarely, life-threatening. Recent discoveries concerning hemangioma pathogenesis provide both an improved understanding and more optimal approach to workup and management. Important detrimental associations can be seen with IH, such as significant structural anomalies associated with segmental IH. Standards of care have dramatically changed evaluation and management of hemangiomas. The goal of timely recognition and therapy is to minimize or eliminate long-term sequelae. New modalities, such as oral propranolol, provide the caregiver with better therapeutic options, which can prevent or minimize medical risk or scarring, but the side effect profile and risk-benefit ratio of such interventions must always be evaluated before instituting therapy. Pediatrics 2013;131:99–108
Infantile hemangiomas (IHS) are the most common pediatric vascular tumors, affecting ~5% of all infants born in the United States. A recent prospective Australian study of newborns noted an incidence of 2.6% by 6 weeks of age, and an American study of similar design found that 4.5% of infants developed IH, all of which were present by 3 months of age. IHSs are benign tumors that are usually not present at birth but instead are noted within the first few weeks of life. Precursor lesions are common but often subtle; findings may include telangiectasias, pallor, a bruiselike appearance, and, rarely, ulceration. IHSs typically have an initial proliferative phase, with rapid growth of the tumor in the first several months of life. This is followed by an involution stage, with slow, spontaneous resolution spanning years. After involution of the vascular component, a residual involuted vascular component remains.

Although many of these lesions resolve spontaneously without concern, a significant proportion lead to function-threatening and cosmetically disfiguring consequences. For functionally significant or potentially deforming lesions, timely intervention is important to minimize the possibility of a poor outcome and permanent scarring. Many important and management-altering discoveries have occurred regarding IH in the past decade. The following highlights the most important of these findings.

**PATHOPHYSIOLOGY**

IHSs are vascular tumors that involve the proliferation of benign endothelial-like cells that possess histochemical markers (GLUT-1, Lewis Yantigen, FcyRII, and merosin); these markers are also present on placental blood vessels. The immunohistochemical profile differentiates IHS from other vascular birthmarks or tumors.

The pathophysiology associated with the unique natural history of these lesions, with initial rapid proliferation followed by gradual involution and regression, has not been completely elucidated. One etiologic hypothesis speculates that cells are “embolized” from the placenta. Another suggests that IHSs result from somatic mutations in a gene mediating endothelial cell proliferation. Recent data suggest an endothelial progenitor cell as the source of origin of the tumors. It has been speculated that hypoxia, either systemically (eg, due to placental insufficiency) or in a specific “niche” area of poorly perfused tissue, stimulates endothelial progenitor cells to proliferate inappropriately. The following summarizes evidence for these various theories (see Table 1).

The placental theory is attractive because it would explain the programmed life cycle of IH. Subsequent to North’s discoveries regarding the histochemical similarities of IH and placenta, Barnes et al noted that placenta and IH have high levels of genetic similarity when compared with other vascular tumors and normal structures. Walner et al noted that IH tend to develop along embryonic fusion lines of the facial placodes. Piecing these 2 seemingly disparate facts together, Mihm et al suggested that IH might represent “benign metastases” originating from the placenta or other cells that proliferate in areas of low oxygen tension, such as the “end artery, vascular dead end” sites occurring in embryonic fusion planes. Pittman et al were unable to detect the presence of maternal-fetal chimerism in IH tissue, but this does not rule out the possibility of the placental origin of IH tissue because the placenta is predominantly fetal in origin.

It has also been hypothesized that immature endothelial cells and pericytes, which coexist in the late stages of fetal development, perhaps maintain persistent proliferative properties for a period of time postnatally, leading to the development of IH. However, Boye et al demonstrated the clonality of IH cells, making it less likely that a disparate group of cells serve as the source of this tumor.

Hypoxia has been proposed as a driving factor for the pathogenesis of vascular proliferation in general. IH proliferation may be a homeostatic attempt to normalize hypoxic tissue. Epidemiologic

<table>
<thead>
<tr>
<th>Table 1 Pathogenesis of IH: Hypotheses and Supporting Data</th>
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<td>Placental embolization</td>
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<td>Somatic mutation or hyperreactivity of an endothelial-type cell</td>
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<td>upregulated in IH</td>
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<td>Hypoxia stimulates the release of EPCs; EPCs then home to hypoxic sites</td>
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Hypoxia stimulates the release of EPCs; EPCs then home to hypoxic sites. Epidemiology: hypoxia-associated factors (low birth weight, advanced maternal age) overrepresented in IH population; IH occur in “end artery, vascular “dead-end” embryonic fusion plane sites IH associated with retinopathy of prematurity; GLUT1 is a sensor for hypoxia and present on IH cells; Hypoxia induced mediators of stem-cell trafficking increased in children with IH.
findings support this hypothesis, given that factors that are thought to be linked to hypoxia, such as low birth weight and advanced maternal age, are overrepresented in IH populations. Another supportive finding is the association of IH with retinopathy of prematurity, a condition known to be linked to ischemia. GLUT-1, present on IH tissue, is a facilitative glucose transporter that is an important sensor for hypoxia.

The growth of IH likely involves angiogenic peptides, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor, which induce proliferation of blood vessels. Receptors for these growth factors are also crucial in endothelial cell regulation, and a misbalance of VEGF-receptor-1 expression with consequent hyperactivity of VEGF-receptor-2 function has been noted in IH tissue. The suppressive effect of glucocorticoids may be mediated through VEGF-A. Additionally, insulinlike growth factor-2, which stimulates angiogenesis, is upregulated in proliferating but not involuting IH.

Endothelial progenitor cells (EPCs) are vascular stem cells with the capacity to contribute to postnatal vascular development. There is now compelling evidence that these EPCs play an etiologic role in the development of IH. A subset of progenitor cells isolated from IH tissues, which possess the surface markers CD34+ CD133+, are of particular interest. These EPCs have been shown to differentiate into endothelial cells in vitro and are increased 15-fold in IH compared with controls. Cultured EPCs from patients with IH stain positively for known hemangioma markers GLUT1, CD32, and merosin. Several mediators of EPC trafficking and vasculogenesis, such as VEGF-A and hypoxia inducible factor-1 alpha (a transcription factor that regulates the formation of new blood vessels by EPCs), were found to be elevated in blood and IH specimens taken from children with proliferating IH.

A major breakthrough occurred when Khan et al were able to successfully inject CD133+ EPCs from human hemangioma tissue into immunodeficient mice. These mice then developed GLUT1 vascular tumors, which recapitulated the development of human IH, providing investigators with the first viable IH animal model. These studies highlight the importance of CD133+ EPCs in the pathophysiology of IH and provide a means of testing putative therapies in this animal model.

**EPIDEMIOLOGY AND DIAGNOSIS**

Traditionally, misuse of the term “hemangioma” to describe other vascular lesions has impeded the collection of accurate demographic data. In particular, misdiagnosis of port wine stains, venous and arterial malformations, and vascular tumors such as tufted angiomas, affected the accuracy of many studies performed in the past. In 2007, a large, multicenter, prospective study was conducted by pediatric dermatologists skilled in distinguishing vascular lesions, 1058 children with IH were identified. The tumors were more commonly seen in patients who were female, white (non-Hispanic), premature, of low birth weight, a product of multiple gestation, or born to mothers with advanced maternal age. Placenta previa and preeclampsia were also found to be more common.

Two less common types of “hemangioma mimickers,” congenital hemangiomas, occasionally confuse practitioners but do not possess the classic attributes of IH. Both noninvoluting congenital hemangiomas and rapidly involuting congenital hemangiomas are “fully formed” at birth or can even be involuting or ulcerating. They may possess telangiectases and a rim of pallor. In contrast to IH, they lack GLUT1 surface markers, and thus histochemical evaluation is often useful in distinguishing between these vascular lesions.

Rapidly involuting congenital hemangiomas lesions rapidly involute, often within the first year, whereas noninvoluting congenital hemangiomas persist for a prolonged period.

Hemangiomas are now classified into 3 primary subtypes: segmental, focal (see Fig 1), and indeterminate. Waner et al found that focal hemangiomas were 3 times more common than diffuse or segmental hemangiomas on the face. The segmental subtype is associated with a higher risk of complications, functional compromise, deformity, and ulceration, as well as a greater need for therapy. Other IH that are regarded as being higher risk and may have a greater need for therapy are outlined in Table 2.

One of the most important complications associated with segmental IH is PHACE syndrome. A novel neurocutaneous syndrome associated with facial hemangiomas described by Frieden et al in 1996, the acronym PHACE refers to posterior fossa brain abnormalities, hemangiomas, arterial malformations, coarctation of the aorta and other cardiac defects, as well as eye abnormalities. Although less well known, this syndrome may be more common that Sturge-Weber syndrome (facial port-wine stain with associated glaucoma and neurologic anomalies). In a multicenter study of children with large facial IH (see Fig 2), 31% met diagnostic criteria for PHACE syndrome.
Criteria for the diagnosis of this disorder were delineated by using a standard consensus method with review of published data and a multidisciplinary team of experts. Current criteria are listed in Table 2, as are those for possible PHACE (see Table 3). The syndrome has a 9:1 female-to-male predominance. Ninety-eight percent of patients with PHACE syndrome have a large segmental IH present on the face or head. Rarely, the disorder can occur in association with IH located elsewhere or even in the absence of IH; in such circumstances, consensus criteria would term this “probable PHACE syndrome.”

Brain and cerebral vascular anomalies are the most common extracutaneous features of PHACE syndrome; neurologic and cognitive impairments remain the greatest source of morbidity in these patients. Central nervous system arterial anomalies are the most common vascular abnormalities seen in PHACE. Cerebrovascular accidents in IH patients with PHACE syndrome have been reported, with no previous specific anomaly; these patients tend to stabilize neurologically over time. In addition, structural abnormalities involving the posterior fossa and cerebellum have also been associated with PHACE syndrome.

A number of cardiac abnormalities can occur in this syndrome, the most common of which is coarctation of the aorta. The overall incidence of eye abnormalities is small and includes microphthalmia and optic nerve hypoplasia.

Facial hemangiomas that are ≥5 cm in diameter should prompt evaluation for PHACE including MRI and magnetic resonance arteriogram of the brain, cardiovascular imaging, and an ophthalmologic examination. The vessels of the upper chest and neck should also be evaluated.

Large, segmental IH in the anogenital region also carry a risk for associated underlying anomalies (see Fig 3). Several pneumonics have been coined (PELVIS, LUMBAR, SACRAL) to emphasize major features, which include a lumbosacral or perineal IH in association with spinal cord, anogenital, and renal anomalies.

Infants with multiple classic focal IH may have extracutaneous involvement (see Fig 4). Although significant mortality was historically attributed to multifocal hemangiomas with organ involvement, termed “diffuse neonatal hemangiomatosis,” it is now appreciated that multifocal hemangiomas often do not involve extracutaneous sites and that medical consequences are variable when they do. The commonly involved extracutaneous site is the liver, and hepatic ultrasound should be performed in patients with ≥5 cutaneous IH. Consumptive hypothyroidism has been associated with IH and other large vascular lesions of the liver. This is a result of excessive iodothyronine deiodinase expression, and such patients require monitoring and aggressive thyroid hormone supplementation.

**MANAGEMENT**

Although most IHs proliferate and involute without functional impairment, a significant minority requires some form of intervention. It is important to consider the psychological as well as medical impact of IH, particularly when located on the face. Many central facial lesions leave residual scars or structural deformities, which may have lifelong effects. In the past, treatment options for IH were limited and their potential side effects considerable. Although most IHs do not pose significant risks, and careful observation is still the appropriate management option for many lesions, the introduction of relatively safer topical and systemic agents now allows earlier and easier intervention in appropriate cases (Table 4). However, a Cochrane analysis of interventions for IH noted that a lack of well-designed clinical trials and the absence of US Food and Drug Administration–approved medications for IH limits the ability to clearly identify the single best treatment option.

Until recently, intralesional and systemic corticosteroids were the mainstay of...
therapy for problematic IH. Intralesional injection can be used for localized lesions. Prednisone, administered orally at doses of 1 to 3 mg/kg per day, is an effective therapy for the majority of patients.45 In a quantitative systematic literature review, Bennett et al found that systemic corticosteroids had a 84% response rate with 36% rebound in infants with problematic IH.46 However, corticosteroid therapy has significant side effects, including increased risk for systemic infection, hypertension, increased appetite, stomach irritation, growth suppression, and cardiomyopathy. In addition, some IHs are resistant to corticosteroid therapy. On the other hand, corticosteroids remain useful in certain situations, particularly in those who cannot tolerate other therapeutic options.

Other systemic therapeutic options have included interferon and vincristine.47 Adverse effects have limited the utility of both of these drugs. In particular, reports of serious side effects with interferon, including blood abnormalities and spastic diplegia in up to 20% of patients are cause for concern.48 Similarly, vincristine, a vinca alkaloid used widely in cancer chemotherapy, is efficacious for life-threatening IH but also has limited use due to the strong vesicant qualities of the drug, with need for central line access for chronic administration as well as potential peripheral mixed sensory-motor neurotoxicity.49 Of note, some of the data for interferon and vincristine may be complicated by the misdiagnosis of Kaposiform hemangioendotheliomas or other vascular tumors as IH.

In recent years, propranolol therapy has become increasingly more useful in the management of IHs that require intervention. Leaute-Labreze et al first fortuitously discovered the efficacy of β-blockers for the treatment of IH in 2008.50 An infant developed cardiomyopathy after systemic corticosteroid therapy for a large facial IH. When propranolol therapy was initiated for this complication, a remarkable flattening and fading of the IH occurred. The investigators subsequently documented the drug’s efficacy as a first-line, as well as second-line (after steroid use), therapy. All 11 patients were noted to have softening and change in color from red to purple of their IHs within 24 hours of starting propranolol. Subsequently, >170 reports and studies have substantiated the usefulness of this drug.51–53 A prospective study comparing propranolol to placebo documented drug efficacy.54 In a recent multicenter retrospective chart review, propranolol therapy was found to be more clinically efficacious and cost-effective than oral corticosteroids in the treatment of IH.55 In addition, propranolol therapy led to fewer surgical interventions and had fewer side effects compared with oral corticosteroids. Most recently, a response rate of 98% was noted in a systemic review of 41 studies of >1200 children treated with propranolol. The mean dose was 2.1 mg/kg per day, and mean treatment duration was 6.4 months. Serious side

### TABLE 3 Anomalies Reported in PHACE Syndrome

<table>
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<th>Category</th>
<th>Abnormality</th>
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<tr>
<td>Structural brain</td>
<td>Posterior fossa: Dandy-Walker complex, cerebellar hypoplasia/atrophy, subependymal and arachnoid cysts</td>
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<td></td>
<td>Hypoplasia or agenesis of cerebrum, corpus callosum, septum pellucidum, vermis</td>
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<td></td>
<td>Polymicrogyria: microcephaly, heterotopia, absent pituitary or partially empty sella turcica</td>
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<td>Cerebral vascular</td>
<td>Dysplasia of the large cerebral arteries</td>
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<td>Absence or moderate to severe hypoplasia of the large cerebral arteries</td>
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<td>Aberrant origin or course of the large cerebral arteries</td>
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<td>Saccular aneurysms</td>
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<td>Persistent embryonic arteries (predominantly trigeminal)</td>
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<td>Pial enhancement</td>
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<td>Cerebral sinus malformations</td>
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<td>Sinus pericranii</td>
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<td>Dural arteriovenous malformations/pial malformations</td>
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<td>Intracranial hemangioma</td>
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<td>Arterial stenosis or occlusion with or without Moyamoya collaterals</td>
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<td>Absent foramen lacerum</td>
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<td>Acute arterial stroke</td>
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effects were rare, occurring in <1% of patients.56 Unfortunately, direct compari-
tive studies of these 2 agents have not been performed.

Propranolol is a systemic nonselective β-blocker that has been used for decades in pediatric patients with cardio-
vascular disease with standard dosing of 0.5 to 4mg/kg per day. Currently, many uncertainties exist regarding the appropriate and optimal use in children with IH, including optimal dosing, frequency of dosing, duration of therapy, age of therapy initiation, and timing and method of tapering to minimize the chance of rebound. An ongoing interna-
tional multicenter study may shed significant light on these issues.57

Theories regarding propranolol’s mechanism of action include an initial capillary vasoconstrictive effect, suppression/blockade of growth factors with induction of apoptosis of endothelial cells,51,58 and blockade of GLUT1 receptors.59 CD34+ endothelial progenitor cells in IH express factors influencing the renin-angiotensin system. Because the renin-angiotensin system might account for propranolol-induced involution,60

Although systemic propranolol is clearly efficacious, rare side effects, a few of which may be life-threatening, are cause for concern. These include symptomatic hypoglycemia, hypotension, bronchial hyperreactivity, seizure, restless sleep, constipation, cold extremities,59 Hypoglycemia has been the most commonly noted serious effect. Careful monitoring, particularly of medically fragile infants (eg small, premature, failure to thrive) is required. Those patients with PHACE syndrome should be evaluated for cerebral vascular anomalies because poor cerebral perfusion secondary to abnormal vessels can place them at higher risk for hypotensive stroke. Epinephrine injections for emergency treatment of allergic reactions may be ineffective in children on chronic β-blocker therapy. Therefore, the risk-benefit ratio must be considered when deciding to use pro-
pranolol in children with a history of anaphylactic allergic reactions that might require epinephrine therapy. Collaborative care is often optimal for appropriate propranolol treatment of IH, including a pediatrician, dermatologist, ophthalmologist, cardiologist, and other specialists, if needed.

Topical agents are appropriate therapy in some situations (eg, small, thin lesions), and their use is sometimes driven by parental anxieties or the desire for active therapy. The risks of adverse effects are less with topical rather than systemic agents, but there is limited data on efficacy. Topical clobetasol has been used with some success, particularly in small periorbital lesions. However, concerns regarding atrophy, glaucoma, and cataracts exist with this drug. Investigators have also consid-
ered the utility of topical, rather than systemic, β-blockers. Timolol maleate is a nonselective topical β-blocker that has been approved for the treatment of system.
ocular glaucoma and hypertension in children and infants by the Food and Drug Administration. The ophthalmologic literature suggests that the side effects of timolol might be similar to those found in oral propranolol; however, in studies of ophthalmic preparations of timolol used topically for the treatment of IH, adverse effects reported to date are limited to a single episode of severe sleep disturbance. Nonetheless, experts urge caution with the drug and recommend using no more than 1 drop twice a day to affected lesions.

Recent studies showing efficacy of this topical agent for IH are promising, but most published works consist of individual cases or small pilot studies. The largest study to date found that the greatest indicators of optimal therapeutic response were increased concentration and duration of drug treatment, as well as superficial nature of the lesion.

Other therapeutic options have been considered, but risk-benefit issues have thus far limited extensive investigations into these therapies. Angiogenesis inhibitors are theoretically a natural choice for the treatment of hemangiomas. Sirolimus (also known as rapamycin), an inhibitor of mTOR, negatively affects cell proliferation and metabolism as well as angiogenesis. In vivo and in vitro studies have demonstrated suppression of IH growth in a mouse model. The drug appears to limit stem cell replicative capabilities and acts in a mechanism distinct from that of corticosteroids. Although this is a potentially attractive therapeutic option, possible risks related to inhibition of angiogenesis, particularly in a growing organism raise concerns. At this time, it is most appropriate to restrict use to clinical trials until better safety data are available.

Procedural and multimodal therapies have been used to treat IH, but controversy exists regarding their appropriate role, and few evidence-based, controlled studies are available that evaluate pediatric laser therapy. Batta et al published a controlled trial in which the author noted no significant difference in outcome when pulsed dye laser (PDL; 585–595 nm) therapy was used in the treatment of IH; however, the suboptimal fluences used, lack of appropriate cooling during treatment, and positive evidence that laser-treated lesions healed faster weakened the validity of their assessment. Most experts believe that PDL therapy can diminish pain and hasten healing in ulcerating lesions, particularly in those located in the perineal area that have not responded to topical or systemic therapeutic measures. Treatment can also decrease redness and residual telangiectasias.

The ideal form of laser therapy is in a state of evolution, but PDL is the most commonly used modality. This therapy can safely diminish and sometimes eliminate superficial lesions with minimal requirements for anesthesia and only rare scarring. It penetrates to a depth of ~1 mm and is therefore most useful for superficial lesions or ulcers. Longer wavelength alexandrite or neodymium-doped yttrium aluminum garnet laser therapy is sometimes used for recalcitrant lesions but carries a higher risk for scarring. Fractionated CO₂ laser holds promise for diminishing textural changes and scars that can develop in affected children. Multimodal therapy, using systemic agents in conjunction with judicious use of laser or other procedural therapy, can optimize therapy for selected patients (see Figs 5, 6, and 7). Some experts use PDL as adjunctive or “mop-up” therapy to treat residual telangiectasia or erythema, whereas others believe in early utilization when lesions are flatter and more amenable to therapy. Occasionally, surgical excision is the optimal therapeutic intervention. Appropriate lesions are often large pedunculated IH located in a site where a surgical scar will be less noticeable. In some instances, surgical intervention is inevitable because permanent, baggy residual scars develop. In such instances, health care providers may opt to remove the lesion early in its life cycle, given that a surgical intervention and scar are inevitable.
SUMMARY
Recent discoveries have led to an improved understanding of the pathogenesis and clinical behavior of IH. The best scientific evidence to date supports the hypothesis that IHs originate from a subset of endothelial progenitor cells (CD133+) that are stimulated and proliferate under hypoxic conditions. These cells theoretically “hno” to areas of relative hypoxia, such as embryonic fusion planes. Perturbation of angiogenic factors may also play a role in the inappropriate proliferation of these cells. The clinician must be aware of potential anomalies that can occur in association with large segmental IH. Facial lesions raise concern for PHACES, whereas lumbo-sacral and perineal lesions should raise suspicion for associated spinal cord, renal, and genital anomalies. When diagnosis is uncertain and in patients with high-risk lesions (Table 2), referral to a multidisciplinary vascular anomaly center with experienced subspecialists is optimal for patient care.

Newer treatment options for IH may well pose less risk for the patient, allowing the practitioner to intervene in a relatively safe, and more timely manner. Propranolol is now first-line therapy for many practitioners, and it is hoped that future studies will confirm its efficacy and safety. Timolol, a topical β-blocker, may have a particular role in the treatment of superficial lesions. Pulsed dye and other laser modalities may be useful as adjunctive or “mop-up” therapy. Other antiangiogenic agents may prove to be more effective in the future. However, it is important to proceed cautiously when implementing new therapies and evaluate appropriately for both short and long-term safety issues. The risk-benefit ratio of any therapy must be scrutinized, keeping in mind that “watchful waiting” may often be appropriate, but timely intervention is sometimes crucial in minimizing long-term sequelae such as functional deformity or permanent scars.

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giotensin system in proliferating in-
fantile haemangioma may account for the


HEAD BANGING: A few weeks ago, I saw two girls collide while trying to ‘head’ a ball during a high school soccer game. One fell to the ground holding her hand to her face. I immediately thought that she had fractured her nose. However, the longer she stayed on the ground the more worried I became. Eventually, she got up and unsteadily made her way to the sideline. A few questions confirmed my suspicions: she had a concussion. It did not seem much of a knock so I was a bit surprised, especially since on my farm, I often see our ram hitting everything with his head and emerging unfazed. According to an article in The New York Times (Science: October 1, 2012), animals that repetitively bang their heads (e.g. woodpeckers and antlered mammals) have developed specific adaptations to prevent brain damage. Their brains tend to be a bit smaller and have a smooth surface compared to the richly folded and textured human brain. Also, the skull tends to be quite thick and there is little fluid between the brain and the skull, with the result that the brain does not jostle back and forth after impact—a key mechanism of injury in humans. Lastly, the animals minimize side-to-side torsion on their brains by banging their heads only along a single plane. Gannets, large seabirds that dive for fish, have an even more difficult problem. They dive from 100 feet—hitting the water at 60 mph—and continue chasing fish underwater, using their wings to propel them. A supersized skull would be heavy. Instead, the skull tends to be quite thick and there is little fluid between the brain and the skull, with the result that the brain does not jostle back and forth after impact—the skull is narrow, faced with air pockets along the face, and designed to displace the energy of impact to the side. The human skull, while remarkable, is not designed to withstand the same sort of impact that rams, woodpeckers, and gannets routinely withstand. The implications to me are clear: always wear a bike helmet and be a bit careful whipping your head around for headers in a soccer game.

Noted by WVR, MD
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Tina S. Chen, Lawrence F. Eichenfield and Sheila Fallon Friedlander

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