Prevalence and Clinical Characteristics in Patients with Complicated Infantile Hemangioma: A Single Center Study

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ABSTRACT:

Background: Infantile hemangiomas (IHs) are the most prevalent benign vascular tumors in children. While most IHs are uncomplicated, a minority may develop complications, including ulceration, disfigurement, and visual disturbance which can lead to significant morbidities.

Objectives: To analyze the prevalence of complicated IHs, identify the clinical characteristics, management, and treatment responses in patients with complicated IHs

Methods: Retrospective, descriptive study was conducted at the Pediatric Dermatology Clinic of Queen Sirikit National Institute of Child Health, encompassing pediatric patients under 1 year old diagnosed with IH from January 2019 to December 2023.

Results: Among 300 IH patients, the complicated IHs were found in 54 cases (18.0%). The mean age was 4.2±2.59 months. The complications included ulceration (n=39; 72.2%), disfigurement (n=9; 16.7%), visual disturbance (n=1; 1.9%), hepatic hemangioma (n=5; 9.3%), subglottic hemangioma (n=1; 1.9%), and PELVIS syndrome (n=1; 1.9%). Ulceration was the most common complication, mostly located in the diaper area (n=11; 28.2%; P <0.001) and lips (n=10; 25.6%; P 0.004), with larger IHs (≥ 5 cm) were more prone to ulcerate than smaller IHs (P <0.001). Most of the patients underwent multiple treatment modalities including oral propranolol (n=54; 100%; mean duration 10.8 months), topical timolol (n=5; 9.3%), antibiotics (n=22; 40.7%), and pulsed dye laser used for ulcerated IHs (n=28; 51.9%). All complicated IH patients regressed after treatments.

Conclusion: Ulceration represented the most frequent complication, predominantly observed in the diaper region, lip, and in lesions exceeding 5 cm in size. Understanding the timing of onset, clinical characteristics, and treatments can serve as valuable guidance for early intervention to prevent complications.

Key words: Infantile hemangioma; prevalence; clinical characteristics; complications; treatments

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Introduction

Infantile hemangiomas (IHs) are the most prevalent benign vascular tumors in children, with an estimated incidence ranging from 4 to 10 per 100 live births[1,2]. They are observed more frequently in females and are linked to risk factors such as prematurity, low birth weight (especially lower than 1,000 grams), maternal pre-eclampsia, and a family history of IH[3]. Most IHs are solitary and mostly located in the head and neck region.

Distinguished from vascular malformations by natural history, IHs typically emerge within the second to third weeks of life and exhibit continuous growth within the first year, reaching their maximum size at 6-9 months of age[4]. These lesions may present as superficial, deep, or mixed subtype, indicating their soft-tissue depth. Precursor lesions may either be present at birth or become evident in the early neonatal period, followed by a proliferative phase, a plateau phase, and a spontaneous involution phase, which usually begins after 6 to 12 months[5].

Ulceration is the most frequent complication of IHs, potentially leading to significant morbidities such as bleeding and an increased risk of secondary bacterial infection. Periorbital IHs can potentially cause visual disturbances. Other complications like organ disfigurement (lesions affecting the nose, mouth, and ear), airway obstruction (lesions in the beard area), and heart failure (particularly with lesions in the liver) may also occur[5].

The primary goals of management should focus on preventing or reversing life- or function-threatening complications, avoiding disfigurement, reducing psychosocial stress, and effectively treating any arising complications. Treatment strategies are determined by factors such as lesion size and location, potential complications, patient age, and the growth phase of the IHs[6].

Oral propranolol has emerged as the treatment of choice for problematic IHs due to its efficacy and safety profile. Other therapeutic approaches, including systemic corticosteroids, topical beta-blockers, surgical excision, and laser therapy, may be considered in select cases. Completed involution of IHs occurs at an approximate rate of 10% per year, with 30% involuted by 3 years of age, 50% by 5 years, 70% by 7 years, and over 90% by 9 years. However, more recent insights suggest that the regression phase is completed in 90% of patients by 4 years of age[6].

Objectives

The primary objective of this study is to assess the prevalence of complicated IHs among patients attending the Pediatric Dermatology Clinic at , Queen Sirikit National Institute of Child Health (QSNICH) from 2019 to 2023.

Secondary objectives include identifying the clinical characteristics, examining the management practices, and evaluating treatment responses in patients with complicated IHs.

Materials and methods

Study design

The observational retrospective, descriptive study was conducted at the Pediatric Dermatology Clinic of QSNICH, encompassing pediatric patients under 1 year of age who were diagnosed with IH from January 2019 to December 2023. Patients who lost to follow-up, defined as having less than two consecutive months of follow-up during treatment, were excluded due to the inability to evaluate treatment responses.

Data collection and variable definition

Data collection involved reviewing electronic clinical files and outpatient department cards. Various demographic variables such as sex, age at lesion onset, age at first visit, underlying conditions, perinatal history, and birth weight were recorded.

Furthermore, data of IH characteristics and natural history were gathered, encompassing clinical subtype, location, size by largest diameter (categorized as <5 cm or ≥ 5 cm), morphology, and complications. IHs were categorized by clinical subtype based on tissue penetration as superficial, deep, and mixed. Classification by morphology included localized, segmental, multiple (2-4 IHs), and multifocal (≥ 5 IHs). Complicated IHs included ulceration, disfigurement, visual disturbance, and other associated structural anomalies.

The treatment approaches were classified into pharmacological interventions (e.g., oral propranolol, topical timolol, and other drugs) and laser treatments, specifying the frequency and settings. Assessment of treatment efficacy based on improvements in color and/or diameter of the IH lesions.

Ethics

This research adheres to all applicable national regulations and institutional policies and aligns with the principles outlined in the Helsinki Declaration. The study received approval from the Research Ethics Review Committee of QSNICH with IRB approval number: REC.026/2567.

Table 1 Demographic features and sample baseline characteristics of IH patients.

Total	**N = 300**
Sex, n (%)	
Male	80 (26.7)
Female	220 (73.3)
Mean age of lesion onset (months)	0.8 (SD 1.18)
Mean age at first visit (months)	4.2 (SD 2.84)
Underlying diseases, n (%)	
None	287 (95.7)
Subclinical hypothyroidism	2 (0.7)
G6PD deficiency	4 (1.3)
Others	7 (2.3)
Gestational age, n (%)	
Preterm	54 (18.0)
Term	184 (61.3)
Unknown	62 (20.7)
Birth weight, n (%)	
< 2500 grams	55 (18.3)
≥ 2500 grams	171 (57.0)
Unknown	74 (24.7)
Clinical subtype, n (%)	
Superficial	190 (63.3)
Deep	36 (12.0)
Mixed	74 (24.7)
Location, n (%)	
Head and neck	173 (57.6)
Trunk and extremities	110 (36.7)
Diaper area	17 (5.7)
Morphology, n (%)	
Single (localized / segmental)	255 (85.0)
Multiple (2-4 IHs)	34 (11.3)
Multifocal (≥ 5 IHs)	11 (3.7)

G6PD Glucose-6-Phosphate Dehydrogenase; *IHs* Infantile hemangiomas

Statistical analysis

Statistical analysis was conducted utilizing IBM® SPSS® Statistics version 26.0. Categorical variables were assessed as percentages, while continuous variables were reported as mean and frequency. Differences between groups for continuous variables were analyzed using independent sample t-tests, and the distribution of categorical variables was evaluated using chi-square tests. All p-values are two-sided, with statistical significance set at < 0.05.

Results

In this study, a total of 300 patients diagnosed with IH were predominantly female (73.3%). The mean age at lesion onset was 0.8 months (SD 1.18), while the mean age at the first visit was 4.2 months (SD 2.84). A majority of patients (95.7%) had no underlying diseases. Fifty-four patients (18.0%) were born prematurely, and 55 patients (18.3%) had low birth weight. The subtypes of IHs included superficial (n=190; 63.3%), deep (n=36; 12.0%), and mixed (n=74; 24.7%). The anatomical location of IHs comprised the head and neck regions (n=173; 57.6%), trunk and extremities (n=110; 36.7%), and diaper area (n=17; 5.7%). The morphology of IHs was categorized as single lesion (localized or segmental) (n=255; 85.0%), multiple lesions (n=34; 11.3%), and multifocal lesions (n=11; 3.7%) (Table 1).

Table 2 Complicated IH and other associated structural anomalies.

Complicated IH, n (%)	**N = 54**
Ulceration	39 (72.2)
Disfigurement	9 (16.7)
Visual disturbance	1 (1.9)
Hepatic hemangioma	5 (9.3)
Subglottic hemangioma	1 (1.9)
PELVIS syndrome	1 (1.9)

IH Infantile hemangioma; *PELVIS* Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, Skin tag

* Two patients experiencing more than one complication

Complications were observed in 54 patients (18.0%), with two patients experiencing more than one complication. The mean age for those who developed complications was 4.2 months (SD 2.59). The complications of IH included ulceration (n=39; 72.2%), disfigurement (n=9; 16.7%), visual disturbance (n=1; 1.9%), hepatic hemangioma (n=5; 9.3%), subglottic hemangioma (n=1; 1.9%), and PELVIS syndrome (n=1; 1.9%) (Table 2).

Ulcerated IH was documented in 39 patients. The clinical subtypes of ulcerated IHs included superficial (n=20; 51.3%), deep (n=4; 10.3%), and mixed (n=15; 38.5%). Among patients with ulcerated IH, 25 patients (64.1%) had lesions < 5 cm in size, while 14 patients (35.9%) had lesions ≥ 5 cm. The diaper area was the most frequent site of ulceration (n=11; 28.2%), followed by the lip (n=10; 25.6%). Other locations included periocular area (n=1; 2.6%), cheek (n=2; 5.1%), ear (n=2; 5.1%), neck (n=2; 5.1%), trunk (n=2; 5.1%), upper extremity (n=8; 20.5%), and lower extremity (n=1; 2.6%) (Table 3).

Disfigurement was noted in 9 patients, all of whom had localized morphology with lesions < 5 cm in size, located on the nose (n=5; 55.6%), lip (n=3; 33.3%), and ear (n=1; 11.1%), respectively.

Visual disturbance was reported in only one patient, whose mixed subtype lesion was localized in the periorbital area (upper fornix of

the left eye), measuring 2x2 cm and causing amblyopia.

Five patients were identified with hepatic hemangiomas, all of whom had more than 5 superficial cutaneous subtype lesions, each measuring less than 5 cm, distributed over the head and neck region, trunk, and extremities. One patient experienced ulceration of a lesion on the right cheek. Thyroid function tests for these patients were normal results. Abdominal ultrasound examination revealed multiple hepatic hemangiomas in all five patients.

Table 3 Clinical subtype, location distribution, and size of ulcerated IH compare with non-ulcerated IH.

	All, n (%) N = 300	**Non-ulcerated, n (%) N = 261**	**Ulcerated, n (%) N = 39**	**P**
Clinical subtype				
Superficial	190 (63.3)	170 (65.1)	20 (51.3)	0.094
Deep	36 (12.0)	32 (12.3)	4 (10.3)	0.719
Mixed	74 (24.7)	59 (22.6)	15 (38.5)	**0.032***
Size				
< 5 cm	249 (83.0)	224 (85.8)	25 (64.1)	**<0.001***
≥ 5 cm	51 (17.0)	37 (14.2)	14 (35.9)	**<0.001***
Location				
Head and neck	173 (57.6)	156 (59.7)	17 (43.6)	0.056
Scalp	28 (9.3)	28 (10.7)	0 (0.0)	0.108
Forehead	17 (5.7)	17 (6.5)	0 (0.0)	0.333
Periocular area	21 (7.0)	20 (7.7)	1 (2.6)	0.244
Nose	18 (6.0)	18 (6.9)	0 (0.0)	0.300
Cheek	34 (11.3)	32 (12.3)	2 (5.1)	0.190
Ear	8 (2.7)	6 (2.3)	2 (5.1)	0.306
Lip	35 (11.7)	25 (9.6)	10 (25.6)	**0.004***
Chin	5 (1.7)	5 (1.9)	0 (0.0)	0.787
Neck	7 (2.3)	5 (1.9)	2 (5.1)	0.215
Trunk	51 (17.0)	49 (18.8)	2 (5.1)	**0.034***
Upper extremity	44 (14.7)	36 (13.8)	8 (20.5)	0.269
Lower extremity	15 (5.0)	14 (5.4)	1 (2.6)	0.454
Diaper area	17 (5.7)	6 (2.3)	11 (28.2)	**<0.001***

The subglottic hemangioma was identified in one patient, who presented with cutaneous lesions localized on both cheeks (deep subtype) and the lower lip (superficial subtype with healed ulceration) without signs of stridor or airway obstruction. A computed tomography (CT) scan revealed the presence of multiple hemangiomas occupying all major salivary glands and the subglottic airway.

Only one patient was diagnosed with PELVIS syndrome, presenting a superficial subtype IH located in the coccyx area, measuring 3 cm. A magnetic resonance imaging (MRI) scan of the lumbosacral spine conducted at 7 months of age indicated a posterior spinal defect at the sacral region, along with lipomyelomeningocele and tethered cord at the L5-S1 level, accompanied by syringomyelia extending up to the T8 level in the distal spinal cord.

Among patients with complicated IH, most underwent multiple treatment modalities. The mean age at the initiation of treatment was 4.8 months (SD 2.89). All 54 patients received oral propranolol, with a mean treatment duration of 10.8 months (range 2-24 months; SD 6.14). Additional treatments included topical Timolol for 5 patients (9.3%), antibiotics for 22 patients (40.7%), and pulsed dye laser (PDL) therapy for 28 patients with ulceration (51.9%). The PDL

therapy utilized a wavelength of 595-nm, with a fluence ranging from 4.5-5.5 J/cm² and a pulse width of 0.45 ms. Treatment sessions varied from 1 to 5 and were conducted consecutively over a period of 2 weeks (Table 4).

Table 4 Management and response of treatment in patients with complicated IH and other associated structural anomalies.

Total	**N = 54**
Oral propranolol, n (%)	54 (100.0)
Mean duration (months)	10.8 (2-24; SD 6.14)
Topical Timolol, n (%)	5 (9.3)
Antibiotics, n (%)	22 (40.7)
Systemic	4 (7.4)
Topical	8 (14.8)
Both	10 (18.5)
Pulsed dye laser, n (%)	28 (51.9)

*Most of the patients underwent multiple treatment modalities

Other specific interventions included the correction of amblyopia in one patient with a periorbital IH and visual disturbance through patching the stronger eye, as well as the complete excision of lipomyelomeningocele performed at 9 months of age in the patient with PELVIS syndrome.

During follow-up, all patients exhibited regression of IHs after treatments. Most ulcerated IHs healed after the second session of PDL therapy, and all nine disfigured IHs exhibited a marked decrease in size and color. All five patients with hepatic hemangioma responded positively, with a reduction in the size of multifocal superficial IHs. Notably, one patient achieved total regression of all multifocal superficial IHs, with previously identified hepatic hemangiomas disappearing on follow-up abdominal ultrasound examinations conducted 6 months after initiating treatment (Figure 1).

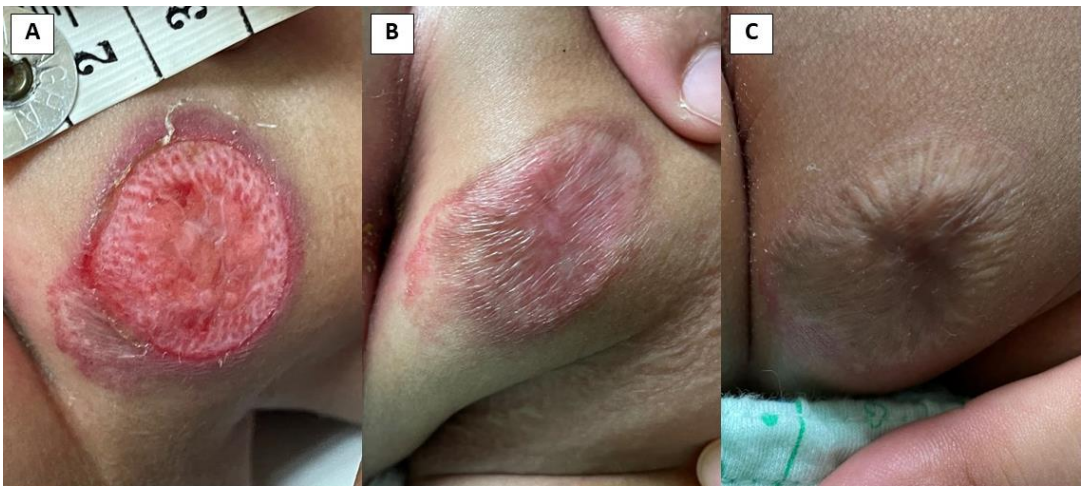

Figure 1 Ulcerated IH located on the buttock of 4.5-month-old patient. A: The lesion prior to PDL therapy, B: The lesion 2 months after the first session of PDL therapy and the initiation of propranolol, C: The lesion 6 months after treatment initiation

Discussion

Our findings regarding the baseline characteristics of IHs are consistent with existing literature, which consistently reports a higher prevalence in females and a predominance of lesions located in the head and neck region. Most of the lesions in this study were superficial and solitary, corroborating previous reports[6,7].

In our study, the prevalence of complicated IHs at QSNICH between 2019-2023 was 18.0%, which is lower than the previously documented rate of 24.1% prior to the introduction of oral propranolol treatment for IHs, as indicated by Haggstrom AN et al[8]. However, it is higher than the recent report of 7.7% by Gomes R et al[7], likely due to our study being conducted at a tertiary referral center that commonly attracts patients with more severe complications.

Notably, the mean age at which complications developed was approximately 4.2 months, aligning with the mean age of the first doctor visit, suggesting that most complications occur during the proliferative phase of IHs. Among the complications observed, ulceration (n=39; 72.2%) was the most prevalent, corroborating findings from Gomes R et al[7] and Haggstrom AN et al[8].

Our analysis revealed that IHs located in the diaper area (P <0.001) and on the lip (P 0.004) exhibited a significantly higher likelihood of developing ulcerations. This observation may be attributed to local factors, including constant friction and maceration[9,10]. In contrast, ulceration was significantly less likely to occur in IHs situated on the trunk (P 0.034). Additionally, larger IHs (≥ 5 cm) were observed to have a higher propensity for ulceration than smaller lesions (P <0.001).

Within the ulcerated group, superficial IHs were the most common subtype (n=20; 51.3%). However, when compared to the non-ulcerated group, mixed IHs showed a significantly higher propensity for ulceration compared to other subtypes (P = 0.032). This finding was corresponded with those reported by Chamlin SL et al[9]. However, our results diverge from Fernández Faith E et al study[11] in which report that superficial IHs have been identified as having an increased risk for ulceration. But our study reinforced the observations documented by Fernández Faith E et al[11] in location and size of ulcerated IHs. There could have been potential reasons for this divergence, such as differences in study design, population, or classification criteria.

IHs located in highly visible regions, particularly the head and neck area, such as the nose, ear, and perioral area, carry a heightened risk of anatomical deformity, cosmetic disfigurement, and potential functional impairment. This acknowledgment may prompt earlier intervention, thereby potentially decreasing the risk of complications[5,12].

One patient in our study exhibited visual disturbances due to an IH lesion localized to the periorbital area. This case underscores the importance of comprehensive management strategies, which should not only include propranolol to mitigate IH proliferation but also address complications such as amblyopia. Timely evaluation and early intervention are crucial to prevent long-term visual impairment[13].

Hepatic hemangioma, which is often observed in patients with multifocal cutaneous IHs, presents a clinical challenge. While many cases may remain asymptomatic and self-limiting, they carry the risk of rapid growth that can lead to tissue compression and severe complications, including high-output cardiac failure due to significant arteriovenous or portovenous shunting. In our study, five of the eleven patients with multifocal IHs (45.5%) were identified as having hepatic hemangiomas via abdominal ultrasonography. Notably, all hepatic hemangioma patients were asymptomatic, with normal thyroid function tests. This highlights the critical need for early

detection of visceral organ involvement in patients with multifocal cutaneous IHs to prevent potentially life-threatening progression and associated complications[14].

The primary management approach for complicated IHs in our study was consistent with recent guidelines, emphasizing the use of oral propranolol[5,6]. However, treatment strategies for ulcerated IHs varied widely, involving multiple modalities. Most of the patients underwent more than one treatment approach, including topical Timolol, systemic and/or topical antibiotics, and PDL therapy, paralleling findings from Fernández Faith E et al[15].

A non-selective beta-blocker, such as Timolol maleate, which is available in a 0.5% ophthalmic solution formulation, has demonstrated both safety and efficacy in the treatment of superficial IHs[16]. The use of topical and/or systemic antibiotics was also found to effectively promote wound healing in ulcerated IHs.

Our study reinforces the efficacy of PDL therapy for managing ulcerative lesions of IHs; indeed, after just two sessions spaced two weeks apart, 82.1% of patients with ulcerated IHs who underwent PDL therapy achieved complete healing within two weeks following the second session, supporting findings from Li Y et al[17].

It is essential to note the limitations of this study. The retrospective design may inherently lack comprehensive data and could introduce biases affecting the results. Conducting the study exclusively at a tertiary referral center may have led to selection bias, as this setting is likely to attract patients with more severe complications. Therefore, the findings may not be generalizable to primary care settings or regions with differing healthcare access. Additionally, the lack of clinical photographs for all patients limits our ability to comprehensively assess the degree of regression and changes in color or size of IHs following treatment. Another limitation is the lack of data on long-term cosmetic and functional outcomes, which are important for assessing treatment efficacy. Future studies should focus on long-term follow-up to evaluate outcomes such as scarring, functional recovery, and psychological impact on patients.

Conclusions

The prevalence of complicated IHs was 18.0%. Complications of IHs, which included ulceration, disfigurement, and visual disturbance, predominantly emerge during the proliferative phase. Diaper area and lip are the most common locations where ulceration occurs, with larger IHs (≥ 5 cm) showing a higher propensity for developing these complications. Understanding the timing of complication onset, clinical characteristics, and treatments of complicated IHs is crucial for improving anticipatory guidance and potentially mitigating preventable complications and disfigurement.

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