STUDY

Hemangiomas of Infancy

Clinical Characteristics, Morphologic Subtypes, and Their Relationship to Race, Ethnicity, and Sex

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Background: Hemangiomas of infancy vary widely in appearance, size, and depth of cutaneous involvement. There is currently no standard classification system for these lesions. While they occur in any race, an increased incidence occurs in girls, light-skinned whites, and premature infants, especially those weighing less than 1500 g. Other epidemiologic and demographic factors have not been well characterized.

Objective: To determine any correlations between hemangioma subtype and anatomic location with demographic factors, complications, and other associated anomalies.

Design: Retrospective chart review of 327 patients with hemangioma of infancy seen between 1997 and 2000 in an ambulatory referral center.

Main Outcomes Measures: Demographic and gestational information, lesion size, associated anomalies, complications, treatments, and outcomes were analyzed together with classification of hemangiomas into 4 groups: localized, segmental, indeterminate, and multifocal. Subtypes were correlated with race and ethnicity, the incidence of complications, and overall outcome.

Results: Of 472 hemangiomas (327 patients), 339 (72%) were localized, 84 (18%) were segmental, 37 (8%) were indeterminate, and 12 (3%) were multifocal (8 or more noncontiguous lesions). Segmental lesions were larger and were more frequently associated with developmental abnormalities. They also required more intensive and prolonged therapy and were associated with more complications and a poorer overall outcome ($P<.001$). Lesions on Hispanic patients were more likely to involve mucous membranes, to be segmental ($P<.004$), to be associated with abnormalities ($P=.05$), especially PHACE syndrome ($P=.05$), and to have more complications ($P=.01$). Increased incidence of segmental hemangiomas was the only factor in Hispanic infants associated with complications, more extensive treatment, or associated anomalies.

Conclusions: Hemangiomas of infancy can usually be classified as localized, segmental, indeterminate, and multifocal, based on clinical features. Segmental lesions have a higher frequency of complications and associated abnormalities, and this type of hemangioma seems to present with increased frequency in Hispanic infants.

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HEMANGIOMAS OF infancy are the most common benign tumors in children. Their characteristic natural history, with a proliferative phase in early infancy followed by an involutional phase, has been well described.[1,2] Epidemiologic observations include a marked female predominance, a propensity for light skin types, and a higher incidence in premature infants, especially those weighing less than 1500 g.[2-5]

The clinical appearance of cutaneous hemangiomas depends on the level(s) of the skin affected. Superficial hemangiomas involve the superficial dermis and appear as bright red "strawberry" lesions, whereas deep hemangiomas involve the deep dermis and subcutis resulting in a tumor with a bluish cast or normal skin color. Combined superficial and deep hemangiomas, often referred to as *mixed hemangiomas*, involve the dermis and subcutis and demonstrate clinical features of both types. The degree of superficial involvement and other morphologic characteristics such as plaques and nodules have been reported to affect long-term outcome.[6] In addition to size and lesional morphologic characteristics, some hemangiomas involve a broad anatomic region or a recognized developmental unit (such as the entire ear or tip of the nose), whereas others, including small plaques and large and small nodules, are discrete and well localized.[7]

More than half of hemangiomas involve the head and neck, and the distri-

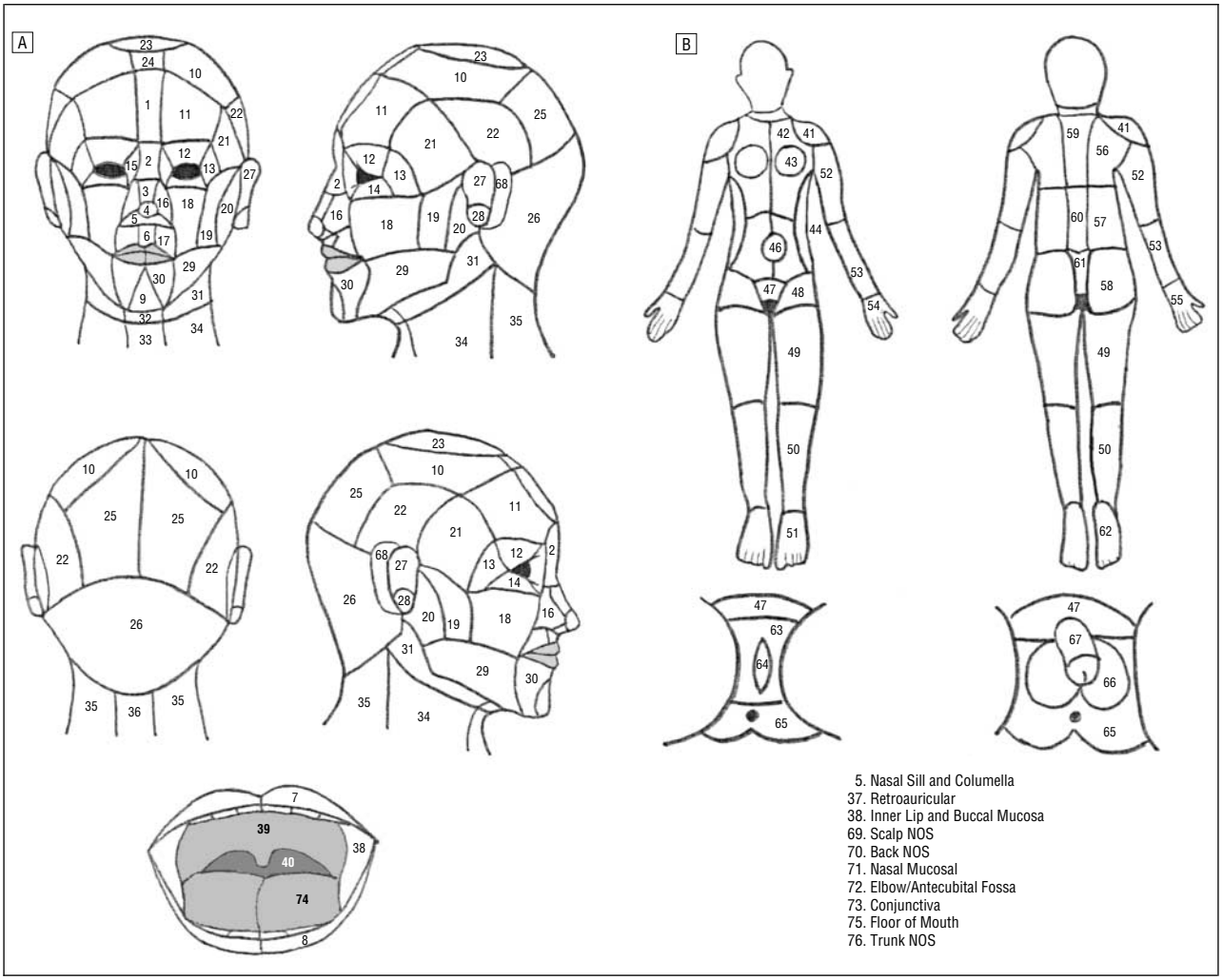

Figure 1. Diagram of numerical anatomic locations used to classify hemangiomas by site. The partial list in part B applies to parts A and B of this figure and represents the numbered anatomic locations that could not be illustrated (adequately) on the diagram.

bution seems to favor certain sites, possibly related to embryologic fusion lines and facial developmental metameres.[8] The importance of anatomic location is well recognized as a major factor in determining whether complications such as visual axis occlusion, airway involvement, ulceration, or permanent disfigurement may occur.[9-12]

We undertook this retrospective study to understand in more detail the clinical correlations between various hemangioma subtypes, locations, rates of complications, and need for treatment(s). In addition, inclusion of sex, race, and ethnicity in our database allowed us to correlate clinical observations with these factors.

METHODS

DATA GATHERING

Using the University of California, San Francisco, computerized medical record database, we compiled a list of patients 22 years or younger diagnosed with hemangioma (*International Classification of Diseases, Ninth Revision* code 228.01) and seen in the University of California, San Francisco, Pediatric Dermatology practice over a 4-year period between January 1997 and December 2000. All available charts were retrieved and reviewed. Demographic information regarding race, sex, birth, and gestation was obtained (reported full-term births were analyzed as being of 40 weeks' gestation). Pictures of individual lesions and written descriptions were used to determine size, location, and subtype.

INCLUSION CRITERIA

Each patient in this study was examined by 1 of 2 pediatric dermatologists. Only hemangiomas of infancy were included, using clinical and (when necessary) radiologic criteria.[13]

LESION LOCATION AND SIZE

Photographs of individual lesions or written descriptions were used to map each lesion. As part of the mapping process, the anatomic location of the lesion was converted to a numerical value according to the diagrams shown in **Figure 1**. Mucous membrane involvement was defined as any lesions that affected sites 7, 8, 38, 39, 64, 67, 71, 73, 74, and 75 from Figure 1.

When patients presented with more than 1 lesion, each lesion was mapped individually except in the case of multifocal (8 or more noncontiguous) lesions. A specific numerical site was assigned regardless of the proportion of involvement of that anatomic site. The degree of involvement of the site was

Figure 2. Localized nodular-mixed hemangioma on the chest (site 42 from Figure 1) of a 9-month-old white girl.

ascertained by a parallel analysis of individual surface area. The surface area of individual lesions was calculated by multiplying the width by the length.

LESION TYPE

Lesions were classified, based on unblinded agreement of 2 of us (K.G.C. and I.J.F.), into 4 groups: localized, segmental, indeterminate, and multifocal. Lesions were then subtyped as indicated below.

Localized lesions demonstrated clear spatial containment, usually with involvement of only 1 or 2 mapped sites (Figure 1). In some cases, larger lesions were classified as localized because they were either focal (ie, appearing to arise from 1 central focus of growth) or lacked evidence of a linear or geometric pattern that might associate them with a specific area of developmental growth. Localized lesions were further subdivided into nodules (rounded surface) or plaques (flat or plateaulike surface). Nodular lesions were identified as superficial, deep, or mixed. Plaque-type hemangiomas were subdivided by thickness and surface characteristics. Thus, there were 9 subtypes of localized lesions: (1) nodular-superficial flat; (2) nodular-superficial prominent (having an exophytic or pedunculated appearance); (3) nodular-mixed (**Figure 2**); (4) nodular-deep; (5) plaque-thin (flat-topped with a thickness of approximately 1-2 mm) (**Figure 3**); (6) plaque-thick (>2 mm); (7) plaque-telangiectatic (mostly composed of telangiectasias); (8) plaque-papular (composed of clusters of papules); and (9) localized-superficial not otherwise specified.

Segmental lesions demonstrated linear and/or geographic localization over a specific cutaneous territory and were usually associated with at least some plaquelike features. They were often unilateral and usually sharply demarcated at the midline, but there were exceptions, particularly nasal and lip lesions. Although some of these segments were dermatomal in distribution, many involved areas that did not correspond to specific cutaneous dermatomes. Some seemed to correspond to developmental facial metameres. Still others were of uncertain developmental origins. Segmental lesions were divided into 5 subtypes: (1) segmental-superficial telangiectatic; (2) segmental-superficial papular; (3) segmental-superficial thin (**Figure 4** and **Figure 5**); (4) segmental-superficial thick

Figure 3. Localized plaque-thin hemangioma on the scalp (site 24 from Figure 1) of a 2-year-old white girl.

(**Figure 6**); and (5) segmental-mixed (**Figure 7**). The actual dimensions of many segmental lesions were not recorded owing to their large size. While most involved broader anatomic areas than localized lesions, relatively small segmental lesions were also observed. The most notable examples were nasal tip hemangiomas, which, when fully involving the nasal tip, were considered segmental rather than focal because they were judged to corresponded to the embryologic developmental unit known as the nasal placode. Small "satellite" hemangiomas in the same cutaneous territory as a segmental lesion were not considered separate entities.

The category of *indeterminate lesions* was needed because there were some hemangiomas that we could not confidently categorize as either localized or segmental. Large deep lesions, for instance, were often included in this category because it was frequently difficult to determine whether they were segmental. Indeterminate lesions were subcategorized as superficial (**Figure 8**), mixed, or deep.

Hemangiomas were considered *multifocal* if the infant had 8 or more individual noncontiguous lesions of any morphologic characteristic. In these patients, the individual hemangiomas were not mapped, but the number of individual lesions was documented and used to calculate the mean number of lesions per patient.

HEMANGIOMA-RELATED COMPLICATIONS

Complications included lesional ulceration, bleeding, pain, infection, high-output cardiac failure, postural or functional difficulties (such as inability to turn the head in nuchal lesions), airway compromise, severe scarring, eating difficulty, auditory canal occlusion, ophthalmologic problems (including astigmatism and amblyopia), and "worrisome rapid growth." The latter was generally growth thought to be causing a risk to a vital structure like the eye or judged to have significant possibility of causing permanent disfigurement.

ASSOCIATED ABNORMALITIES

Associated abnormalities included anomalies characteristic of PHACE syndrome (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities),[14] urogenital abnormalities,[15] spinal involvement (such as tethered spinal cord or hemangioma tissue radiologically involving the deep paraspinal tissue),[15] and mediastinal hemangiomas. They also included other abnormalities such as cardiac defects without

Figure 4. A, Lateral view of a large facial segmental-superficial telangiectatic/thin hemangioma involving sites 4 through 9, 11, 13 through 21, 29, and 30 from Figure 1 on a 4½-month-old white girl. B, Head-on view of the same lesion showing involvement of the columella and extension beyond the midline on the right lower lip. Central facial areas are thicker.

Figure 5. Small segmental-superficial thin hemangioma involving both sides of the lower lip and the tongue (sites 8 and 74 from Figure 1) on a 7-week-old white girl.

other evidence of PHACE syndrome and other structural or developmental abnormalities such as limb hypertrophy or cleft palate. Hemangiomas of the parotid gland or airway[16,17] were not included in this category. Parotid involvement was not routinely assessed or documented in the records, while airway involvement was considered a complication rather than an anomaly. We did not diagnose any cases of associated hypothyroidism, but no routine monitoring for hypothyroidism was performed because this potential complication was not widely appreciated during the period of the study.[18]

TREATMENT

Treatments, either alone or in combination, included systemic therapies such as oral prednisone and subcutaneous interferon as well as localized therapies such as intralesional steroids, topical steroids, topical medicaments other than steroids (eg, topical antibacterial agents and colloidal dressings), oral antibiotics, eye patching, laser treatments, and embolization.

Figure 6. Large facial segmental-superficial thick hemangioma with some graying (signs of involution) involving sites 13, 19 through 22, 27, and 28 of Figure 1 on 2-year-old Hispanic girl. Note the nondermatomal distribution and the involvement of the ear.

Figure 7. Small segmental-mixed hemangioma on sites 4 through 6 from Figure 1 on a 2-month-old Hispanic girl. This lesion shows features of the so-called Cyrano nose as well as columella involvement.

Figure 8. Indeterminate-superficial hemangioma involving the right upper lip (sites 6 and 7 on Figure 1) on a 21-month-old white girl. Note the sharp demarcation and linear nature, which suggest that this could be a forme fruste of a segmental hemangioma.

(Detailed analyses of specific treatments and their results are not reported herein.)

OUTCOMES

For the purposes of this study, the outcome of each lesion was defined by its status at the last recorded patient visit. Outcomes were classified as (1) good if the final note indicated that the lesion was stable or improving and only as-needed follow-up was required; (2) lost to follow-up; (3) requiring surgical referral; and (4) poor or indeterminate if the lesion was still in the process of being regularly observed by a dermatologist at the conclusion of the study.

STATISTICAL ANALYSIS

Dichotomous variables were compared using the Mantel-Haenszel χ^2 test. To assess the relative contribution of ethnicity and lesion type to complication and clinical outcome, logistic regression analyses were performed. Sex proportions were analyzed by assuming that the catchment population was 50% female and using the binomial test for proportions. Continuous and integer variables were compared using the Kruskal-Wallis 2-sample test (Stata 7.0, College Station, Tex). All *P* values were 2-tailed; $P \leq .05$ was considered significant and no adjustments were made for multiple comparisons.

RESULTS

Our data were drawn from the records of 327 patients with a total of 472 lesions; 44 other patients whose lesions could not be clearly diagnosed or for whom insufficient information was available were excluded. There were 257 girls (79%) and 70 boys (21%) ($P<.001$). Of 129 patients whose charts revealed information about gestational age, 47 (36%) were born at 37 weeks or earlier, and the overall mean gestational age for these patients was 36.8 weeks (median, 39; range, 26-41.5 weeks) (**Table 1**).

A total of 36% of patients had lesions at birth, while 40% developed lesions within the first month of life. The mean age at first visit was 11.8 months (median age, 4.5; range, 0.2-158.3 months). Excluding 161 patients who were seen in our clinic only once (generally because they were referred to us for one-time consultation), the mean duration of follow-up was 16.1 months (median, 8.1; range, 0.2-123.6 months).

Information regarding birth weight was available for 31 patients. Their mean birth weight was 2.7 kg (median weight, 2.7; range, 0.9-4.5 kg). Of 36 patients whose chart contained information about multiple gestations, 19 patients were of multiple-gestation pregnancies, with 17 twin and 2 triplet pregnancies. A positive family history of vascular birthmarks was documented in 32 patients (10%).

The most commonly involved anatomic segment (6% of the lesions) was the anterior cheek (site 18), followed in order of decreasing frequency by the forehead (site 11) and the preauricular area (site 20) (Figure 1). Mucous membranes were involved in 48 lesions (10%), excluding the multifocal group. Sixty-six lesions (14%) underwent ancillary studies to assist in their diagnosis and/or management. These methods included radiography, magnetic resonance imaging, magnetic resonance angiography, ultrasound, echocardiography, computed tomogrpahy, and bronchoscopy.

The mean surface area of 355 lesions with documentation of size was 8.6 cm^2 (median, 3.6; range, 0.01-108 cm^2). Forty percent of the lesions had some type of complication (**Table 2**). Ulceration was observed in 75 lesions (21%) along with bleeding (usually minor) in 27, cutaneous infections in 14, and significant pain in 12. Other complications included high-output cardiac failure without structural heart anomalies (n=1); airway compromise (n=5); severe scarring (n=32); worrisome rapid growth (growth that threatened a vital structure or held a significant possibility of causing permanent disfigurement) (n=100); inability to turn the head in neck lesions (n=3); difficulty with oral intake (n=4); auditory canal occlusion (n=5); and ophthalmologic impairment, including visual axis obstruction, astigmatism, and amblyopia (n=27). A total of 174 lesions in 140 patients received some form of treatment (**Table 3** and **Table 4**). Systemic therapy was used either alone or in conjunction with topical medications to treat 83 lesions (18%) in 67 patients (20%). Four infants were treated with interferon alfa; all had received prior systemic corticosteroid therapy. By the end of our study, 397 lesions

Table 1. Patient Characteristics by Race/Ethnicity and Sex

	No. (%) of Patients	No. of Lesions per Patient	Gestational Age,* wk (n)	Birth Weight,* lb/kg (n)	No. (%) of Patients With Gestational Complications	Follow-up, mo	% of Females
Race/ethnicity							
White	208 (64)	1.9	36.5 (76)	5.6/2.5 (20)	21 (10)	16.6	80
Hispanic	58 (18)	2.3	37.1 (27)	7.4/3.3 (5)	7 (12)	17.5	74
Asian	26 (8)	1.4	39.5 (9)	5.3/2.4 (2)	5 (19)	13.3	69
Black	9 (3)	3.7	34.1 (8)	3.6/1.6 (3)	2 (22)	7.2	78
Middle Eastern	3 (1)	1.0	40 (1)	NA†	0	84	67
Other	23 (7)	1.4	38 (8)	8.3/3.7 (1)	3 (13)	9.3	87
Sex							
Female	257 (79)	1.9	37.2 (97)	5.8/2.6 (24)	32 (12)	17.5	. . .
Male	70 (21)‡	2.1	35.7 (32)	5.7/2.5 (7)	6 (8)	10.8	. . .
Total	**327**	1.4	36.8 (129)	5.8/2.6 (31)	**38** (12)	16.1	79

*Of patients of that particular ethnicity/race or sex.
†NA indicates not applicable.
‡Statistically significant.

Table 2. Distribution of Hemangioma-Associated Complications

	No. of Lesions	No. (%) of Lesions With Complications	No. of Complications	No. of Complications per Lesion
Race/ethnicity				
White	312	120 (38)	185	0.6
Hispanic	74	35 (47)	68	0.9†
Asian	36	15 (42)	24	0.7
Black	14	6 (43)	10	0.7
Middle Eastern	3	1 (33)	1	0.3
Other	33	11 (33)	17	0.5
Sex				
Female	371	151 (41)	248	0.7
Male	101	37 (37)	57	0.6
Lesion type				
Localized	339	104 (31)	148†	0.4†
Segmental	84	60 (71)	97†	1.4†
Indeterminate	37	20 (54)	32	0.9
Multifocal	12	4 (33)	6	0.5
Total	**472**	**188** (40)	**305**	0.6
With anomalies	31	25 (81)	49	1.6
PHACE*	15	11 (73)	27	1.8
Urogenital	2	2 (100)	4	2.0
Spinal	7	7 (100)	11	1.6
Other	11	9 (82)	11	1.0

*PHACE indicates association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities.
†Statistically significant.

(84%) had a good outcome (follow-up as needed); 39 (8%) were referred for surgical intervention, 21 (4%) were lost to follow-up, and 15 (3%) had poor/indeterminate outcome (ie, still in treatment and/or requiring regular follow-up).

LESIONS WITH ASSOCIATED ABNORMALITIES

Twenty-two patients (7%) had 31 lesions (7%) with associated abnormalities (**Table 5** and **Table 6**). Two patients, 1 with 1 lesion, and 1 with 3 lesions, had more than 1 associated anomaly. There were 11 patients with a total of 15 hemangiomas who had PHACE syndrome, 2 with urogenital abnormalities, 7 with spinal involvement (4 with a tethered spinal cord, 3 with spinal hemangiomas extending deeper than the subcutaneous tissue), and 11 had associated deep structural abnormalities (3 skeletal, 3 mediastinal hemangiomas, and 5 cardiac anomalies without other elements of PHACE syndrome). Two patients, 1 with urogenital and 1 with mediastinal involvement, also had spinal involvement. The most commonly involved anatomic sites of hemangiomas associated with anomalies were the nonmucosal lower lip (site 30), the mandibular area (site 29), the preauricular area (site 20), and the lateral cheek (site 19) (Figure 1). Of 6 infants with sacral lesions (site 61), 3 (50%) had an associated tethered spinal cord. Of 84 segmental lesions, 83% (n = 70) were facial, whereas only 54% (n = 203) of nonsegmental lesions were facial ($P<.001$). Of the 70 facial segmental lesions, 14 (20%) were associated with

Table 3. Lesion Characteristics by Race/Ethnicity and Sex

	No. of Lesions	Lesion Size, cm²	Lesion Type, No.				No. (%) With Abnormalities	No. (%) of Treated Lesions	No. (%) of Lesions Treated Systemically*	No. (%) of Lesions With PRN† Follow-up
			Localized	Segmental	Indeterminate	Multifocal				
Race/ethnicity										
White	312	8.1	230	50	24	8	16 (5)	114 (36)	47 (41)	265 (85)
Hispanic	74	10.9	40	22‡	9	3	8 (11)	28 (38)	20 (71)‡	58 (78)
Asian	36	7.6	27	7	2	0	1 (3)	14 (39)	8 (57)	31 (86)
Black	14	5.3	10	3	0	1	1 (7)	6 (43)	2 (33)	8 (57)
Middle Eastern	3	3.6	3	0	0	0	0	1 (33)	0	3 (100)
Other	33	10.8	29	2	2	0	5 (15)	11 (33)	6 (55)	32 (88)
Sex										
Female	371	8.9	263	72	27	9	22 (6)	138 (37)	67 (49)	312 (84)
Male	101	7.8	76	12	10	3	9 (9)	36 (36)	16 (44)	85 (84)
Total	**472**	8.6	**339**	**84**	**37**	**12**	**31** (7)	**174** (37)	**83** (48)	**397** (84)

*Percentage given is from treated lesions only.
†PRN indicates as needed.
‡Statistically significant.

Table 4. Hemangiomas Characterized by Specific Lesion Type*

Lesion Type	No. of Lesions	Lesion Size, cm²	No. (%) of Lesions With Abnormalities	No. (%) of Ancillary Evaluations	No. (%) of Lesions Treated	No. (%) of Lesions Treated Systemically	No. (%) of Lesions With PRN Follow-up
Localized	339	6.7†	6 (2)†	23 (7)†	95 (28)	26 (27)	303 (89)
Nodular superficial thin	48	0.97		0	14		41
Nodular superficial prominent	72	4.4		3	24		63
Nodular mixed	66	11.6		5	14		59
Nodular deep	48	8.9		11	6		43
Plaque thin	48	3.9		3	14		45
Plaque thick	42	8.0		1	19		38
Plaque telangiectatic	5	13.6		0	3		5
Plaque papular	5	10.2		0	1		5
Superficial NOS	5	0.97		0	0		4
Segmental	84	28.8†	20 (24)†	28(33)	56 (67)	42 (75)†	57 (68)†
Telangiectatic	4	NA		0	1		3
Papular	1	NA		0	0		1
Plaque thin	11	NA		2	9		9
Plaque thick	15	90.0		9	12		11
Mixed	53	24.6		17	34		33
Indeterminate	37	21.5	5 (14)	10 (27)	19 (51)	13 (68)	28 (76)
Superficial	10	17.2		1	7		8
Mixed	8	12.6		0	5		7
Deep	19	27.3		9	7		13
Multifocal	12	NA	0	5 (42)	4 (33)	2 (50)	9 (75)
Total	**472**	8.6	**31** (7)	**66** (14)	**174** (37)	**83** (48)	**397** (84)

*PRN indicates as needed; NA, not applicable; and NOS, not otherwise specified.
†Indicates statistically significant.

PHACE syndrome. One other patient with several features of PHACE syndrome, including a sternal raphe and congenital heart disease, had a segmental trunk and arm hemangioma rather than facial. No visceral involvement was documented in patients with multifocal hemangiomas during the study period.[19,20]

Lesions without associated anomalies had a mean surface area of 8.2 cm² (median, 3.2; range, 0.01-90 cm²). Those with 1 associated anomaly had a mean surface area of 13.4 cm² (median, 2.25; range, 0.0199 cm²), and those with 2 associated anomalies were even larger, with a mean surface area of 40.1 cm² (median, 6.3; range, 6-108 cm²). In addition, some segmental lesions too large to be easily measured had associated abnormalities (Table 4).

ETHNIC AND RACIAL DIFFERENCES

There were no significant differences in sex ratios and only minor differences in gestational age and birth weight between ethnic groups (Table 1), although Hispanic patients had slightly higher gestational age and birth weight than non-Hispanics. Hispanics were also more likely to have segmental lesions than whites (30% vs 16%; $P = .002$) and all other ethnic groups combined (30% vs 15%;

Table 5. Distribution of 31 Hemangiomas With Concomitant Abnormalities by Type

Abnormalities	No. of Hemangiomas Associated With Abnormalities	No. on Lesion Type			
		Localized	Segmental	Indeterminate	Multifocal
PHACE*	15	0	14‡	1	0
Urogenital	2†	0	2‡	0	0
Spinal (spinal involvement, tethered cord)	7†	1	3	3	0
Other (skeletal anomalies, mediastinal involvement, cardiac anomalies)	11†	5	2	4	0

*PHACE indicates association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities.
†Includes hemangiomas that had multiple associations.
‡Statistically significant.

Table 6. Distribution of 22 Patients With Concomitant Abnormalities by Race/Ethnicity

Abnormalities	No. of Patients With Abnormalities	No. of Patients						
		White	Hispanic	Asian	Black	Middle Eastern	Other	Females
PHACE*	11	6	4‡	0	0	0	1	10‡
Urogenital	2†	2	0	0	0	0	0	2
Spinal (spinal involvement, tethered cord)	5†	2	2	0	1	0	0	4
Other (skeletal anomalies, mediastinal involvement, cardiac anomalies)	6†	3	1	1	0	0	1	2

*PHACE indicates association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities.
†One patient had both abnormalities.
‡Statistically significant.

Table 7. Characteristics of the Patients by Lesion Type

Lesion Type	No. of Lesions	No. of Patients*	Gestational Age,† wk (n)	Birth Weight,† lb/kg (n)	No. (%) of Lesions With Gestational Complications	Follow-up, mo	No. (%) of Lesions From Multiple-Gestation Pregnancy
Localized	339	227	36.5 (130)	5.2/2.3 (27)	33 (10)	15.1‡	24 (7)
Segmental	84	78	38.7 (40)‡	7.2/3.2 (15)‡	11 (13)	22‡	3 (3.6)
Indeterminate	37	34	35.4 (16)	4.7/2.1 (1)	5 (13)	11.7	4 (11)
Multifocal	12	12	32.5 (8)	3.2/1.4 (3)	1 (8)	8.2	0
Total	**472**	**327**	36.7 (194)	5.7/2.6 (46)‡	**50** (11)	16.1	**31** (6.6)

*Twenty-four patients had several types of lesions.
†Of patients with the particular lesions.
‡Statistically significant.

P<.004) (Table 3). They had a marginally higher incidence than non-Hispanics of mucous membrane involvement compared with all other lesions combined (10/55 lesions [18%] for Hispanics vs 26/260 lesions [10%] for non-Hispanics; *P*=.08). Lesions in Hispanics were only slightly more likely to occur concomitantly with abnormalities than in non-Hispanics, but they were specifically and significantly more likely to be associated with PHACE syndrome (*P*=.05) (Tables 5 and 6). The incidence of complication per lesion was significantly higher (*P*=.01) in Hispanic patients (Table 2), and lesions of Hispanic patients were treated significantly more often with systemic medications (*P*=.02).

LESIONAL TYPES

There were 339 localized (72%), 84 segmental (18%), 37 indeterminate (8%), and 12 multifocal lesions (3%) (Table 4). Age distribution with respect to age of onset was similar between types. Segmental and indeterminate lesions were associated with a slightly higher rate (13% for both) of gestational complications than other hemangioma types (**Table 7**). Segmental lesions occurred on patients of older gestational age and higher birth weight (*P*<.001 for gestational age and birth weight), whereas multiple lesions occurred on patients with a significantly lower birth weight compared with other lesions (*P*=.04) (Table 4). Segmental lesions received longer follow-up (*P*<.001) than all other lesions combined, whereas localized lesions received shorter follow-up (*P*<.001) and had fewer ancillary evaluations (*P*<.001) than other lesions (Table 4).

Segmental lesions were significantly larger than other lesions (*P*<.001) (Table 4) and were more often associated with urogenital anomalies (*P*=.002) and PHACE syndrome (*P*<.001) (Table 5). They were more likely to develop in Hispanic patients (*P*<.004) (Table 3) and had a

higher rate of complications ($P<.001$)(Table 2). Twenty segmental lesions (24%) were ulcerated compared with 55 nonsegmental lesions (14%) ($P=.03$). When compared with all types combined, segmental lesions were treated more frequently and more often with systemic therapy ($P<.001$ for both). Segmental lesions had a higher frequency of poor or indeterminate outcomes (32% for segmental vs 12% for nonsegmental lesions; $P<.001$) and surgical referral (19% for segmental vs 6% for nonsegmental) at the end of our study.

SEX DIFFERENCES

Segmental lesions were somewhat more likely to occur in female than male infants (19% in girls vs 12% in boys; $P=.08$), but sex difference was most striking in PHACE syndrome, where 14 of 15 cases occurred in girls. There were no additional differences in sex with respect to age of onset, gestational age, number of gestational complications, duration of follow-up, number of lesions per patient, lesion size, frequency of mucous membrane involvement, frequency of associated anomalies, number of complications, frequency of treatment, or frequency of as-needed follow-up (Tables 1-3).

MULTIVARIABLE ANALYSIS

Logistic regression analysis was performed to assess which factors were most associated with lesion severity, defined as (1) presence of concurrent abnormalities, (2) occurrence of hemangioma-related complication, and (3) poor overall outcome. Hispanic ethnicity was not independently predictive of abnormalities (odds ratio [OR], 0.6; 95% confidence interval [CI], 0.07-4.7; $P=.60$), complications (OR, 1.1; 95% CI, 0.06-2.00; $P=.80$), or poor outcome (OR, 0.8; 95% CI, 0.3-2.4; $P=.70$). In contrast, segmental lesions had associated anomalies (OR, 9.5; 95% CI, 4-23; $P<.001$), complications (OR, 4.6; 95% CI, 2.6-8.3; $P<.001$), and poor or indeterminate outcome (OR, 0.3; 95% CI, 0.1-0.6; $P=.002$) independent of ethnicity or sex.

COMMENT

Our study, which retrospectively gathered information on 327 infants with 472 hemangiomas, affirms previously reported information regarding sex, age of onset, gestational age, and birth weight distribution,[1,4,21] but extends and adds to those observations. Specifically, we found increased morbidity, associated anomalies, and less favorable outcome with segmental hemangiomas than with localized lesions, as well as an increased incidence of segmental hemangiomas in Hispanic infants.

The categorization of hemangiomas into localized and segmental types was valuable for prognosis. Segmental hemangiomas had significantly higher rates of complications and higher incidence of developmental anomalies, therapeutic interventions, ancillary evaluations, surgical referral, use of systemic therapies, and poor outcome. Segmental hemangiomas occurred in children born at a later gestational age and with higher birth weight than in patients with other types of hemangiomas. This finding is the inverse of the known association of hemangiomas with prematurity, again raising the possibility that there may be developmental differences between segmental and localized hemangiomas.

Indeterminate hemangiomas were those that we were unable to confidently categorize as being either segmental or localized. Their complication rate and need for treatment were between those of localized and segmental lesions, suggesting that some may be formes frustes of segmental hemangiomas.

Multifocal lesions had a greater rate of ancillary radiologic evaluations to exclude visceral involvement. Although patients with this type of lesion had as many as 30 individual lesions, rates of complications and need for treatment were comparable to those of the localized type, and no significant extracutaneous hemangiomas were discovered.

The complication rates and associated anomalies in our study were relatively high, undoubtedly owing at least in part to the referral nature of our practice, and therefore are not necessarily representative of all hemangiomas of infancy. PHACE syndrome was identified in 11 patients and tethered spinal cord in 3. All of these patients had segmental hemangiomas with the exception of 1 infant with an indeterminate lesion and tethered spinal cord.

Despite the potential referral bias in our practice, most patients did not have associated anomalies, and more than three quarters of the lesions had a good outcome (as-needed follow-up). While some might return for later reevaluation and treatment of scarring or other complications, this study reinforces the good overall prognosis of hemangiomas as an aggregate. The contrast between the overall good prognosis and the large number of complications further emphasizes the need for increased vigilance at sites and in lesional types that are at higher risk for complications and/or adverse outcome.

Among the patients with PHACE syndrome, there was a male infant with a large segmental truncal and arm hemangioma, multiple cardiac defects, and midline congenital xyphoid scar as well as a supraumbilical raphe. Although he did not have a facial hemangioma, which is a defining characteristic of PHACE syndrome, he had multiple other characteristic anomalies and thus was diagnosed as having a variant of PHACE syndrome. His case adds weight to the concept that segmental hemangiomas at any anatomic site may have associated structural defects.

The presence of extracutaneous hemangiomas in association with large segmental facial hemangiomas also deserves comment. Although we did not look for them systematically, large mediastinal hemangiomas were found in 3 patients, a finding that has been reported in several previous cases.[22-24] With improved imaging techniques, we may discover that this occurrence is more common than previously realized. Although not observed in our series, large facial hemangiomas have also been associated with extensive gastrointestinal tract involvement.[25,26]

Although several patients with segmental hemangiomas had parotid involvement, this was not included

as an associated anomaly because it is a common finding in large preauricular hemangiomas and was not systematically recorded. Similarly, airway hemangiomas (present in 5 patients) were included only as complications, not as anomalies. It should be noted that, because of the exclusion of airway and parotid involvement as anomalies, and because imaging studies were performed only when clinically indicated, the overall association between anomalies and segmental lesions represents a minimum estimate.

Although racial differences have been previously reported,[5] to our knowledge, our data are the first to demonstrate that Hispanic patients have greater morbidity and more complex hemangiomas than all other racial and ethnic groups. Furthermore, we demonstrated that this is associated with a striking prevalence of segmental lesions among Hispanics. The cause of the increased risk for segmental-type hemangiomas in Hispanics is not known. Other birth defects, such as neural tube defects, are more common in Hispanic infants.[27,28] Moreover, another vascular anomaly, so-called cerebrocutaneous angiomatosis, is more common in Hispanics.[29] The higher incidence among Hispanics may have either a genetic or an environmental basis and deserves further study. While referral bias (ie, preferential referral of segmental hemangiomas over localized hemangiomas) cannot be excluded, the magnitude of the difference is large.

In conclusion, hemangiomas of infancy are very common tumors, but only a minority cause clinically significant problems. The challenge to clinicians is to recognize which hemangiomas need vigilant observation and/or intervention. Our study shows that lesional type is a significant prognostic factor, and that segmental hemangiomas have a higher rate of complications, more associated anomalies, and poorer outcomes. Moreover, in the population studied, Hispanic infants had a disproportionate number of segmental hemangiomas. We hope that our observations will provide the basis for prospective studies looking at lesional types and issues of race and ethnicity. Further refinement of the classification schema may also come out of these studies, particularly if data regarding pregnancy history, family history, gestational age, and birth weight are gathered systematically. Such studies could help shed more light on the origins of this common, but poorly understood, tumor of infancy.

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