Published in final edited form as:
Arch Ophthalmol. 2012 July ; 130(7): 889–893. doi:10.1001/archophthalmol.2012.213.

Incidence and Clinical Characteristics of Periocular Infantile Hemangiomas

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Abstract

Objective—To report the incidence, demographics, and clinical findings among a population-based cohort of children with periocular infantile hemangiomas.

Design—Retrospective population-based cohort.

Participants—All patients (< 19 years of age) diagnosed with periocular infantile hemangiomas while residing in Olmsted County, Minnesota, from January 1, 1965, through December 31, 2004.

Methods—The medical records of all potential patients identified by the Rochester Epidemiology Project were reviewed.

Main Outcome Measures—Incidence, demographics, and clinical findings of periocular infantile hemangiomas.

Results—A total of 43 children were diagnosed with periocular infantile hemangiomas during the 40-year period, yielding an incidence of 5.4 per 100,000 <19 years (95% CI: 3.8–7.1), or a birth prevalence of 1 in 1586 live births. Thirty (70%) were female (p<0.001). There was a history of maternal infertility in approximately 1 in 5 children and premature birth in 1 in 8 children. Twenty-six (60.5%) had other abnormalities, including secondary hemangiomas in 9 (20.9%). The majority of patients (n = 41, 95%) had unilateral disease and most hemangiomas (n = 37, 86%) were located on the upper eyelid.

Conclusions—In this population-based study, periocular infantile hemangiomas occurred in 1 in 1586 live births and were most prevalent on the unilateral upper eyelid of Caucasian females. Prevalent associations included maternal infertility and premature birth. Other abnormalities, including secondary hemangiomas in 1 in 5 children, were common in this cohort.

Infantile hemangiomas are the most common tumor of childhood, consisting of benign vascular proliferations of endothelial cells.[1] These abnormal proliferations affect approximately 1 in 10 children under the age of one[2] and have a predilection for the head and neck region.[3] Risk factors for their development include female gender, Caucasian race,

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No authors have any financial/conflicting interests to disclose

low birth-weight or premature birth, and infants whose mothers underwent chorionic-villus sampling during the prenatal period.[4–8]

Recently, the reported prevalence of infantile hemangioma has been observed to be steadily increasing with the rising rate of low birth-weight babies, presumably due to increased use of assisted reproductive technologies.[8, 9] There is, however, no known population-based study on periocular infantile hemangiomas from the United States. The purpose of this study is to describe the incidence, demographics, and clinical characteristics among a population-based cohort of children diagnosed with periocular infantile hemangioma over a 40-year period.

Subjects and Methods

The medical records of all patients less than 19 years of age who were diagnosed with periocular infantile hemangiomas from January 1, 1965, through December 31, 2004, while residing in Olmstead County, Minnesota, were retrospectively reviewed. Institutional Review Board approval was obtained from Mayo Clinic and Olmsted Medical Group. Periocular infantile hemangioma was defined as any hemangioma that was located within the orbit or eyelids, inferior to the glabella, lateral to the nasal bone, and medial to the zygomatic arch. Potential cases were identified using the resources of the Rochester Epidemiology Project, a medical record linkage system designed to capture data on any patient–physician encounter in Olmsted County, Minnesota.[10] The population of Olmstead County is relatively isolated from other urban areas and virtually all medical care is provided to its residents by Mayo Clinic, Olmsted Medical Group, and their affiliated hospitals.

A list of potential cases from the two institutions, generated by a comprehensive diagnostic code search, identified 649 patients. The codes searched included the terms hemangioma or benign neoplasm associated with the following descriptors: eyelid, lid, canthus, orbit, head, face, scalp, forehead, glabella, temporal region, zygomatic region, malar region, parotid region, cheek, skin, subcutaneous tissue, and unspecified site. Each record was meticulously reviewed by an ophthalmologist (BGM) for confirmation of a periocular infantile hemangioma based on the criteria listed above. Cases were excluded if the hemangioma was not located within the specified region, was found to have a diagnosis other than infantile hemangioma, or was diagnosed outside the time period of this study. Forty-three patients met the inclusion criteria and were included in the study. The 43 medical records were reviewed for demographics including sex, race, date of diagnosis, as well as perinatal, developmental, medical, and familial histories. Clinical characteristics of the periocular hemangioma including size, location, and final outcome were reviewed.

The birth prevalence of periocular infantile hemangiomas was calculated using the number of live births occurring in Olmsted County from January 1, 1965, to December 31, 2004. The incidence of periocular infantile hemangiomas in this county was determined by using annual age-and sex-specific Caucasian population figures obtained from the US Census. The Poisson distribution was used in calculating the 95% confidence intervals.

Results

Forty-three new cases of childhood periocular infantile hemangiomas were diagnosed during the 40-year study period, yielding an annual incidence of 5.4 (95% confidence interval: 3.8–7.1) per 100,000 patients < 19 years, or a birth prevalence of 1 in 1586 live births. The demographic characteristics of the 43 patients are summarized in Table 1. There were 30 (69.8%) females (p=0.0095). Of the 30 patients reporting race, 28 (93%) were Caucasian

and 2 (7%) were Hispanic. A history of premature birth occurred in 5 (12%) patients, maternal infertility in 9 (21%), and amniocentesis in 3 (7%). The mean maternal and paternal ages recorded at childbirth for each patient was 27.6 and 29.0 years, respectively. A positive family history of vascular malformations was observed in 2 (4.6%) patients.

Most patients were diagnosed by their pediatrician (35, 81%) and treated by an ophthalmologist (21, 50%), as illustrated in Table 2. The location of the hemangiomas in the 43 patient cohort is summarized in Table 3. Nineteen (44%) patients had hemangiomas of the right eyelid, 22 (51%) of the left eyelid, and 2 (5%) patients had bilateral hemangiomas. Most (n=37, 86%) hemangiomas were located on the upper eyelid. In the 21 (49%) patients that had clinical measurements, the mean size of the hemangioma at diagnosis was 1.66 cm^2 (range, 0.04 to 7 cm^2). Only 1 (2%) of the 43 patients reported bleeding of the hemangioma, while no patients had ulcerative changes nor other adverse sequelae.

The occurrence of other, non-ocular disorders among the 43 study patients is shown in Table 4. Seventeen (40%) of the 43 patients had unremarkable medical histories, 3 (7%) had a secondary hemangioma in the head-neck-nonfacial region, 3 (7%) had a secondary hemangioma in the facial region, 2 (5%) had a secondary hemangioma in the buttock region, and 1 (2%) had a secondary hemangioma in the abdominal region.

Discussion

In this population-based cohort of children diagnosed with infantile hemangiomas over a 40-year period, periocular involvement occurred in 1 in 1586 live births. One in 5 had a history of maternal infertility and 1 in 8 were born prematurely. Nine (20.9%) had an additional hemangioma outside the periocular region. The majority of patients were Caucasian females with unilateral upper eyelid involvement.

This report, to the best of our knowledge, is the first population-based study on periocular infantile hemangiomas in the United States. Infantile hemangiomas, located anywhere on the body, are reported to occur in 2.6% of newborns under the age of 2 weeks, and in 10% of children under the age of one year.[2, 11–14] Though the majority appear within the first year of life, 30% present at birth,[12] as was similarly observed in this cohort. Finn and coauthors further subclassified hemangiomas by location, reporting that 60% are found in the head and neck region, 25% in the truncal area, and 15% in the extremities.[3, 15] Haggstrom et al found similar distributions in a large prospective cohort study.[16] Though the majority of infantile hemangiomas are found within the head and neck region, the incidence from this study, 5.4 children per 100,000 in patients < 19 years of age, demonstrates the infrequency of an infantile hemangioma being located solely within the periocular region.

The clinical features of this cohort confirm that females are more likely to develop hemangiomas than males by a ratio of 3:1. Both Drolet and co-authors, and Stigmar and co-authors report a similar gender predominance, with the Stigmar study reporting female involvement in 75% of their cohort.[17, 18] It is unclear why infantile hemangiomas are more common among females. Schwartz and co-authors hypothesize that this predominance may be an overestimate, stating that both their study and the Stigmar study found females to be more likely than males to have larger periocular hemangiomas with more severe amblyopia, and therefore requiring ophthalmic referral earlier and more frequently.[18, 19] However, because the current study is population-based, and includes all patients diagnosed with periocular hemangioma in any department at our institution, our findings confirm that females are, unrelated to referral or other bias, more likely than males to develop periocular infantile hemangiomas.

Other risk factors for the development of infantile hemangiomas include race, prematurity and low birth weight, maternal infertility, clomid use, and chorionic-villus sampling.[4–8, 20] Similar to other studies, the majority of patients from this cohort were Caucasian (28 patients of 30 reporting race).[19, 21] In this cohort, maternal infertility (20.9%) and premature birth (11.6%) were commonly associated risk factors, but low birth weight (n=0), use of clomid (n=1), or chorionic-villus sampling (n=0) were not. Except for race, only 15 (35%) of our 43 patients had one of the previously reported risk factors.

The majority of this patient cohort (86%) had lesions of the upper eyelid. Previous studies show similar findings,[21–24] though the reason for this predilection has yet to be determined. Approximately 21% of the 43 patients had secondary hemangiomas in addition to their periocular lesion. Twenty-nine percent of patients in a study by Haik et al had secondary hemangiomas outside the periocular region,[12] while Drolet et al reports a rate of 20% in patients with infantile hemangiomas of any location.[17] Other co-morbidities observed in this population include 2 (4.7%) patients with a family history of vascular malformations. It has been previously reported that 32% of patients with infantile hemangioma have a first-degree relative with a vascular anomaly, with 12% specifically having familial-type infantile hemangiomas.[25] This strong genetic component was not observed in this cohort. Another recently described co-morbidity is retinopathy of prematurity (ROP). Praveen et al found that 16.8% of their cohort had infantile hemangiomas and ROP, compared to 6.7% with hemangioma but no ROP.[26] This was found to be independent of birth weight and postnatal steroid use. No patients in this cohort had retinopathy of prematurity.

Ulceration is the most common complication of hemangiomas[16, 20] and has been reported to occur in 5–16% of cases, more frequently in larger, segmental lesions that outgrow their blood supply.[16, 27, 28] Ulceration is most commonly observed during the proliferative phase of growth, though it can be seen in any phase.[28] The location of the hemangioma is also a predictor of ulceration. Chamlin et al found that hemangiomas of the anogenital region, neck, and lower lip were most likely to ulcerate, and hemangiomas of the upper eyelid were the least likely to ulcerate.[28] This finding, in combination with the smaller sizes of hemangiomas in this cohort, may explain why ulceration was not observed in any patients. In addition, the previous studies reporting ulceration rates of 5–16% were not population-based and thus likely to be an overestimate.

Infantile hemangiomas are associated with PHACES syndrome, a rare condition in which a patient has a segmental-type hemangioma along with structural and developmental anomalies.[29, 30] Twenty percent of infants with segmental hemangiomas are reported to have one or more criteria for PHACES, compared to the overall estimated incidence of 2.3% in patients with any type of hemangioma.[29] Ophthalmic involvement occurs in anywhere from 16–21% of affected patients and most commonly consists of microphthalmia ipsilateral to the hemangioma.[29–33] In contrast to the risk factors for infantile hemangiomas, PHACES is observed more frequently in singleton, term infants with normal birth weight, and at an even higher female to male ratio of 8–9:1.[29, 32] No patients within this cohort were diagnosed with PHACES syndrome.

Besides the standard set of complications that can affect hemangiomas of any location, periocular hemangiomas are particularly of concern because of the risk for ocular complications including amblyopia, strabismus, ptosis, proptosis, and optic nerve compression.[17, 18, 21, 23] Because of the potential to develop these complications, it is recommended that patients with periocular hemangiomas be closely followed by ophthalmology. In this patient cohort, primary care providers diagnosed the majority of the hemangiomas (n=35, 81%), but only half (n=21, 49%) were referred to ophthalmology for management. The ramifications of this low referral rate include unnecessary adverse visual

outcome for patients that could have been prevented by earlier referral and diagnosis. Although some periocular hemangiomas may appear to be at a low-risk for adverse visual sequelae, an ocular evaluation is important to ensure the best outcome for the patient.

There are several limitations to the findings in this study. Its retrospective design is limited by non-standardized and incomplete data collection. Additionally, some infantile hemangiomas may be asymptomatic or subcutaneous, thereby going unnoticed by the patient's caretaker or physician. Although the vast majority of patients in Olmsted County are managed by the two medical systems within the community, some residents may have sought care outside of Olmsted County, thereby further underestimating the true incidence in this population. Our ability to generalize these findings to other populations is limited by the demographics of Olmsted County, a relatively homogeneous semi-urban white population. Finally, the study was limited by incomplete medical records relating to the size, morphologic subtype, depth, and status of the hemangioma at initial and final examination.

In this population, periocular infantile hemangiomas occurred in 1 in 1586 live births, and were most prevalent on the upper eyelid of Caucasian females. One in 5 children had history of maternal infertility, and 1 in 8 were born prematurely. The majority of children had other, non-ocular abnormalities, including a secondary hemangioma in twenty-one percent.

Acknowledgments

This study was made possible in part by the Rochester Epidemiology Project (Grant # R01-AG034676 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases), and by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY.

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Aorta, Eye abnormalities, and Sternal abnormalities or ventral developmental defects) syndrome. J AAPOS. 2005; 9(2):169–173. [PubMed: 15838446]

Table 1

Demographic and Perinatal Characteristics of 43 Children Diagnosed with Periocular Infantile Hemangiomas in Olmsted County, MN, 1965–2004.

Characteristic	No. of Patients (%)
Males (%) / Females (%)	13 (30) / 30 (70)
Premature birth *	5 (12)
Mean birth weight in grams [range], n=38	3356 [2239–4527]
Birth Parity	
Singleton	38 (88.3)
Twin	1 (2.3)
Unknown	4 (9.3)
Pregnancy	
Maternal infertility	9 (21)
Amniocentesis	3 (7)
Hydronephrosis	1 (2)
Maternal Clomid use	1 (2)
Preeclampsia	1 (2)
Pyelonephritis	1 (2)
Chorionic-villus sampling	0 (0)
In-vitro fertilization	0 (0)
Delivery	
Spontaneous vaginal	25 (58)
Forceps-assisted	8 (19)
Cesarean section	2 (5)
Vacuum-assisted	1 (2)
Unknown	7 (16)
APGAR score < 5 at 5 minutes	0 (0)
Mean maternal age at birth in years (range)	27.6 (16–37)
Mean paternal age at birth in years (range)	29.0 (21–38)
Family History of Vascular Malformations	2 (4.6)
Hemangiomas	1 (2.3)
Telangiectatic nevi	1 (2.3)
Timeline of diagnosis in days	
Median age of onset (range)	45 (birth to 27.3 months)
Median age at diagnosis (range)	121 (birth to 9.5 years)

* Born at <37 weeks gestation

Table 2

Diagnosis and Management of 43 Childhood Periocular Infantile Hemangiomas by Medical Specialty.

Medical Specialty	No. of Patients (%)
Initial diagnosis made by:	
Primary care specialty	35 (81)
Ophthalmology	5 (12)
Dermatology	1 (2)
Emergency Medicine	1 (2)
Plastic Surgery	1 (2)
Management by:	
Ophthalmology	21 (50)
Primary care specialty	13 (30)
Dermatology	3 (7)
Lost to follow-up	6 (14)

Table 3

Location of Periocular Infantile Hemangiomas in 43 Children Diagnosed Over a 40-year Study Period.

Location	No. of Patients (%)
Eyelid Laterality	
Right	19 (44)
Left	22 (51)
Bilateral	2 (5)
Upper Eyelid	**37 (86)**
Upper Eyelid (not further defined)	19
Upper eyelid (nasal)	7
Upper eyelid (temporal)	7
Upper eyelid (central)	3
Upper eyelid (central and temporal)	1
Lower Eyelid	**5 (12)**
Lower eyelid (not further defined)	4
Lower eyelid (temporal)	1
Other	**1 (2)**
Eyelid (not further defined)	1

Table 4

Co-morbidities in Patients with Periocular Hemangiomas.

Co-morbidity	No. of Patients (%)
Additional Hemangiomas	
Head/Neck/Nonfacial	3 (7)
Facial	3 (7)
Buttock	2 (5)
Abdomen	1 (2)
Cardiovascular Findings	
Aortitis	1 (2)
Cardiac murmur	1 (2)
Dermatologic Findings	
Pilonidal cyst	2 (6)
Seborrheic dermatitis	2 (6)
Developmental Disorders	
Attention-deficit disorder	1 (2)
Oppositional-defiant disorder	1 (2)
Muscoloskeletal Abnormalities	
Digit malformations	1 (2)
Slipped Capital Femoral Epiphysis	1 (2)
Sacral dimple	1 (2)
Torticollis	1 (2)
Neurologic Findings	
Choroid plexus cyst	1 (2)
Other Findings	
Recurrent otitis media	4 (9)
Asthma	3 (7)
ANCA vasculitis	1 (2)
Phimosis	1 (2)
PHACES syndrome	0 (0)