Late growth of infantile hemangiomas in children >3 years of age: A retrospective study

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Background: The proliferative phase of infantile hemangiomas (IHs) is usually complete by 9 months of life. Late growth beyond age 3 years is rarely reported.

Objective: To describe the demographic and clinic characteristics of a cohort of patients with late growth of IH, defined as growth in a patient >3 years of age.

Methods: A multicenter, retrospective cohort study.

Results: In total, 59 patients, 85% of which were female, met the inclusion criteria. The mean first episode of late growth was 4.3 (range 3-8.5) years. Head and neck location (55/59; 93%) and presence of deep hemangioma (52/59; 88%) were common characteristics. Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities (PHACE) syndrome was noted in 20 of 38 (53%) children with segmental facial IH. Systemic therapy (corticosteroid or β-blocker) was given during infancy in 58 of 59 (98%) and 24 of 59 (41%) received systemic therapy (β-blockers) for late IH growth.

Limitations: The retrospective nature and ascertainment by investigator recall are limitations of the study.

Conclusion: Late IH growth can occur in children after 3 years of age. Risk factors include head and neck location, segmental morphology, and involvement of deep dermal/subcutaneous tissues. (J Am Acad Dermatol 2019;80:493-9.)

Key words: β-blocker; corticosteroid; growth hormone; infantile hemangioma; late growth; segmental morphology.

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The proliferative growth phase of infantile hemangiomas (IHs) is typically completed within the first 6-12 months of life.[1] The rate of involution is variable, but recent studies demonstrate that in untreated IH, involution is usually complete by age 4 years.[2,3]

Growth of IH in children >3 years (36 months) of age is distinctly unusual. Two previous case series have reported late IH growth. Brandling-Bennett et al described 23 patients with prolonged IH growth after age 9 months or rebound growth after 1 year of age in infants receiving IH treatment. Only 1 infant had documented IH growth after 36 months (at age 44 months). Risk factors for late growth in this cohort included segmental or indeterminate morphology (100%), deep dermal/subcutaneous involvement (100%), parotid gland involvement (39%), and head and neck locations (100%).[4] Phillips et al highlighted late growth in 20 patients after propranolol therapy, including 6 patients who were >36 months of age.[5] Three other cases of late growth, all in children with posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities (PHACE) syndrome and growth hormone (GH) deficiency, demonstrated late IH growth upon administration of exogenous GH treatment.[6,7] We report on late growth (after 36 months of age) in 59 patients, including their clinical characteristics, associated anomalies, and previous therapies.

CAPSULE SUMMARY

- Growth of infantile hemangiomas after 3 years of life is rarely reported.
- Risk factors for late growth include segmental distribution, deep involvement, and head and neck location.
- Identifying risk factors for late growth will aid therapeutic management and enhance guidance for parents of affected infants.

MATERIALS AND METHODS

We performed a retrospective chart review of patients with late IH growth seen at the University of California, San Francisco. We contacted members of the Hemangioma Investigator Group, the Birthmark Research Section of the Pediatric Dermatology Research Alliance, and sent a single query via the Society for Pediatric Dermatology listserv asking whether physicians had seen cases of unusually prolonged IH growth. We also reviewed data from a previously reported large retrospective cohort study of rebound growth after propranolol administration.[8] The initial clinical evaluation period for late growth was 2006-2017 (median 2011).

Institutional review board approval was obtained from the Committee of Human Research at the University of California, San Francisco, and other institutional review boards on the basis of local requirements. Contributing institutions included Royal Children's Hospital Melbourne, Children's Hospital of Philadelphia, The Hospital for Sick Children Toronto, Lenox Hill Hospital, Catholic Children's Hospital Wilhelmstift, Duke University Medical Center, Children's Hospital New Orleans, Hospital de la Santa Creu i Sant Pau, The Sainte-Justine University Hospital Center, and Columbia University Medical Center.

Inclusion criteria were documented growth of IH in children after 36 months of life and medical records with sufficient information regarding patient demographics, hemangioma features and growth characteristics, and prior treatments. Patients were excluded if adequate follow-up was not obtained.

Medical records were reviewed by using a standardized data abstraction form. For segmental hemangiomas involving the face, segment numbers were assigned according to the patterns identified by Haggstrom et al,[9] by using either clinical photographs or cartoons depicting hemangioma distribution. Information on late growth included age of onset, type of growth (eg, recoloration, increase in volume), recurrent or worsening ulceration, number of episodes of late growth, and any known provoking factors. For those patients with >1 IH, only data for those with late growth were analyzed. We collected specific details of therapy during infancy and late growth, including indications for treatment, dosage, duration, outcomes, and any rebound growth noted when tapering or stopping treatment.

RESULTS

Forty-nine patients were accrued via investigator recall, including further details regarding the 6 patients reported by Phillips et al.[5] The 10 patients previously reported by Shah et al with IH growth after 36 months of age were also included.[8]

Table I summarizes demographic characteristics and clinical features of the cohort. There was a strong female predominance (5.5:1) and a high percentage of white non-Hispanic and Hispanic infants (81%). IHs with late growth tended to be large in size, with 45 of 59 (76%) being >10 cm^2 and 26 of 59 (44%) >100 cm^2.

Abbreviations used:

GH: growth hormone
GHR: growth hormone receptor
HemSCs: hemangioma stem cells
IH: infantile hemangioma
PHACE: posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities

Of the 59 IH cases, 38 (64%) were segmental, 14 (24%) were indeterminate, and 7 (12%) were localized. The S3 segment was the most common facial area affected (Fig 1). The S3 location often involved the parotid gland (13/28; 46%), but IH regrowth was seen in other portions of S3, such as the central lower lip (Fig 2). Multiple segments were involved in 17 of 38 (45%) cases of IH. The 7 infants with localized and 14 with indeterminate IH also had certain sites of predilection, with 12 of 21 (57%) having either nasal tip or periocular/eyelid involvement. Anatomic sites of regrowth predominantly involved the head and neck (55/59; 93%); 4 patients (7%) had IH regrowth at other sites only: 3 on the torso and 1 on the extremities. Of all IH cases, 88% (52/59) had a deep component, with 12 of 59 (20%) being purely deep and 40 of 59 (68%) having both superficial and deep (mixed) involvement. PHACE syndrome was present in 20 of 38 patients with segmental facial IH (53%).

Indications for treatment included risk for disfigurement (39/59, 66%), airway involvement (12/59, 20%), visual disturbance (14/59, 24%), ulceration (16/59, 27%), and feeding difficulties (4/59, 7%). Table II summarizes treatments administered during the initial treatment phase and for late growth. All but 1 patient received systemic therapy during infancy (58/59; 98%). In the initial treatment phase, 8 of 58 (14%) received only corticosteroids, with the remainder receiving β-blockers or β-blockers plus corticosteroids. The median age at first administration of oral propranolol was 3 months with a mean ± standard deviation duration of 22.1 ± 13.0 (range 3-52, median 16) months. In total, 84% (42/50) experienced rebound growth during taper or after completion of therapy. Of these 42 patients, 15 (36%) required a second or third round of systemic therapy. All 24 patients who received systemic treatment for late growth were prescribed a systemic β-blocker; 45% (11/24) of patients were still undergoing treatment at the time of data entry. Other treatments for late growth included topical timolol, oral sirolimus, pulsed dye laser, and reconstructive surgery.

The age of first appearance of late growth ranged from 3 years (the minimum age definition) to 8.5 years, with recurrent episodes observed up to age 11 years (mean ± standard deviation 51.2 ± 1.9 months, median 42 months). Apart from tapering of systemic therapy, no distinct trigger could be identified in most cases. None received exogenous GH. In 2 patients, a marked increase in body mass index was observed. Magnetic resonance imaging was obtained after late regrowth in both cases. In 1 patient, the previously noted IH in the neck, submandibular space, and parotid area was completely replaced by fat at 8.75 years of age. In a second patient 11 years of age, there were similar findings of asymmetric fat in the neck without evidence of increased blood vessels.

DISCUSSION

The findings in this cohort demonstrate that late growth of IH at or after 36 months of age can occur. By using information from the rebound growth study of Shah et al, it is possible to estimate an incidence of late IH growth requiring systemic therapy of ~1% (10/997 patients), confirming that late growth is uncommon, even in infants with IH requiring systemic treatment.[8]

Hemangioma-specific features of late growth

Features associated with late growth included larger than average size, segmental morphology, the presence of PHACE syndrome, deep cutaneous and subcutaneous involvement, and head and neck location. In a large prospective cohort of 1096 cases reported by Haggstrom et al,[9] 14% of cases were segmental IH, whereas 64% were segmental in our cohort. The median size in Haggstrom et al[9] was 3.6 cm^2, whereas in our study, three-quarters were >10 cm^2 and nearly half >100 cm^2.

IH with a deep component, either mixed or purely deep, were observed in 88% in the current cohort compared with 44% in a study by Chiller et al[10] and 59% in a study by Baselga et al.[11] Deep IH involvement has been recognized as a major risk factor for rebound growth in infants treated with propranolol.[8]

Head and neck location was seen in 93% of our cohort versus 56% of a cohort reported by Haggstrom et al.[9] This difference could be explained by referral bias, but overrepresentation of late growth in specific regions of the face (S3) suggests that these areas might be particularly prone to late growth. Involvement of >1 segment (45%) or bilateral involvement (29%) were also frequent. PHACE syndrome was present in 20 of 38 (53%) patients with at-risk facial segmental IH, higher than

Table I. Demographic and clinical characteristics of enrolled patients with infantile hemangiomas with late growth

Feature	Value, N = 59,* n (%)
Demographics	
Sex	
M	9 (15)
F	50 (85)
Race/ethnicity	
White/non-Hispanic	40 (68)
White/Hispanic	8 (13)
Black	2 (3)
Asian	4 (7)
Other	5 (9)
Size (surface area), cm^2	
0-10	14 (24)
>10-50	12 (20)
>50-100	7 (12)
>100	26 (44)
Morphology	
Segmental	38 (64)
Indeterminate	14 (24)
Localized	7 (22)
Subtype	
Deep	12 (20)
Mixed	40 (68)
Superficial	7 (12)
Associated structural anomalies†	
PHACE syndrome	20 (53)
LUMBAR syndrome	0 (0)
Hemangioma location‡	
Facial (all, including parotid)	53 (76)
Parotid	13 (19)
Scalp or neck	12 (17)
Trunk	4 (6)
Extremities	1 (1)
Distribution of involved facial segments†	
S1	16 (42)
S2	12 (32)
S3	28 (74)
S4	11 (29)
≥2 facial segments	17 (45)
Bilateral	11 (29)
Clinical features of late growth	
Increase in redness and discoloration	42 (71)
Increase in volume	42 (71)
Increase in telangiectasia	4 (7)
Worsening airway disease	1 (2)
New or other hemangioma growth	1 (2)

LUMBAR, Lower body hemangioma, urogenital anomalies, myelopathy, bony deformities, anorectal malformations and arterial anomalies, renal anomalies; *PHACE*, posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities.
*N = 59. Includes just the infantile hemangiomas with late growth in the original locations.
†N = 38. Includes only segmental morphology.
‡N = 70. Includes all regrowth hemangioma sites; 11 patients had >1 location involved.

the ~30% previously reported.[12] Another interesting anatomic correlation is the finding of late IH growth (even fairly small IHs) involving the eyelid, nasal tip, and lip. These anatomic sites (as well as the parotid) have relatively decreased density of type I collagen and subcutaneous fat, suggesting that the cellular milieu (ie, soil) within which the IH grows might in some way play a role in the growth and involution.

Cellular origins and mesenchymal cell phenotype

IH are believed to be derived from fetal mesenchymal cells[13] and retain facultative stem cell properties, even after differentiation to their endothelial cell phenotype[14] and even as IH endothelial cells transition to adipocytes upon involution.[15] The finding of fat as an explanation for increased volume, rather than increased vascular growth, observed in 2 patients, suggests that the adipocytes present after IH involution could be more sensitive to growth signals. Residual hemangioma stem cells (HemSCs) likely persist in the regions of previous IH growth, even after apparent involution. Arguably, growth could be due to the sheer number of residual cells capable of growth or the intrinsic growth characteristics.

Growth hormone and other factors stimulating IH growth

Four cases of late growth after administration of exogenous GH in patients with IH and PHACE syndrome have been reported.[6,7] In vitro analysis of IH tissue indicated the presence of growth hormone receptors (GHRs) in the IH endothelium, suggesting that GHR-positive HemSCs might have persisted subclinically after involution and were stimulated by exogenous GH.[6] Such a response might also occur with surges of endogenous GH, as seen during rapid growth spurts during childhood, but this remains speculative.

Possible effects of therapy on hemangioma growth and involution

All but 1 patient received systemic therapy during infancy, and most were treated with propranolol. One possible explanation for persistent proliferative potential in IH residua relates to the so-called Hayflick limit, the observation that most cells undergo a finite and predictable number of cell divisions before becoming senescent.[16] Although this limit has not been proven to occur in IH, hypothetically systemic therapy could decrease the number of cell divisions, permitting rebound and late growth. Studies looking at telomere length in IH at varying stages might help to explore this possibility.

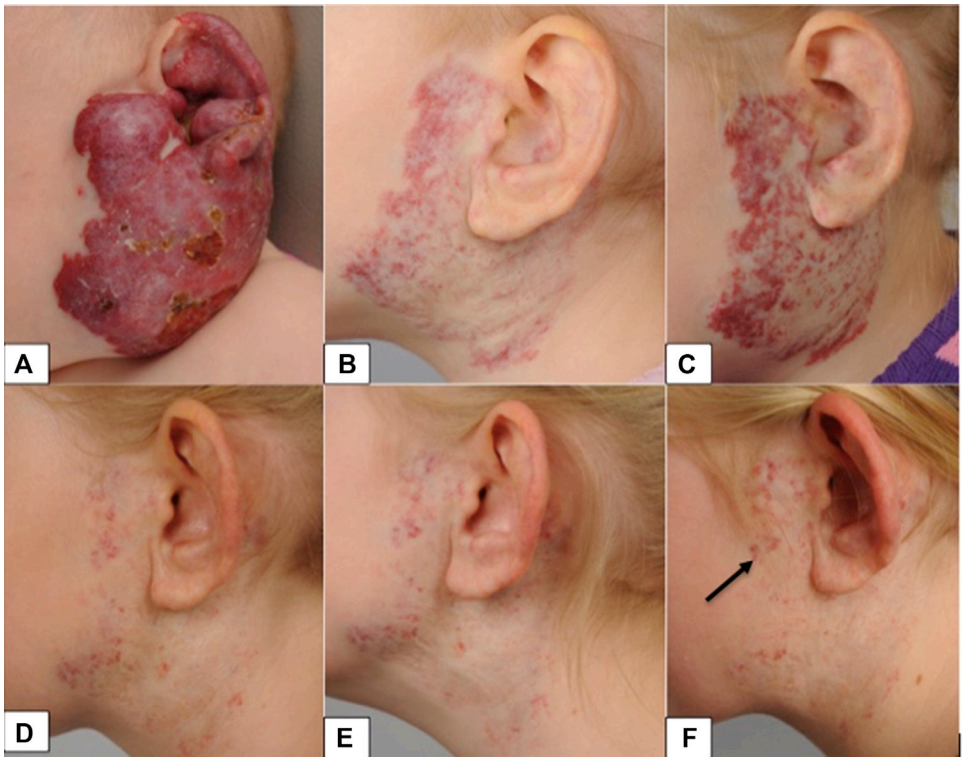

Fig 1. Clinical example 1 of late infantile hemangioma growth. **A**, Patient with S3 segmental hemangioma at 4 months of age before treatment. **B**, Patient at 2 years of age on propranolol. **C**, Patient at 3 years of age 1 year off of propranolol therapy with significant regrowth. **D**, Patient at 5.8 years of age on propranolol. **E**, Patient at 6.3 years, off all therapy with regrowth (increased telangiectasias) in the preauricular area. **F**, Patient at 7.8 years of age off all therapy with further regrowth (soft tissue fullness and increased telangiectasias) and fullness in the preauricular area (*arrow*).

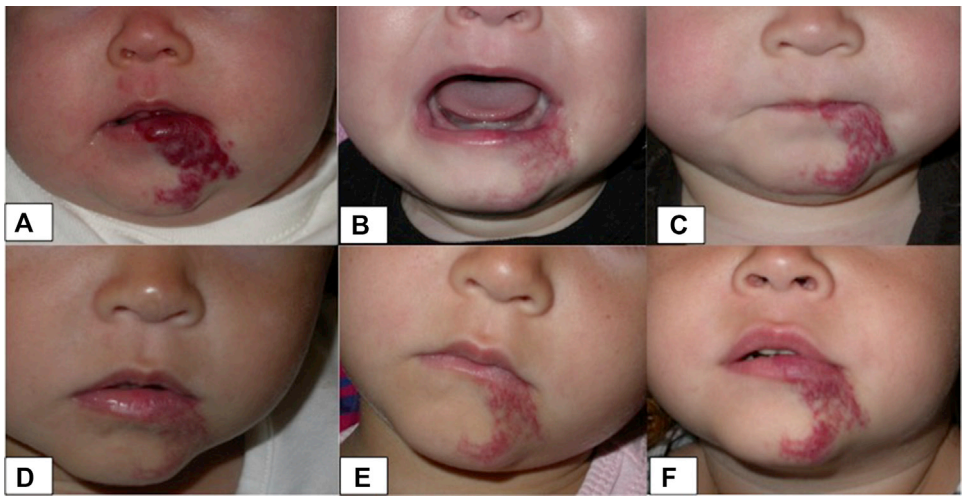

Fig 2. Clinical example 2 of late infantile hemangioma growth. **A**, Patient at 2 months of age before treatment with propranolol 2 mg/kg/d. **B**, Patient at 13 months of age, 2 months after discontinuation of propranolol. **C**, Patient at 17 months of age off all therapy. Propranolol at 2 mg/kg/d reinitiated at this time. **D**, Patient at 24 months of age, after stopping second course of propranolol. **E**, Patient at 3 years of age off all therapy. **F**, Patient at 4 years of age off all therapy, with increased redness.

Table II. Specifics of therapy for infantile hemangiomas in the initial treatment phase and late growth

Timing of growth	Feature	Value
Initial treatment phase	Therapies during initial treatment phase,* n (%)	8 (14)
	Systemic corticosteroids only	31 (53)
	Propranolol only	1 (2)
	Nadolol only	18 (31)
	Both systemic steroids and systemic β-blocker	
	Propranolol therapy specifics†	6.0 ± 7.18
	Age at initiation, mo, mean ± SD	3 (2-6)
	Age at initiation, mo, median (IQR)	22.1 ± 13.2
	Total duration of therapy, mo, mean ± SD	2.5 ± 1.88
	Maximum dose, mg/kg/d, mean ± SD	13.7 ± 8.0
	Duration of therapy on maximum dose, mo, mean ± SD‡	16 (33)
	Multiple episodes of propranolol therapy in initial treatment phase, n (%)	41 (84)
	Rebound growth following discontinuation of propranolol, n (%)	
Late growth	Therapies during late growth,§ n (%)	0 (0)
	Systemic corticosteroids	23 (50)
	Oral propranolol	1 (2)
	Oral nadolol	12 (26)
	Timolol topical	4 (9)
	Pulse dye laser‖	1 (2)
	Debulking surgery‖	1 (2)
	Sirolimus	1 (2)
	Rapamycin topical	
	Propranolol therapy specifics¶	3.6 ± 0.93
	Age at reinitiation, y, mean ± SD	10 (43)
	Therapy ongoing, n (%)	4.9 ± 0.79
	Age at discontinuation, y, mean ± SD#	2.0 ± 0.60
	Maximum dose, mg/kg/d, mean ± SD	6 (25)
	Multiple episodes of propranolol therapy for late growth, n (%)	

IQR, Interquartile range; *SD*, standard deviation.
*N = 58. One patient did not receive therapy during initial treatment phase.
†N = 49. Ten patients did not receive propranolol therapy during initial treatment phase.
‡N = 39. Ten of 49 patients did not have data on duration of maximum dosage.
§N = 46. Thirteen patients did not receive therapy for late growth.
‖Not specified if for late growth or cosmetic purposes.
¶N = 23. Thirty-sex patients did not receive propranolol therapy for late growth.
#N = 13. Eleven of 24 patients receiving ongoing therapy for late growth.

Propranolol has been shown in both in vitro and in vivo experiments to decrease endothelial and stromal cell proliferation and to decrease expression of specific angiogenic factors without substantially altering the stem cell reservoir.[14,17] More research is needed to determine whether other medications, such as sirolimus, or higher doses of propranolol, might be useful in targeting residual HemSC and preventing late regrowth. Such medications, if well tolerated, could potentially help prevent rebound, shorten the duration of therapy, and provide a more definitive cure for IH.

Limitations

Limitations of the study include the retrospective study design and potential recall bias in identifying cases with late growth, except those ascertained via the propranolol rebound study cohort.[8]

Conclusions

Late growth of IH in children >3 years of age and even as late as 8.5 years of age can rarely occur. Clinicians need to be aware of this and associated risk factors to provide guidance regarding the natural history of the disease anticipated by family members of IH patients.

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