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ARTICLE

Growth Characteristics of Infantile Hemangiomas: Implications for Management

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What's Known on This Subject

IHs are the most common tumor of infancy. They vary tremendously from small, benign growths to large, function-threatening tumors. This clinical heterogeneity creates formidable challenges for primary care providers.

What This Study Adds

For pediatricians on the front line, this information on hemangioma growth and hemangioma referral patterns is key. These findings have important implications for when IHs that need referral should be referred and when reassurance can generally be offered in managing an affected infant's condition.

ABSTRACT

OBJECTIVES. Infantile hemangiomas often are inapparent at birth and have a period of rapid growth during early infancy followed by gradual involution. More precise information on growth could help predict short-term outcomes and make decisions about when referral or intervention, if needed, should be initiated. The objective of this study was to describe growth characteristics of infantile hemangioma and compare growth with infantile hemangioma referral patterns.

METHODS. A prospective cohort study involving 7 tertiary care pediatric dermatology practices was conducted. Growth data were available for a subset of 526 infantile hemangiomas in 433 patients from a cohort study of 1096 children. Inclusion criteria were age younger than 18 months at time of enrollment and presence of at least 1 infantile hemangioma. Growth stage and rate were compared with clinical characteristics and timing of referrals.

RESULTS. Eighty percent of hemangioma size was reached during the early proliferative stage at a mean age of 3 months. Differences in growth between hemangioma subtypes included that deep hemangiomas tend to grow later and longer than superficial hemangiomas and that segmental hemangiomas tended to exhibit more continued growth after 3 months of age. The mean age of first visit was 5 months. Factors that predicted need for follow-up included ongoing proliferation, larger size, deep component, and segmental and indeterminate morphologic subtypes.

CONCLUSIONS. Most infantile hemangioma growth occurs before 5 months, yet 5 months was also the mean age at first visit to a specialist. Recognition of growth characteristics and factors that predict the need for follow-up could help aid in clinical decision-making. The first few weeks to months of life are a critical time in hemangioma growth. Infants with hemangiomas need close observation during this period, and those who need specialty care should be referred and seen as early as possible within this critical growth period. *Pediatrics* 2008;122:360–367

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Key Words
hemangioma/therapy, hemangioma/complications, hemangioma/growth, infant-newborn, infant, hemangioma/prognosis, skin neoplasms/growth

Abbreviation
IH—infantile hemangioma

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INFANTILE HEMANGIOMAS (IHS) are the most common tumor of infancy.[1] They vary tremendously from small, benign growths to large, function-threatening tumors. This clinical heterogeneity creates formidable challenges for primary care providers. In particular, it is often difficult to decide which patient with an IH is at higher risk and which will need and benefit most from referral for specialty care.

Hemangiomas have a unique natural history. Most are not apparent at birth and undergo rapid growth during infancy followed by involution during the first several years of life.[2–7] The rapid changes during early infancy can be alarming to parents, who see a small "scratch" or "bruise" rapidly evolve into a bright red tumor. Although the

TABLE 1 **Features of IHs With Highest Risk for Morbidity According to Anatomic Location and/or Morphology of the Hemangioma**

Anatomic Location/Morphology	Associated Risk
Facial, large segmental	PHACES syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal clefting)
Nasal tip, ear, large facial (especially with prominent dermal component)	Permanent scarring, disfigurement
Periorbital and retrobulbar	Ocular axis occlusion, astigmatism, amblyopia, tear-duct occlusion
Segmental "beard area," central neck	Airway hemangioma
Perioral	Ulceration, disfigurement, feeding difficulties
Segmental overlying lumbosacral spine	Tethered spinal cord, genitourinary anomalies
Perineal, axilla, neck, perioral	Ulceration
Multiple hemangiomas	Visceral involvement (especially liver, gastrointestinal tract)

general outlines of hemangioma growth characteristics have long been recognized, specific details about hemangioma growth and information regarding differences in growth patterns between hemangioma subtypes are lacking.

Historically, hemangiomas have been classified in a variety of ways. An important descriptive classification is related to the depth of soft tissue involvement: superficial, deep, and mixed.[5,6,8] More recently, IHs were also divided by whether they are spatially confined (localized) or whether they cover a territory (segmental).[9,10,11] This latter classification schema has proved helpful in predicting risk for complications and need for treatment. In particular, several recent studies delineated the clinical characteristics that are most strongly associated with complications and need for treatment.[9,12] These include large size, facial location, and segmental morphology (Table 1).

We now report data from the same cohort and specifically address another challenging dimension of hemangioma management: the specific growth characteristics during infancy and their implications for management. In addition, we review current IH referral patterns, including the age at the time of the first referral visit, and compare this with hemangioma growth patterns.

METHODS

Details regarding the recruitment, investigator training, consent, and enrollment of patients by the Hemangioma Investigator Group have been described previously.[12,13] In summary, a total of 1096 patients were enrolled during a 13-month period (September 2002 through October 2003) at 7 pediatric dermatology centers in the United States and 1 site in Spain, with clinical follow-up continued through June 2004.

At the initial visit, investigators collected demographic and clinical data. When patients had >1 hemangioma, detailed information was obtained for up to 4 hemangiomas, with selection being determined by investigators on the basis of size and/or clinical importance. In the case of multiple hemangiomas, hemangioma "A" was deemed to be the clinically most important hemangioma (typically the largest) unless another hemangioma had more clinical importance (eg, a small orbital hemangioma versus a large truncal one).

During each clinic visit, hemangioma assessments included size, stage of growth, morphologic subtype, and depth of involvement. Hemangioma size was recorded using "hemispheric" measurements.[14] A soft tape measure was draped over the hemangioma, and the longest diameter and a measurement perpendicular to it were noted, giving a measurement in cm^2.

Classification into 1 of 6 classic growth stages[1,5,12] was based on a global assessment that included parental history, assessment of interval growth, and investigator assessment as follows: nascent, referring to a premonitory mark; early proliferative, denoting the rapid proliferative phase; late proliferative, reflecting ongoing albeit less rapid growth; plateau phase; involution; and abortive (hemangiomas that did not undergo proliferation, even over time).

Hemangiomas were also classified by morphologic subtypes and description of depth of skin/soft tissue involvement (Table 2). At each visit, investigators also noted whether a follow-up visit with them was needed. These follow-up visits were scheduled on an as-needed basis, rather than at predetermined time intervals. In patients with 1 worrisome hemangioma and several smaller ones, follow-up information was recorded only for the most clinically worrisome hemangioma(s). Investigators at all sites received standardized training on classification of hemangiomas (eg, segmental, localized,

TABLE 2 **Classification of Hemangiomas According to Growth Phase of the Lesion (Stage), Clinical Morphology (Morphologic Subtype), and Depth of Skin/Soft Tissue Involvement (Description)**

Stage	Morphologic Subtype	Description
Nascent		
Early proliferative	Localized	Superficial
Late proliferative	Segmental	Deep
Plateau	Indeterminate	Mixed
Involuting		
Abortive		

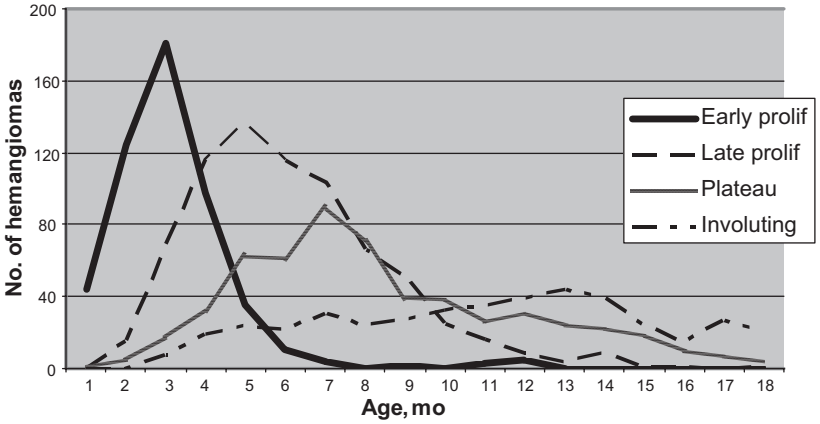

FIGURE 1
Growth analysis of the hemangioma cohort. The number of hemangiomas at each stage is compared with the age of the patient at each visit. The vast majority of early proliferative growth occurs before age 5 months, and overall growth is nearly always complete by 9 months of age.

indeterminate) and on measurement techniques via both a training manual and a live training session.

Exclusion Criteria

For focused analysis on growth characteristics, patients were excluded when they were older than 18 months at the time of enrollment. In addition, because certain growth measures (eg, size) required sequential visits to document change, patients were excluded when they had only 1 documented visit. This resulted in availability of a total of 526 hemangiomas in 433 patients for growth analysis. Comparisons between the included and excluded groups showed no statistical difference in hemangioma description, subtype, and stage, except that there were more hemangiomas in the involution stage in the excluded group. General information on the cohort has been included in analysis of demographic attributes, pregnancy, complications, and treatment.[10,12]

Growth Analysis

The 2 major growth characteristics analyzed were the age of the infant at each hemangioma growth stage and hemangioma growth rate (reported as the change in size in cm^2 averaged per month during the time between interval visits). At each visit, the age of the infant and growth stage of the hemangioma (eg, early proliferative, late proliferative) were noted. Because patient visits were conducted on an as-needed basis, more growth data were available for infants who had more frequent visits. Growth characteristics of treated and untreated hemangiomas were analyzed separately with treatments including pulsed dye laser; topical, intralesional, and oral steroids; interferon; vincristine; and surgery.

Of the 526 eligible patients, 367 had segmental or localized hemangiomas with consecutive visits for which data were available to examine growth rate. Of these, 173 (50%) hemangiomas had documented increase in size with time. Each of these hemangiomas had individual growth rate calculations based on change in size (in cm^2) over time. These calculations used the mathematical assumption that interval growth occurred in a linear manner. Because proportionate size increases in hemangiomas would be expected solely on the basis of somatic growth, growth rate calculations were adjusted accordingly. Expected body surface area increases for each age interval were adjusted for by assuming that the surface area increase at each age interval corresponded to the female 25th percentile curve of the 2000 Centers for Disease Control and Prevention growth charts. This percentile was selected both because the majority of affected infants were female and because the cohort included a substantial number of preterm patients.

Data from individual hemangioma growth rates were reported as growth rate per month, which allowed for interhemangioma comparisons of differences in growth rates on the basis of the age of the patient/hemangioma and other clinical variables. Mathematical averages and SDs were calculated for each variable. Growth of the entire subgroup was analyzed, as well as growth comparisons between specific hemangioma subtypes (segmental and localized) and hemangioma descriptions (superficial and deep). In addition to growth rates, a comparison of ages between deep and superficial hemangiomas at each stage was performed with a mixed-effects regression model with a fixed effect of type of hemangioma (superficial or deep) and a random-subject effect. This analysis used data from all visits before 18 months of age for superficial, deep, or mixed hemangiomas. Each growth stage was analyzed separately.

Referral Analysis

This analysis included the patient age when the hemangioma was first noted by the parent, patient age at the first presentation to pediatric dermatology, and specialty of the referring physician. The time difference between age first noted by parents and age of presentation to a specialist was calculated for each hemangioma.

Statistical Analysis

Statistical analysis was conducted by an independent statistician using SAS (SAS Institute, Cary, NC).

RESULTS

Age Versus Growth Stage

Treated and untreated hemangiomas were analyzed separately, but because the results were very similar,

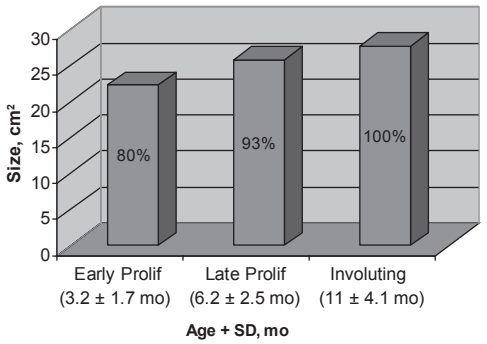

FIGURE 2
The average hemangioma size (cm²) in the early proliferative, late proliferative, and involuting growth stages. Hemangiomas reached 80% of their final size during the early proliferative stage.

growth data for these 2 groups are not reported separately. The stage of hemangioma growth compared with chronological age is summarized in Figs 1 and 2. The early proliferative growth stage was essentially complete by 5 months of age. Overall growth including both early and late proliferative stages was nearly always completed by 9 months of age (Fig 1). Involution began early in a minority of cases but more typically began at 1 year of age.

Overall Growth According to Size

In size analysis, the largest increase in size occurred in the early proliferative stage (Fig 2). By 5 months of age, the average hemangioma had already achieved 80% of its final size. Although absolute size of hemangioma varied dramatically between subtypes (localized versus segmental), the percentage of growth over time was consistent across all hemangioma subtypes.

Hemangioma Subtype Growth Analysis

Superficial Versus Deep Hemangiomas

Growth characteristics of superficial and deep hemangiomas were compared. As an aggregate during the first 18 months of life, superficial hemangiomas were more likely to be in the involution stage (odds ratio: 2.03; $P < .005$), and deep hemangiomas were more likely still to be in a proliferative stage (odds ratio: 1.80; $P < .005$). For each growth stage, infants with deep hemangiomas were on average 1 month older compared with their counterparts with superficial hemangiomas (Fig 3).

TABLE 3 **Average Size of Hemangiomas in Each Stage**

Stage	Segmental, cm²	Localized, cm²
Early proliferative stage	79.2	6.0
Late proliferative stage	93.4	7.6
Involuting stage	97.4	7.1

Localized Versus Segmental Hemangiomas

The mean size of segmental hemangiomas was 10 times that of localized hemangiomas despite having had an earlier age of presentation to dermatology (4.7 ± 3.5 vs 5.7 ± 4.0 months; Table 3). Of all segmental and localized hemangiomas with documented follow-up visits, 53% had no documented increase in size after the first visit. For both treated and untreated patients, the largest growth rates occurred in the first 3 months of life, and significant increases in size ceased by 9 months of age (Fig 4). Whereas the early (<6 months) growth rates were comparable between localized and segmental hemangiomas, segmental hemangiomas had persistently higher rates of growth after 6 months of age.

Late Growth

Whereas most hemangiomas had cessation of growth after 9 months of age, there was a small subgroup of hemangiomas with continued growth after this period. Only 3% had documented growth after 9 months of age. Of this small subset, 70% were deep hemangiomas or mixed and 70% were of segmental or indeterminate morphologic subtype.

Referral Patterns

More than three quarters (76%) of patients were referred by pediatricians. Although most hemangiomas were noted by parents within 1 month of age (13.8 ±

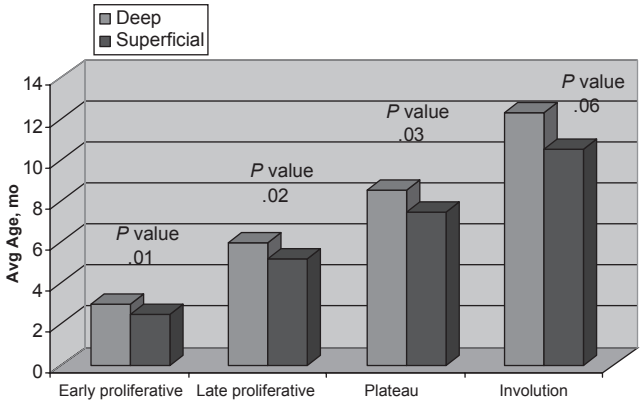

FIGURE 3
Age difference between deep and superficial hemangiomas. Deep hemangiomas reached each growth stage on average 1 month later than superficial hemangiomas.

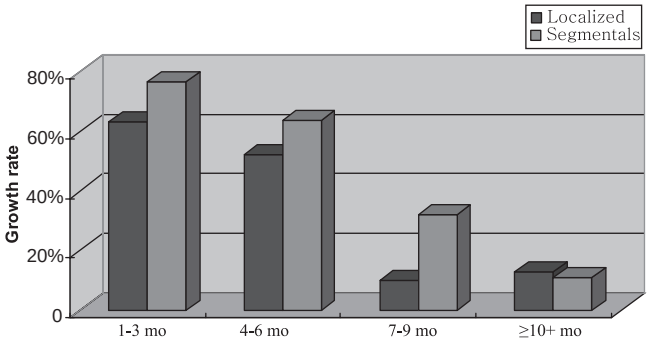

FIGURE 4
Comparison of localized and segmental hemangioma growth rates. Growth rates (% change over time) of both localized and segmental hemangiomas were highest during the first 6 months of life. Segmental hemangiomas had a higher rate of growth in the period from 6 to 9 months of age.

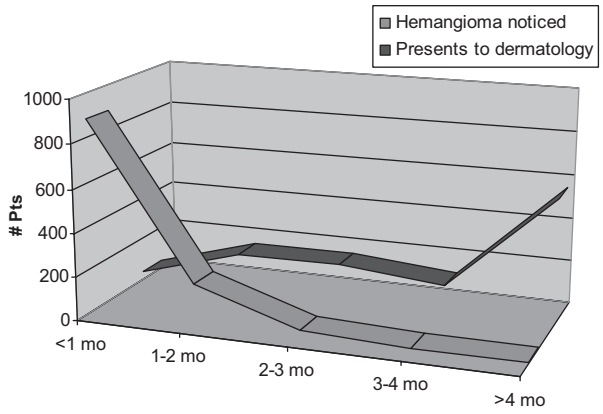

FIGURE 5
Appearance of hemangioma versus presentation to dermatology. Most hemangiomas were noted by parents within 1 month of age (13.8 ± 20.5 days); the average age at presentation to dermatology was 5 months.

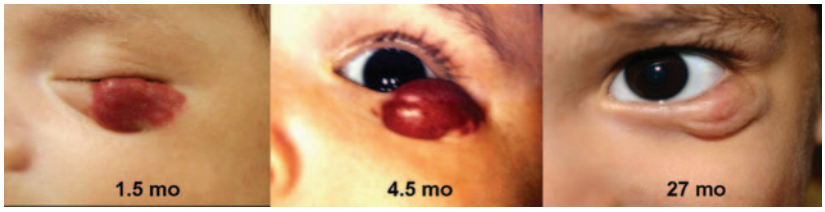

FIGURE 6
Localized hemangioma marking out territory. An example of the concept that once hemangiomas mark out their territory they thereafter proliferate within a defined anatomic area.

20.5 days), the average age at presentation to dermatology was 5 months of age (5.3 ± 3.7 months; Fig 5).

DISCUSSION

Although the general outlines of hemangioma growth and involution have been understood for many decades, this study adds significant information, particularly regarding the early stages of hemangioma growth and timing for effective referrals. On the basis of the results of our study, several key findings are evident and should be helpful in clinical practice, decision-making, and study design for treatment interventions.

Most Hemangioma Growth Is Completed by 5 Months of Age

Regardless of subtype or depth, hemangiomas reached an average of 80% of their final size during the early proliferative stage, a stage that ended at a mean age of 3.2 months (SD: ±1.7), so the majority of growth was completed by 5 months of age in both segmental and localized hemangiomas. In hemangiomas that did exhibited growth beyond 6 months of age, the most dramatic growth still occurred within the first few months of life, and the growth rate after 6 months of age was markedly lower than that noted in the first few months.

The lack of major differences in growth between treated and untreated hemangiomas is noteworthy. Several explanations are possible. First, because most hemangioma growth is completed by 5 months of age, treatment may have been instituted too late in many cases to have an effective impact on growth. Second, selection bias may have diminished differences between treated and untreated patients. Perhaps treated hemangiomas would have grown faster and longer had they not received treatment. Third, current methods to measure treatment response (eg, measurement of size) do not necessarily reflect more subjective and difficult-to-quantify clinical changes, such as lightening of color and softening of the hemangioma. Fourth, current treatments for hemangiomas are only partially effective. Systemic corticosteroids, in particular, have been demonstrated to work best at inhibiting of growth rather than in shrinking hemangioma size.[15,16] The findings do suggest that better ways to measure treatment response as well more effective therapies are needed.

Hemangiomas "Mark Out Their Territory" Early in Life

The concept that hemangiomas mark out their territory and thereafter proliferate within a defined anatomic area is supported by our findings. Previous evidence for this concept includes the clinical observation that nascent hemangiomas (so-called precursor lesions) maintain their shape and anatomic distribution during their proliferative phase[17] as well as studies demonstrating that segmental hemangiomas respect the boundaries of neuroectodermal migration patterns, suggesting patterns with an origin early in fetal life.[10,11]

In this study, segmental hemangiomas were referred on average 1 month earlier, were treated more often, yet were 10 times larger than their localized counterparts. Their large size thus seems to be biologically predetermined and not attributable to a more prolonged radial growth phase. These growth characteristics suggest that once a territory has been marked out, growth continues in a primarily volumetric manner rather than with continued centrifugal spread (Figs 6 and 7). These observations help explain why superficial modalities may not effectively prevent deeper components of hemangiomas from proliferating.[18,19] Superficial modalities such as topical corticosteroids, imiquimod, or pulsed dye laser may be effective for the hemangiomas that are destined to remain small and/or very superficial (eg, their marked

FIGURE 7
Segmental hemangioma marking out territory. Segmental hemangioma demonstrating that once a territory has been marked out growth becomes primarily volumetric rather than by continued centrifugal spread.

territory is fundamentally smaller and/or more superficial) but cannot be expected to affect either deep proliferation or the overall size of segmental hemangiomas.

It is interesting that the rate of growth for segmental hemangiomas in the early proliferative phase is essentially the same as that of localized hemangiomas. During the first 2 months of life, nearly all hemangiomas double in size, suggesting a "preprogrammed" biology that dictates initial rapid proliferation regardless of size or subtype; however, although a 4-cm^2 localized hemangioma may exhibit the same initial growth rate as a 40-cm^2 segmental hemangioma, the absolute size differential can yield potentially important clinical differences in anatomic distortion, risk for complications, perceived level of urgency for referral, and management. In addition, although initial growth rates were comparable to localized hemangiomas, segmental hemangiomas exhibited a trend toward higher growth rates after 6 months of age. The lack of statistical significance of this finding likely reflects the small segmental number of hemangiomas that were followed serially for >6 months. Additional studies that are powered to detect a difference will be needed to determine validity of this finding.

Deep Hemangiomas Appear Later and Grow Longer

Previous studies described a delayed onset of growth of deep hemangiomas when compared with superficial hemangiomas[5,6]; however, it has been unclear whether this was simply a delay in recognition because of the depth of the lesions and more subtle coloration. The growth data in this study suggest that the delay, both in onset and in length of growth, may be a true growth characteristic rather than an observational bias. Deep hemangiomas have an ~1-month delay in onset of growth compared with superficial hemangiomas and exhibit sustained growth, beyond that of superficial hemangiomas, of ~1 month. Growth characteristics of mixed hemangiomas (those with both superficial and deep components) fall in between that of pure superficial and pure deep hemangiomas (unreported data). These findings suggest true differences in growth behavior and the need for more prolonged follow-up for hemangiomas with deeper soft tissue components.

The "Plateau Phase" of Hemangiomas May not Be a True Biological Stage

Historically, hemangioma growth has been divided into growth, plateau, and involution phases.[1,5,20–22] On this basis, we included "plateau" as a stage in our data collection forms; however, the results of this study suggest that plateau phase may not be a truly distinct phase. The age of hemangiomas in this phase lies predominantly within the growth curves of late proliferative and, to a lesser extent, involuting hemangiomas (Fig 1). Recent advances in the understanding of the molecular basis of hemangioma pathogenesis also raise doubts about a true static plateau phase. Hemangioma proliferation is believed to be mediated by a variety of growth factors. Involution is believed to occur via apoptosis, possibly as a result of gradual immunologic recognition of the aberrant hemangioma vascular phenotype of the hemangioma.[23,24] Proliferative factors predominate in the growth stages, and when factors that drive apoptosis exert greater influence, growth slows and involution begins. Clinically, this dynamic balance can be seen in hemangiomas that exhibit superficial changes suggestive of early phases of involution (a diminishing red color on the surface) even as deeper components seem still to be growing. Viewing growth and involution as a continuous dynamic process seems to be a more accurate and updated depiction of hemangioma growth rather than the previous model of static and discrete phases of growth, plateau, and involution.

Implications for Monitoring Patients and Timing of Referral for Specialty Care

Data from this study demonstrate a mismatch between the growth cycle of hemangiomas and the age when most were seen by specialists, suggesting the need for a paradigm shift in the referral patterns of infants with high-risk IHs. Virtually all hemangiomas in this study were noted before 1 month of age, earlier than previous reports,[6,20] yet the average patient presented to pediatric dermatology at 5 months of age, a time when most growth was already completed and when complications such as ulceration and permanent skin distortion may have already occurred.[25] In addition, because current hemangioma treatments are often more effective in arresting growth than in causing significant involution, treatment may be more effective when instituted before most of the growth has already occurred.[5,21]

These growth characteristics also suggest that follow-up intervals need to be tailored to the age of the patient. Very young infants require closer scrutiny than older infants. For example, a 1-month-old infant with a potentially sight-threatening eyelid hemangioma needs follow-up every few weeks rather than every few months. A 2-week-old with a large, segmental facial

hemangioma, even if relatively flat, requires frequent visits and consideration of systemic corticosteroids, whereas a 5-month-old with a stable, asymptomatic hemangioma, even if bulky, may not need follow-up as often.

Many factors likely contributed to the delay in presentation to specialists. Although parents noted most hemangiomas by 1 month of age, but there may be a delay of at least 1 month until the next scheduled well-child visit. In addition, once a referral is made, the wait to see a specialist may involve wait times of several months' duration.

Two changes in physician behavior could help to avoid unnecessary delays in evaluation. First, hemangiomas are not rare. Primary care physicians should be aware of which hemangiomas are most likely to cause complications and/or need treatment (Table 1).[9,12,26,27] This recognition can help expedite referrals of high-risk infants and avoid unnecessary referrals of hemangiomas that are likely to remain innocuous. Second, referrals for high-risk hemangiomas that are growing should be considered urgent rather than routine by both the referring and the consulting physicians. Because the average wait for certain specialists (eg, dermatologists) may exceed several months,[28] specialists who see infants with IHs need mechanisms in place to expedite such appointments, including the education of office staff to give young infants with high-risk hemangiomas priority appointment slots.

Study Limitations

Although this is the largest prospective cohort of IHs to date, the study design is limited in several respects. First, this study population has a referral bias. The hemangiomas referred to pediatric dermatologists are likely to be those at higher risk and thus may not be completely generalizable to a primary care practice. Referral bias undoubtedly caused overrepresentation of higher risk lesions, and the growth characteristics may be skewed toward hemangiomas that are most likely to need close monitoring and/or therapy; however, the majority (55%) of the lesions in this study were localized hemangiomas, which are the most common and the most likely subtype to be encountered in a primary care setting.

Second, limitations in funding limited our ability to evaluate IH growth characteristics optimally. Funding was not available to pay for medical office visits, so return visits were not at standardized intervals but rather as needed on the basis of clinical indications. For patients with multiple follow-up visits, repeated measurements were documented only for hemangiomas that were deemed clinically worrisome. This limited the uniformity of information regarding growth and decreased the total number of patients for whom growth could be analyzed. The lack of standardized follow-up for every hemangioma resulted in more robust information about larger, more aggressive hemangiomas and less about smaller, more benign lesions.

Third, because of the lack of standardized follow-up visits, the rate of growth was calculated on the basis of the difference in size documented at each sequential visit, averaged over the time interval between visits. This mathematical model assumed a linear rate of growth. Because early hemangioma growth is often very rapid, even exponential, this assumption of linear growth likely underestimated early growth, further emphasizing the need for close monitoring and consideration of early referral for high-risk patients.

Last, this study did not include information about hemangioma involution, which could not be evaluated because of the time frame of the study. Additional prospective studies that are specifically designed to evaluate hemangioma growth and involution could provide important additional information; however, this is still the largest and most comprehensive prospective study of IHs to date, and despite its limitations, we still believe that it provides useful information that may aid in and change clinical practice.

CONCLUSIONS

To our knowledge, this study is the first large, prospective study of IHs that provides detailed information correlating hemangioma growth with specific hemangioma morphologies and subtypes. The finding that most hemangiomas reach 80% of their maximum size by 5 months of age demonstrates a need for a paradigm shift in current referral patterns, because the average age for presentation to specialists occurred after most hemangioma growth had occurred. Not all infants with hemangiomas need referral to a specialist, but knowledge of IH growth characteristics together with an understanding of high-risk features can help to assist in clinical decision-making for primary care physicians and pertinent specialists.

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NEXT-GENERATION MRI SCANS OFFER A SHARPER PICTURE OF THE BRAIN'S INNER WORKINGS

"The scanner isn't taking photos of brain cells contemplating the afterlife. Instead, the snapshots capture blood flowing to the cells. Scientists call this measurement BOLD—short for blood-oxygen level-dependent. More blood equals more thought, the theory goes. Combined with traditional MRI (magnetic resonance imaging), the technique has revolutionized neuroscience, providing tantalizing glimpses into the biology of cognition. Scientists call this method of scanning a brain at work functional MRI, or fMRI. Today, nearly every fMRI study relies on blood flow. Although still in its infancy—and flush with ideas but short on results—bloodless MRI will someday usher in a sea change in our understanding of the brain, its proponents say. The new techniques could provide more detailed maps of brains, illuminate the connections between distant regions of the brain, and diagnose diseases like Alzheimer's. Invented in the early 1990s, fMRI was slow to catch on. But the technique eventually became a blockbuster among neuroscientists, says the NIH's Peter Bandettini, an early pioneer who has undergone thousands of scans himself."

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