Eur J Dermatol 2008; 19 (2): 1-5

Denise Josephina Johanna HERMANS[1]
Jan Bernardus Maria BOEZEMAN[1]
Peter Cornelius Maria VAN DE KERKHOF[1]
Paul Nicolas Maria Antonius RIEU[2]
Carine Joanna Maria VAN DER VLEUTEN[1]

[1] Department of Dermatology Radboud University Medical Centre, René Descartesdreef 1, 6525 GC Nijmegen, The Netherlands
[2] Department of Pediatric Surgery Radboud University Medical Centre, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, The Netherlands

Reprints: D.J.J. Hermans <D.Hermans@derma.umcn.nl>

Article accepted on 5/10/2008

Differences between ulcerated and nonulcerated hemangiomas, a retrospective study of 465 cases

Our purpose was to get better insight into the ulceration of hemangiomas, by comparing patient characteristics of non-ulcerated hemangiomas with hemangiomas with active or past ulceration. A retrospective analysis was performed of files of patients who visited the Radboud University Medical Centre Nijmegen (UMCN), the Netherlands, between 1997 and 2007 for one or more infantile hemangiomas. The medical records of 465 patients were reviewed. Twenty three percent of the patients were diagnosed with ulceration. The size of ulcerated hemangiomas was significantly larger (28.6 cm^2 *vs.* 6.0 cm^2, $p < 0.05$). Predilection areas for ulceration were the head-neck region and the anogenital region. Ulceration was significantly most frequently seen in hemangiomas with a superficial (epidermal) component (98.5%, $p < 0.05$) and a segmental distribution (29.3%, $p < 0.05$). Ulceration most frequently took place during the proliferation phase of the hemangioma (83.1%). In the whole study population the male to female ratio was 1:2 compared to a tendency to more girls (1:3) for the group with ulcerated hemangiomas ($p = 0.08$). We conclude that larger, more superficial hemangiomas in areas more susceptible to trauma and contamination were more likely to ulcerate. This study contributes to the possibility of assessing the likelihood of ulceration in an individual patient.

Key words: hemangiomas, ulceration

Although infantile hemangiomas (IH) occur in 10-12% of children younger than 1 year of age, this benign tumor is not well understood. One of these unknown areas is ulceration [1]. Although ulceration is the most common and distressing complication of IH, possibly affecting between 5% and 13% of the IH, little is known about its pathogenesis [1, 2]. In the literature three factors were found that may play a role: localization with a high risk of trauma, local factors such as bacteria (either infection or colonization) *(figure 1)* and tissue hypoxia caused by a fast growing IH that outreaches its blood supply *(figure 2)* [2, 3]. In the past, few studies were carried out that investigated ulcerating IH. The purpose of the present study was to get a better insight into the clinical characteristics of ulcerated IH and non-ulcerated IH in a retrospective analysis of hemangioma patients, who visited our multidisciplinary hemangioma-study group over the past 10 years. For this extensive patient group, the known differences between ulcerated and non-ulcerated IH from earlier studies were investigated again and supplemented with other characteristics that were also considered important. Better knowledge of the differences between ulcerated and non-ulcerated IH will hopefully deliver better insight into the pathogenesis and treatment of this distressing problem in young children.

Patients and methods

Patients

A retrospective analysis was performed of all IH at the Radboud University Medical Centre Nijmegen (UMCN), the Netherlands, from 1997 to 2007. The medical records and photo documentation of 465 patients with a hemangioma were reviewed. The following information was obtained from each patient file:
Hemangioma: ulceration either or not (1), number of IH per patient (2), size (3), anatomic localization (4), type (5), age at time of discovery (6).
Ulceration: phase of growth at time of ulceration (7), duration (8).
Other: sex (9), prematurity/gestational age (10), birth weight (11), multiple gestation (12), (transcervical) chorionic villus sampling (13), atopic constitution/dermatitis (14).

Analysis

Data from the patient files were transported into a database and analyzed to define the characteristics of the study group and subsequently the differences between the ulcer-

doi: 10.1684/ejd.2008.0576

Figure 1. Ulcerated hemangioma involving the scrotal skin.

Figure 2. Large segmental hemangioma on the arm with multiple localizations of ulceration.

ated and non-ulcerated IH. The numeric data were reported as mean ± SEM. For statistical analysis the t-test for unpaired values was used. The other non-numeric data were analyzed with the Fisher exact test. The two tailed hypothesis was employed to interpret data. A p-value ≤ 0.05 was regarded as statistically significant.

Results

After registration of data mentioned above, the files were divided in two groups: IH with active or past ulceration versus IH which never ulcerated. Comparison between the two groups was carried out. In the description below, the results of all examined characteristics are reported.

Ulcerated *vs.* non-ulcerated IH

A total of 465 records of patients was investigated. Of these 107 (23%) were diagnosed with an ulcerated IH versus 358 (77%) patients with one ore more non-ulcerated IH. The patients with an ulcerated IH had a total of 235 IH, 108 ulcerated and 127 non-ulcerated. The 358 patients with only non-ulcerated IH had a total of 815 IH.

Number of IH

The average number of IH in the group of patients with an ulcerated IH was 2.2 (SEM ± 0.5). For the patient-group with only non-ulcerated IH this mean number was 2.3 (SEM ± 0.3). This difference is not statistically significant ($p = 0.9$).

Size of IH

The surface of the IH was measured with a tape-measure in 2 perpendicular directions, using the maximum diameter in each to calculate the final surface.
The mean length and width of the ulcerated IH were respectively 5.1 cm. (SEM 0.4) and 4.3 cm. (SEM 0.3). For the nonulcerated IH this was 2.1 cm. (SEM 0.1), and 1.8 cm. (SEM 0.1). This shows that the ulcerating IH had a significantly larger surface than the non-ulcerated IH (28.6 cm^2 *vs.* 6.0 cm^2, $p < 0.05$). Data concerning the size were only known from 51.6% of the ulcerated IH and 62.0% of the non-ulcerated IH.

Anatomical localization

The IH were classified in 7 different region categories: (1) extremities, (2) head and neck, (3) perineum, (4) groin, (5) trunk, (6) buttock and (7) sacral region. In general, most IH were located on the head and neck region, the extremities and trunk. The predilection area for ulceration was the head and neck region, but also IH in the perineal and buttock area often turned out to be ulcerating. Ulcerated IH were significantly more often localized in the diaper-region ($p < 0.05$) *(table 1)*.
The localization of the IH was not uniformly documented. 29.5% of the non-ulcerated IH had an unknown localization.

Table 1. Localization

Localization		Ulcerated (%)	Non-ulcerated (%)
Extremities		21.3	20.8
Head and neck		47.2	52.9
Torso		12.0	22.4
Perineum	diaper area	12.0	1.5
Buttock		6.5	1.4
Groin		0.9	0.6
Sacral region		0	0.5

Subtype of IH

IH were divided in 3 clinical subtypes; (1) superficial, (2) deep and (3) mixed IH with involvement of both (epi-)dermis and subcutis. When both ulcerated and non-ulcerated IH were compared, ulceration was more frequently seen in the IH with a superficial component. 78.2% of the ulcerated IH had a superficial component compared to 61.1% of the non-ulcerated IH. This was a significant difference ($p < 0.05$). The deep IH ulcerated significantly less frequently ($p < 0.05$) *(table 2)*. It was known whether they were superficial, deep or mixed for 65.0% of the ulcerated IH and 64.9% of the non-ulcerated IH,.

Added to this, IH can be divided in morphological subtypes; localized and segmental IH can be distinguished. Localized IH are focal tumor like lesions. The less commonly occurring segmental IH tend to be more plaque-like and involve a region or segment of skin. Ulcerated IH had a segmental distribution significantly more often (29.3%) compared to 2.1% of the non-ulcerated IH ($p < 0.05$) *(table 2)*. Data concerning the distribution were available for 85.2% of ulcerated IH and 95.5% of non-ulcerated IH.

Phase of ulceration

The growth characteristics of IH can be divided in phases: proliferation phase (0-9 months), a short plateau phase and involution phase (until the age of 10-12 years). Growth characteristics of IH in an individual infant may vary. In this study the phase in which the ulceration occurred was investigated. Most frequently, ulceration took place in the proliferation phase (83.1%), but also in the involution phase (15.3%) and the plateau phase (1.7%). It was known in which phase the ulceration had taken place for 54.6% of the IH.

Duration of ulceration

In 20.4% of cases the duration of ulceration was well documented and varied between 4 days and 7 months, with a mean of 8.1 weeks (SEM 1.6).

Sex

For the patients examined the sex distribution was 67.3% girls and 33.7% boys, which makes a ratio of 1:2. For the group of patients with an ulcerated IH the number of male and female patients was respectively 27 (25.2%) and 80 (74.8%), a ratio of 1:3. This means a tendency to significantly more females with an ulcerated IH compared to female patients with just non-ulcerated IH ($p = 0.08$) *(figure 3)*.

Table 2. Subtypes

Clinical type	Ulcerated (%)	Non-ulcerated (%)
Superficial total	78.2	61.1
Deep	1.5	25.3
Mixed	20.3	13.6
Morphological type		
Segmental	29.3	2.1
Localized	70.7	97.9

Prematurity/gestational age

The mean gestational age in the group with an ulcerated IH was 35.0 weeks (SEM 0.6). For the group with just non-ulcerated IH the mean gestational age was 36.7 weeks (SEM 0.47). This was significantly different ($p = 0.04$).

Prematurity in this study was defined as birth before 37 weeks of gestation. Analysis of the number of prematures in both patient groups, resulted in 61.1% prematures in the patient group with ulcerated IH compared to 26.5% of the children in the patient group with only non-ulcerated IH. This was a significant difference ($p < 0.05$) *(figure 3)*. It was known whether or not they were premature for 33.6% of the patients with an ulcerated IH and 27.4% of the children with non-ulcerated IH.

Subsequently the degree of the prematurity for both groups was compared. For the premature children with ulcerated IH the mean gestational age was 33.1 weeks (SEM 0.6). For the patients with just non-ulcerated IH this mean age was 32.7 weeks (SEM 0.6). This was not significantly different ($p = 0.7$). For 30.8% of the children with an ulcerated IH, the exact gestational age was known, compared to 20.1% of the children with no ulcerated IH.

Birth weight

The mean birth weight found for the patient group with an ulcerated IH was 2,649 grams (SEM 140.7) and 3,022 grams (SEM 189.3) for the other patient group with only non-ulcerated IH. These indicates a tendency to a significantly lower birth weight for children with ulcerated IH ($p = 0.06$).

Birth weight was documented for 18.7% of the patients with an ulcerated IH and for 20.1% of the patients with just nonulcerated IH.

Multiple gestation

For both patient groups it was registered whether or not they were part of twins. In the total study group 5.6% of the patients were part of twins. For the patient group with an ulcerated IH this was 6.5%, for the patient group with non-ulcerated IH this was 5.3%. This is not a significant difference ($p = 0.4$) *(figure 3)*.

Chorionic villus sampling

In this study no chorionic villus sampling was performed in either patient group.

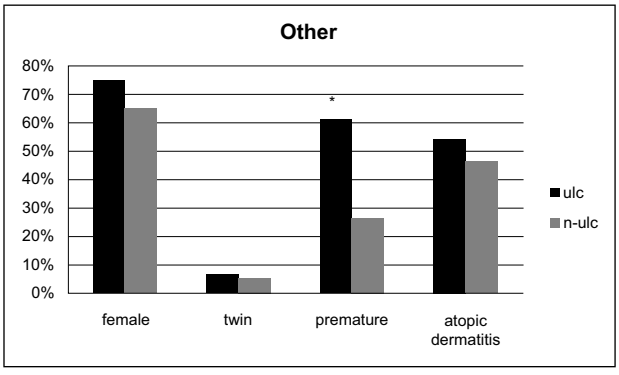

Figure 3. Other.

Atopic dermatitis

In the patient group diagnosed with an ulcerated IH, 54.2% of the children were also diagnosed with atopic dermatitis, in the patient group with only non-ulcerated IH this was 46.5% *(figure 3)*. This is not a significant difference ($p = 0.62$). Overall, not all patient files gave clear information about the presence of atopic dermatitis in the patient. Only for 22.4% of the patients with an ulcerated IH versus 12.0% of the patients with nonulcerated IH was it noted.

Discussion

In this study, ulceration was found in 23% of the IH patients compared to 5-13% described in literature [1, 2]. This can be explained by the fact this study was carried out in an academic centre with a specialized multidisciplinary hemangioma team that serves as a tertiary centre for patients with difficult (ulcerating) IH.

When overviewing the characteristics described, there were no differences concerning the number of IH per patient between the patient group with one or more ulcerated IH versus the group with just non-ulcerated IH. With respect to size-, localization and type of IH, some differences could be recognized, comparable to the recently published results of the American cohort studied by Chamlin *et al.* in 2007 [4].

Ulcerated IH were significantly larger than non-ulcerated IH. In line with this result, segmental IH, which in general cover a substantial skin surface, ulcerated more frequently. Probably, larger IH run a greater risk of becoming mechanically damaged by friction resulting in ulceration. With respect to localization, ulcerated IH were mostly localized in the head- and neck-region, but the diaper area was also a localization with an enlarged risk for ulceration. It seems that traumas like friction and contamination/maceration are more common in these areas. With respect to clinical types, IH with a superficial component were frequently ulcerated as opposed to deeper IH that seldom ulcerated.

Taken together, epidermal involvement and susceptibility to trauma and maceration seem to play a role in pathogenesis of ulceration in IH. These characteristics are connected with the barrier function of the skin. If this is impaired, there seems to be a greater risk of ulceration [2]. In view of this, it was interesting to compare the incidence of atopic dermatitis, in which the barrier function is also impaired, between the patient group with and without ulcerated IH, but no significant difference could be found. Additional prospective studies need to be done to confirm or reject this assumed interesting relationship.

The phase in which ulceration mostly took place was obviously the proliferation phase. This is also known from the literature [2, 4, 5]. The possible reason given in literature is the outgrowth of the blood supply in the fast growing IH, resulting in central necrosis [6, 7]. The mean duration of ulceration turned out to be about 8 weeks. It must be stated that, because our centre is a referral centre for complicated IH, this might be overestimated in this study. Besides this, the exact duration is often unknown because of the difficulty of exact registration. Patients who do better are often lost to follow up and/or return to the general practitioner. Therefore a prospective study should be carried out as well.

In addition, demographic characteristics were studied. From the literature it is known that the female to male rate for IH patients is 2.5-4 to 1 [2]. In our study it was found that the group with ulcerated IH comprised a higher percentage of female patients compared to the patients with non-ulcerated IH. In former studies, hemangioma patients were more likely to be premature. Which could be in relation with the fact that a greater percentage of premature children are female [8-11]. In our study it was observed that the patients with ulcerated IH were more often premature. The mean gestational age of the children with ulcerated IH was also lower. Besides this, the mean birth weight of patients with ulcerated IH also seemed lower although with only a tendency to significance. This last result is also known from the literature [12]. This could mean that prematurity and low birth weight increase the risk of ulceration.

It was striking that in all twin cases, the other twin was unaffected. The number of twins in the studied cohort (5.6%) was higher than the 1.6% twins in the general population, which is in line with a higher incidence of prematurity and lower birth weights in this group. Although ulceration was not more frequent in twins with an IH.

Conclusion

Ulceration is a frequent complication affecting 23% of our studied patients. This high incidence of ulceration makes this Dutch cohort, containing high rates of complicated IH, very appropriate for evaluating the characteristics of ulcerated IH. In summary, larger IH with a superficial component in areas more predisposed for contamination are more at risk for ulceration. We found a high incidence of ulceration in the large group of IH in the head neck region but also a statistical significantly higher percentage of ulcerated IH in the perineum and buttock area. These results will, however, give us more insight into the unknown and multifactorially determinated pathogenesis of ulceration in IH. Besides this, it will probably make it possible to predict whether or not an IH might ulcerate. ■

Acknowledgements. *Financial support: none. Conflict of interest: none.*

References

1. Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. *Curr Probl Pediatr* 1996; 26: 3-39.

2. Frieden IJ, Haggstrom AN, Drolet BA, *et al.* Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 7-9, 2005, Bethesda, Maryland, USA. *Pediatr Dermatol* 2005; 22: 383-406.

3. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. *J Am Acad Dermatol* 2001; 44: 962-72.

4. Chamlin SL, Haggstrom AN, Drolet BA, *et al.* Multicenter prospective study of ulcerated hemangiomas. *J Pediatr* 2007; 151: 684-9 (689.e1).

5. Liang MG, Frieden IJ. Perineal and lip ulcerations as the presenting manifestation of hemangioma of infancy. *Pediatrics* 1997; 99: 256-9.
6. Thomas RF, Hornung RL, Manning SC, *et al.* Hemangiomas of infancy: treatment of ulceration in the head and neck. *Arch Facial Plast Surg* 2005; 7: 312-5.
7. Waner M, Suen JY. Hemangiomas and vascular malformations of the Head and Neck. In: *The natural history of hemangiomas*. New York: Wiley-liss, 1999: 13-45.
8. Amir J, Metzker A, Krikler R, *et al.* Strawberry hemangioma in preterm infants. *Pediatr Dermatol* 1986; 3: 331-2.
9. Haggstrom AN, Drolet BA, Baselga E, *et al.* Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. *J Pediatr* 2007; 150: 291-4.
10. Miller T, Frieden IJ. Hemangiomas: new insights and classification. *Pediatr Ann* 2005; 34: 179-87.
11. Powell TG, West CR, Pharoah PO, *et al.* Epidemiology of strawberry haemangioma in low birthweight infants. *Br J Dermatol* 1987; 116: 635-41.
12. Morrison J. Twin gestation and premature birth. *J Perinatol* 2005; 25: 1-3.