The Nonrandom Distribution of Facial Hemangiomas

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Objective: To map sites of occurrence of facial infantile hemangiomas and correlate these with pattern of tumor growth, clinical complications, and proximity to structural and developmental landmarks.

Design: A retrospective medical record review of 205 patients diagnosed with facial infantile hemangioma.

Setting: Arkansas Children's Hospital, Little Rock, a 250-bed teaching hospital affiliated with the University of Arkansas for Medical Sciences.

Patients: Based on their clinical photographs, 232 of the hemangiomas were mapped on a facial schematic. Each lesion was encoded with a number reflective of its location, and this number was shared by other lesions occurring at the same site. Frequencies of complicating ulceration and airway obstruction were determined by medical record review.

Results: Two patterns of tumor growth were evident among the hemangiomas analyzed: focal (177 lesions [76.3%]) and diffuse (55 lesions [23.7%]). The focal hemangiomas mapped to 22 sites of occurrence, all near lines of mesenchymal or mesenchymal-ectodermal embryonic fusion. The 55 diffuse hemangiomas showed a segmental tissue distribution and thus were designated as frontonasal (15 lesions [27%]), maxillary (19 lesions [35%]), or mandibular (21 lesions [38%]). Ulceration was 3 times more common in patients with diffuse hemangiomas (21 [51%] of 41) than in patients with focal hemangiomas (28 [17%] of 164). Airway obstruction was characteristic of diffuse mandibular hemangiomas.

Conclusions: Facial infantile hemangiomas occurred in 2 distinct patterns of tissue involvement: a focal type with a tumorlike appearance and a less common diffuse type with a plaquelike appearance. The diffuse lesions were more likely to be complicated by ulceration or airway obstruction and showed a strikingly segmental distribution pattern. Focal hemangiomas, in contrast, showed a predilection for regions of embryological fusion.

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INFANTILE HEMANGIOMAS are the most common tumors of infancy and affect between 10% and 12% of all white children.¹ The prevalence among Asian and black infants is, however, considerably less.² Most infantile hemangiomas involve the head and neck, and female infants are affected more commonly than male infants by at least 3-fold.³⁻⁴ Hemangiomas are usually not present at birth, proliferate by cellular hyperplasia during the first year, and then involute.³ As many as 30% of lesions may be evident at the time of birth, usually as relatively inconspicuous, so-called precursor lesions, but their natural history is identical to those lacking any congenital sign, that is, proliferation during the first year of life, followed by involution. This clinical behavior sharply contrasts with that of vascular malformations, which are always present at birth, do not proliferate, and never involute.³ Malformations follow a static path or grow episodically at ages not restricted to the first year of life.

Experience seems to suggest that hemangiomas occur at certain sites more commonly and that at least some lesions display a remarkably similar pattern of distribution (Figure 1). The purpose of this study was to objectively map the sites of location of facial hemangiomas in a large series of patients seen at the Arkansas Children's Hospital Vascular Anomalies Clinic, Little Rock, and to see if they followed any recognizable pattern. Moreover, we hypothesized that determination of these “sites of occurrence” might help us bet-
ter understand the origin and natural history of hemangiomas.

**METHODS**

The first 220 patient medical records that had been entered into our database, with a diagnosis of facial infantile hemangioma, were studied. Records for 14 patients were inadequate for the analysis, and these patients were excluded, leaving 206. The diagnosis of hemangioma was nearly always clinical. Differentiation from vascular malformations was based on their clinical behavior and features. In some cases, confirmation of the diagnosis was made with magnetic resonance imaging. Hematoxylin-eosin–stained tissue sections from resected lesions were available for 119 of the studied patients and were reviewed by one of us (P.E.N.), with histological confirmation of the diagnosis of infantile hemangioma (cellular hemangioma of infancy) in 118 of these. The 1 histologically disparate case, a vascular malformation, was excluded, leaving 205 patients in the study.

The location of each hemangioma was determined from clinical photographs and/or clinic notes and drawings, then carefully marked on a schematic diagram of the face by one of us (M.W.) and verified later for accuracy by 2 additional investigators (A.W. and K.S.). A consistent observation was that lesions fell into 2 groups: (1) focal, tumorlike lesions and (2) diffuse, plaquelike lesions, the latter with a distinctly segmental pattern of tissue involvement. Lesions were independently classified in this regard (ie, focal or diffuse) by 3 different authors, with excellent interobserver agreement. Rare incidences of disagreement in this classification (5 cases) were resolved by discussion. Lesions of the 2 types were thus mapped according to different schematics as indicated below. For the focal hemangiomas, results were compiled as follows: each lesion was mapped on the facial schematic shown in Figure 2A and B and assigned a location number based on position of the approximate center of the lesion, regardless of its size and depth. All lesions mapping to a given anatomic location were assigned the same location (site of occurrence) number, and the “hits” occurring at each site were tallied. In the case of large lesions that fully encompassed more than 1 adjacent site (which was the case for 6 patients), each of those site numbers was assigned and that lesion was considered 2 separate lesions for computational purposes alone. Multiple, noncontiguous lesions from individual patients were scored independently. The diffuse hemangiomas were mapped and tallied similarly, except site designations were limited to frontonasal (I), maxillary (II), or mandibular (III) according to the schematic shown in Figure 2C. Diffuse lesions with bilateral involvement were so noted, but were tallied as a singular lesion. For each patient, the frequency of 3 potential complications of facial hemangiomas—ulceration, airway obstruction, and cardiac failure—were determined by medical record review. Statistical analysis of the distribution of focal lesions among observed sites of occurrence was performed by $\chi^2$ analysis for a binomial distribution, assuming that for a large population of lesions without site bias, all observed sites of occurrence would be equally represented.

**RESULTS**

A total of 232 lesions were mapped for the 205 patients included in the study. Two distinct patterns of tissue involvement were evident: focal (Figures 3, 4, 5, and 6) and diffuse (Figures 7, 8, and 9). As their name implies, focal lesions were localized and tumorlike, whereas diffuse lesions were more widespread and plaquelike. Furthermore, the distribution of diffuse lesions on the face appeared to be segmental. They were therefore designated as frontonasal, maxillary, or mandibular, corresponding with the embryological mesenchymal prominences of the head and face (Figure 2C).

There were 177 focal lesions (76.3%) among the 232 lesions from 164 patients (Table 1), and 55 segmental lesions (23.7% of lesions) from 41 patients (Table 2). For the focal hemangiomas, 22 sites of occurrence were identified (Figure 2A, Table 1), and $\chi^2$ analysis indi-
cated a nonrandom distribution of the lesions among these sites \((P < .001)\). As given in Table 1, the most common focal lesion sites were the mid-cheek (19 lesions; 10.7% [Figure 3; site 12 of Figure 2A]), the lateral portion of the upper lip (17 lesions; 9.6% [Figure 4; site 17 of Figure 2A]), and the upper eyelid (15 lesions; 8.5% [Figure 5; site 5 of Figure 2A]). The nasal tip was the involved site in 9 (5.1%) of the 177 focal lesions (Figure 6). If adjacent sites in the central face are grouped, 24.3% were periocular (sites 5, 6, 8, 9, and 10), 15.8% involved the nose (sites 7, 11, 13, 14, and 15), and 20.3% involved the lips (sites 16, 27, and 18). Thus, 107 (60.5%) of the 177 focal lesions in the study were located in this relatively small, central facial area. The female-male ratio among patients with focal hemangiomas was 3:1.

The most common diffuse lesions involved the mandibular (21 lesions; 38% [Figure 7]) and the maxillary segments (19 lesions; 35% [Figure 8]), followed by the frontonasal segment (15 lesions; 27% [Figure 9]; Table 2). Involvement of the segment was either complete and confluent or partial and nonconfluent. The distinct segmental pattern of distribution was, however, always present even though nonconfluent (Figure 9).

Lesions involving the mandibular segment were often associated with an upper airway obstruction at the hypopharyngeal level, and in 8 (38%) of 21 patients, a tracheotomy was necessary (Figure 7). Airway obstruction was not seen with focal lesions in our series. Bilaterality was common among segmental mandibular lesions (8 [38%] of 21), but was also occasionally noted among the maxillary (1 [5%] of 19) and frontonasal (1 [7%] of 15) lesions (Table 2). Ten (24%) of the 41 patients with segmental lesions had more than 1 segment involved; in 2 of these 10 patients, the multiple segmental lesions were noncontiguous (frontonasal and mandibular; Figure 9). The female-male ratio of patients with segmental lesions was 5.7:1, almost twice that of patients with focal lesions (3:1).

A total of 28 (15.7%) of the 177 focal lesions (affecting 28 [17.1%] of 164 patients) ulcerated, most commonly the lip lesions (Table 1). Ulceration was much more common in patients with segmental lesions (21 [51%] of 41), particularly within lesions affecting the maxillary segment (12 [63%] of 19 of these ulcerated [Table 2; Figure 8]).

**COMMENT**

We describe 2 distinct patterns of tissue involvement in a series of 232 facial hemangiomas affecting 205 patients: a more common focal type, displaying a tumorlike growth pattern, and a less common diffuse, plaquelike lesion with a segmental pattern. We further describe 22 facial “sites of occurrence” for the focal subtype of hemangioma in our
series, with most of the lesions (60%) occurring in a relatively small area in the central face. We found ulceration notably more common in segmental hemangiomas, particularly those involving the maxillary segment. Airway obstruction was most common in segmental hemangiomas of the mandibular segment. In addition, the long-recognized preponderance of hemangiomas among female patients was observed to be more pronounced for diffuse hemangiomas than for focal hemangiomas in this study (by a factor of nearly 2). Important implications of
lip and the mandible (lar processes fuse in the midline and give rise to the lower upper lip, the cheek, and the maxilla, and the mandibular processes eventually form the remainder of the face). The maxillary prominences appear at the cranial end of the fetus. These prominences or primordia represent areas of mesenchymal growth that result from the migration of cranial neural crest mesenchyma is distinctive in that it is derived from neural crest rather than mesoderm. Between the 21st day and the 31st day of embryological development, 5 mesenchymal prominences appear at the cranial end of the fetus. These prominences or primordia represent areas of mesenchymal growth that result from the migration of cranial neural crest cells encoded with specific morphogenetic information prior to their migration. At the inferolateral corners of the frontonasal prominence, 2 ectodermal-covered thickenings known as nasal placodes appear. These continue to develop over the ensuing weeks, differentiating into medial and lateral nasal plates. The medial plates eventually fuse to form the globular process, which in turn gives rise to the nasal tip, the columella, and the philtrum. The lateral plates form the nasal alae. The paired maxillary processes eventually form the remainder of the upper lip, the cheek, and the maxilla, and the mandibular processes fuse in the midline and give rise to the lower lip and the mandible (Figure 10). The grooves or furrows between these growth centers eventually become obliterated by mesenchymal proliferation, thereby fusing the centers. Facial clefts develop when 2 or more of these centers fail to fuse, and craniofacial cysts result from entrapment of epithelium along these lines of fusion.

All of the focal lesions in this series of facial hemangiomas mapped to regions in close proximity to lines of fusion between mesenchymal growth centers or between the latter and facial ectoderm. Although rigorous mathematical analysis of this phenomenon is precluded by the inherent lack of precision in determining lesion surface areas and centers of growth from a clinical examination of patients, as well as the exact placement of the lines of embryological fusion, the phenomenon is nevertheless intuitively striking. This is shown in Figure 11 by superimposition of schematic representations of the sites of hemangioma occurrence with the zones of development of the various facial prominences. Sites 1, 10, and 21 are located at the junction between the maxillary prominence and facial ectoderm. Sites 2, 3, 4, 5, 6, 8, and 9 are located along the junction between the frontonasal prominence and the facial ectoderm. Sites 11 and 17 are located along the lines of fusion between the maxillary prominence and the lateral nasal placode and the paired medial placodes, respectively. Sites 13, 14, 15, and 16 are found along the lines of fusion between the frontonasal prominence and the lateral nasal placode (site 13) and the paired medial nasal placodes (sites 14, 15, and 16). Sites 12 and 18 are located at the line of fusion between the maxillary and the mandibular prominences. Sites 19, 20, and 22 are located at the junction between the mandibular prominence and the second arch ectoderm. Site 7 is located in the “gooseneck” of the frontonasal prominence, sandwiched between fusion lines of that prominence with the facial ectoderm.

The relative concentration of focal hemangiomas in the central face further strengthens the association between lines of developmental fusion and sites of hemangioma occurrence. This central area bounded by the eyebrows superiorly, the lips inferiorly, and the lateral corners of the eyes, although representing approximately 20% of the facial area, accounted for 60% of the focal hemangiomas in this study. This area contains the highest density of fusion lines found on the face including those between the frontonasal prominence and periorbital ectoderm (sites 5, 6, 8, and 9), between the maxillary prominence and the frontonasal prominence (sites 11 and 17), between the paired nasal placodes (sites 13, 14, 15, and 16), between the maxillary prominence and periorbital ectoderm (site 10), and between the maxillary and mandibular prominences (site 18).
It is not clear what influences the unique, neural crest-derived mesenchyma of the head, particularly at sites of tissue fusion, may have on hemangioma development. One might reasonably postulate that quantitative or qualitative abnormalities in neural crest-derived tissue might predispose local areas to hemangioma development. Neural crest-derived mesenchyma (“neuromesenchyma”) has unusual properties that might be postulated to make it a particularly receptive field for externally derived vascular precursors. For instance, it has been shown in chick-quail chimeras that this neurally derived mesenchyma, unlike mesodermally derived mesenchyma, has no endogenous angioblasts and must rely on in-migrating angioblasts and vascular sprouts for vascularization.9 Angioblast migration in these chimeras is particularly prominent in the head region, implying the possibility of heightened production of motility or chemotactic factors.10 Perhaps hemangiomas occur preferentially in regions where these neural crest-associated angiogenic mechanisms are elevated, possibly near sites of neuromesenchymal fusion.

Further clues may reside in the unusual properties of hemangioma endothelial cells. Recent studies in our laboratory demonstrated that the endothelial cells comprising infantile hemangiomas, unlike normal dermal and subcutaneous capillaries, highly express glucose transporter isoform 1 (GLUT1).11 Subsequent work has shown that not only GLUT1, but also several other functionally unrelated markers of cellular specialization, namely, Fcγ receptor II, merosin, and Lewis Y antigen, are also expressed by infantile hemangioma capillaries and that all of these markers persist throughout the natural life of the hemangioma.12 These markers are not coexpressed by a variety of other benign vascular processes, such as pyogenic granuloma, granulation tissue, tufted angioma, kaposiform hemangioendothelioma, or vascular malformations,12 or by the recently described congenital nonprogressive hemangioma.13 The only other vasculature known to share this constellation of markers is that of placental chorionic villi. These findings have established infantile hemangioma, the subject of this study, as a unique clinicopathological entity, not to be confused with other “hemangiomas.”

The fascinating and unexpected relationship between infantile hemangiomas and the placenta has led us to consider 2 hypotheses that might explain this connection: (1) angioblasts might be driven to differentiate toward the placental vascular phenotype at sites of hemangioma occurrence as the result of either somatic mutation or abnormal local inductive influences,12 or (2) cells of placental origin might embolize to receptive fetal tissues during gestation or birth.12 The embolic theory in particular may explain the increased incidence of hemangiomas in the offspring of mothers who underwent chorionic villus sampling during pregnancy.14 How might these hypotheses constructed to explain the hemangioma-placenta connection relate to the apparent predilection of hemangiomas for regions of cranial embryonic fusion reported here? Perhaps these regions of growing neuromesenchyma are simply “fertile ground” for growth of either embolized placental cells or aberrant angioblasts by virtue of their inherent need to attract invading vascular precursors, as
described previously. Another possibility concerns the vascular structure of the developing face: the arterial supply to facial placodes is via end arteries that might favor entrapment of embolized cells in their areas of perfusion; arterial anastomoses across the facial clefts can develop only after placode fusion. These areas of placode advancement and eventual fusion may possess other as yet undiscovered characteristics favoring hemangiogenesis. Qualitative or quantitative abnormalities in these characteristics, perhaps involving neural crest migration or differentiation, might further support this process.

The segmental hemangiomas deserve special consideration. Plaquelike hemangiomas have been associated with a clinically recognized set of structural malformations and anomalies that has been designated as the PHACE or PHACES syndrome. This acronym refers to the association of posterior fossa brain malformations, facial hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, eye anomalies such as retinal angiomas and cataracts, and orbital pits or clefting.15 Several of these associated anomalies, such as lingual thyroid and sternal clefting, appear to have their origin between 6 and 8 weeks of gestational age, suggesting a so-called developmental-field defect.15 Furthermore, the parotid glands are frequently involved by overlying plaquelike hemangiomas. These glands also begin their development as tubular invaginations of mandibular ectoderm into the underlying mesenchyma at about 6 weeks of intrauterine life. This suggests that the precursors of parotid hemangiomas may be or may become located in that region during this early time frame, with proliferation held in check until latter in gestation or after birth. These considerations remain highly speculative, but suggest the possibility that the differential patterns of tissue involvement seen in the focal and segmental type hemangiomas may reflect the timing of deposition of hemangioma precursor cells, with earlier events resulting in segmental hemangiomas and later events resulting in focal hemangiomas near lines of mesenchymal fusion.

In summary, we have described 2 distinct patterns of tissue involvement in a large series of facial infantile hemangiomas: a more common focal type with a tumoralike appearance and a less common diffuse type with a segmental distribution pattern and plaquelike appearance. Hemangiomas of the segmental type were more commonly complicated by ulceration or airway obstruction than those of the focal type. Furthermore, we describe 22 sites of occurrence among the focal hemangiomas in our study that mapped close to lines of fusion between mesenchymal growth centers (placodes) or between the latter and facial ectoderm. Furthermore, most of these focal lesions occurred in a relatively small area of the central face that contains the highest density of fusion lines on the face. We have discussed evidence supporting an embryological basis for the observed nonrandom distribution of facial hemangiomas and the possible relevance of the recently discovered antigenic similarities between infantile hemangioma and human placenta. This study represents a serious, groundbreaking attempt with a relatively large series of hemangiomas to make sense of the long-suspected tendency of hemangiomas to occur preferentially at certain locations. However, further studies evaluating the presented pathogenic hypotheses in much larger collections of hemangiomas including not only facial hemangiomas, but those occurring in other body regions, appear warranted.

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