Brief Report

DOI: 10.5582/ddt.2021.01066

Analysis of onset and clinical characteristics in Japanese patients with infantile hemangioma

Aya Hashimoto[1], Kayo Kunimoto[1,*], Ami Kawaguchi[1], Yutaka Inaba[1], Chikako Kaminaka[1], Yuki Yamamoto[1], Nobuyuki Kakimoto[2], Tomohiro Suenaga[2], Takashi Takeuchi[2], Hiroyuki Suzuki[2], Masatoshi Jinnin[1]

[1] Department of Dermatology, Wakayama Medical University, Wakayama, Japan;
[2] Department of Pediatrics, Wakayama Medical University, Wakayama, Japan.

SUMMARY Infantile hemangioma (IH) is a common benign tumor during infancy, although the detailed mechanism behind it has not been fully elucidated. Based on previous studies, we hypothesized that formation of hemangioma might be triggered by secondary physiological events (perinatal hypoxia or mechanical stress during delivery) in patients carrying germline risk mutations. We aimed to clarify the mechanism by evaluating whether head and neck lesions were more frequent in patients in who IH appeared after birth compared with those in who it was present at birth. Clinical data of 62 lesions in 51 patients with IH were collected. All patients were analyzed for correlation of onset with gender, localization, family histories, gestational age, birth weight, and clinical subtypes. Distribution of lesions on the head and neck was slightly more frequent in the after-birth IH group, compared with those with IH present at birth, but without significant difference (47.6% *vs.* 40.0%, $p = 0.32$). On the other hand, the ratio of superficial and deep type IH at birth was significantly altered compared with that in IH after birth (19:0 *vs.* 26:7, $p = 0.039$). In addition, IHs appearing after birth tended to more commonly have multiple lesions than those with IH present at birth, with statistically significant difference (25.8% *vs.* 0%, $p = 0.0164$). There may therefore be different triggers for IHs at birth and IH after birth. Further studies with greater number of patients are necessary to validate these findings.

Keywords Distribution, infantile hemangioma, onset

1. Introduction

Infantile hemangioma (IH) is one of the most common benign tumors during infancy. It occurs in an estimated 3-10% infants, with a recent increase in prevalence (*1*). IH typically appears at approximately 2 weeks of age and rapidly proliferates within 6-10 months followed by spontaneous involution over 7-10 years (*1*). Most IHs become apparent after birth, but a portion of the patients have precursor lesions at birth (*2*). Risk factors of IH include low birth weight, multiple gestation, preterm birth, progesterone therapy, and family history (*1*).

Detailed mechanisms have not been fully elucidated, but there are several hypotheses seeking to explain its specific clinical manifestation. One hypothesis is emboli of placental cells. Gene expression patterns of cellular markers differ from those of endothelial cells in the surrounding skin, but resemble those of endothelial cells lining fetal microvessels in the human placenta (*2*). A second hypothesis is related to hypoxia. The intrauterine hypoxia associated with glucose transporter (GLUT)-1 and indoleamine 2,3-dioxygenase may have a role in pathogenesis (*1*). A third hypothesis is related to endothelial progenitor cells or stem cells. Endothelial progenitor cell generated IH-like lesions in immunologically-deficient mice (*3*).

Meanwhile, we previously identified germline mutations in genes encoding tumor endothelial marker 8 (TEM8) and vascular endothelial growth factor receptor (VEGFR)-2, resulting in VEGFR-1 down-regulation and endothelial proliferation, survival, adhesion and migration by activating VEGF signaling through VEGFR2 (*4*). Considering the emergence after birth and age-dependent involution of IH, we hypothesize that formation of hemangioma is triggered in patients carrying the germline risk mutations by secondary physiological events, for example perinatal hypoxia or mechanical stress during delivery (*2*). Consistently, when the distribution of 104 lesions in 100 patients with IH was analyzed, lesions in the jaw or chin area were significantly less frequent than in other areas (*5*). Mechanical stress to the jaw or chin areas may be less

than in other areas in normal cephalic delivery.

If mechanical stress during delivery is really one of the causes of IH, in this retrospective study, we tried to prove the hypothesis that head and neck lesions would be more frequent in the IH group with patients in who IH appeared after birth compared with those with IH present at birth.

2. Materials and Method

2.1. Clinical assessment and patient material

We conducted a retrospective study of 51 Japanese patients with IH who visited Wakayama Medical University Hospital between August 2019 and March 2020. All patients were diagnosed based on clinical manifestation and/or image findings.

The following variables, obtained from medical records and clinical pictures, were collected for the analysis: date of onset, gender, number of lesions, localization (head and neck, limbs, or trunk), family histories, gestational age, birth weight, and clinical subtype.

Clinical subtypes were defined according to the depth of soft tissue involvement. Superficial-type IHs involve the superficial dermis and manifest with a raised, lobulated and bright red appearance (*2*). Deep-type IHs arise from the reticular dermis and/or the subcutis layer, and appear as a bluish-hued subcutaneous nodule or tumor. Mixed-type IHs have features of both subtypes.

2.2. Statistical analysis

Statistical analysis was carried out with the Fisher's exact test for comparison of frequency. $P < 0.05$ was considered statistically significant.

3. Result and Discussion

3.1. Clinical characteristics of patients with IH in our study

We collected the clinical data of 62 lesions in 51 patients with IH (32 girls, 19 boys). Distribution of the 62 lesions was 28 lesions on the head or neck (45%), 19 on limbs (31%), and 15 on trunk (24%). No patients had segmental IH. The clinical subtypes of the 62 lesions were 45 superficial (73%), 7 deep (11%), and 10 mixed (16%). Eight cases (13%) had multiple lesions. In 51 patients with IH, only one patient had notable family history. Information on gestational age was available for 26 cases, four of whom were born earlier than 37 weeks. Birth weight was available for 25 patients, four of whom were born at low birth weight (< 2,500 g).

Reportedly, girls are more likely than boys to have IH (*2*). For example, in the recent investigation by Anderson *et al.* there were 644 females and 355 males, and approximately 44% of lesions were located in the head and neck (*6*). The majority of IHs occur as solitary lesions, but approximately 20% of patients have multiple lesions (*7*). Superficial IH are thought to be the main clinical subtype (*8*). Furthermore, formation of hemangioma is believed to be primarily sporadic, whereas, although rare, there are some cases of familial IH (*2*). Accordingly, the characteristics of the 51 patients in our study, such as gender, localization, number of lesions, clinical subtype, and family histories, are consistent with previous reports.

On the other hand, Katelyn *et al.* reported average gestational age at birth (38.7 weeks) and birth weight (3.28 kg) of infants diagnosed with IH between 1976 and 2010 (*6*). In the present study, the mean birth weight of six infants with IH present at birth was 2.82 kg and that of the 19 infants with IH appearing after birth was 2.92 kg (Table 1). These birth weights were lower than the previous result, perhaps due to racial differences.

3.2. Correlation of onset with clinical characteristics in infants with IH

Next, we classified 51 patients with IH into two groups according to the timing of onset; those with IH present at birth (n = 20) and those whose IH appeared after birth (n = 31: average 18 days after birth). All patients were analyzed for correlation of onset with gender, localization, family history, gestational age, birth weight, and clinical subtypes (Table 1).

Table 1. Clinical characteristics in infants with infantile hemangioma

Items	Number of cases	
	At birth (n = 20)	After birth (n = 31)
Gender		
Female	14	18
Male	6	13
Localization		
Head and neck	8	20
Limbs	8	11
Trunk	4	11
(Multiple)	(0)	(8)
Clinical type		
Superficial	19	26
Deep	0	7
Mixed	1	9
Family histories		
+	1	0
–	19	30
Unknown	0	1
Gestational age		
1 < 37 week	1	3
≥ 37 week	6	16
Unknown	13	12
Birth weight		
Mean weight (kg)	2.82	2.92
Low birth weight	1	3

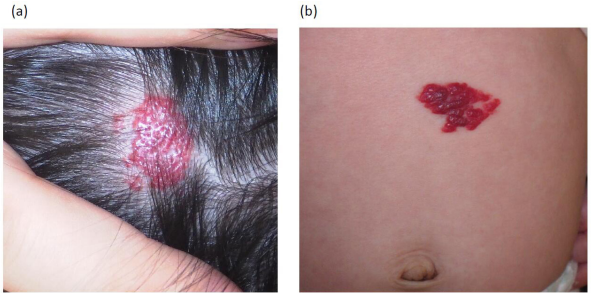

Figure 1. Representative clinical manifestation of multiple infantile hemangioma appeared 11 days after birth: head (a) and upper abdomen (b).

Table 2. Correlation of onset with number of lesions

Items	at birth	after birth	all
single	20	23	43
multiple	0	8	8
all	20	31	51

Table 3. Correlation of onset with clinical subtypes

Items	at birth	after birth	all
superficial	19	26	45
deep	0	7	7
all	19	33	52

There was no statistically significant correlation between timing of onset and the gender ratio (girl:boy = 14:6 *vs.* 18:13, $p = 0.55$). The most frequent location of the 20 cases of IH present at birth was the head and neck ($n = 8$), and limbs ($n = 8$) followed by the trunk ($n = 4$). In contrast, among infants with IH that appeared after birth, 8 cases had multiple lesions. Of the 23 cases of single IH, the most common site was the head and neck ($n = 13$), followed by the limbs ($n = 5$) and the trunk ($n = 5$). Of the 19 lesions on the 8 infants with multiple IH, 7 were on the head and neck, 6 were on the trunk, and 6 were on the limbs. Clinical images of representative patients with multiple lesions of IHs are shown in Figure 1. The distribution of lesions on the head and neck was slightly more common in the group with IH that appeared after birth, compared with those with IH present at birth, but without significant difference (47.6% *vs.* 40.0%, $p = 0.32$).

As described in the Introduction, we hypothesized that the expansion of endothelial cells within the lesion might be triggered by physiological factors, such as mechanical stress during delivery. As a limitation of this study, medical records on delivery (*e.g.*, vaginal delivery or cesarean section) were not available. Direct evidence could not therefore be shown, but we tried to clarify the mechanism by evaluating whether head and neck lesions were more frequent in the group in which IH appeared after birth compared with the patients in which it was present at birth. As a result, there was such a tendency, but the difference was not statistically significant.

On the other hand, we unexpectedly found IH that appeared after birth tended to have multiple lesions more commonly than those with IH present at birth, with statistically significant difference (25.8% *vs.* 0%, $p = 0.0164$) (Table 2). Given that recognition of multiple lesions will be easier and earlier than solitary lesions, our result may indicate that there may be different triggers between IHs present at birth and those appearing after birth. In other words, IH present at birth are likely caused by a local trigger, while IH appearing after birth may be induced by systemic factors in addition to local triggers, such as cytokines related to systemic neovascularization or sensory nerve growth after birth.

In addition, clinical subtypes of IHs at birth were as follows: 19 superficial and one mixed. On the other hand, clinical subtype of IHs after birth was 26 superficial, 7 deep, and 9 mixed. The ratio of superficial and deep IH present at birth was significantly different to that in IH after birth (19:0 *vs.* 26:7, $p = 0.039$) (Table 3). Thus, deep type IH was significantly more common in infants with IH appearing after birth than those with IH present at birth. The reason may be simply because of the difficulty and time taken to recognize deep type IHs due to the depth of the lesions and normal skin coloration.

Among four patients with IH born at < 37 weeks, one had IH present at birth and three had IH after birth. Among the four patients with IH with low birth weight, one had IH at birth and three developed IH after birth. There was no statistically significant correlation between onset and these parameters.

In conclusion, IHs appearing after birth tended to more commonly have multiple lesions than those with IH present at birth, with statistically significant difference. Our result suggests that there may be different triggers between IHs present at birth and those appearing after birth. Further studies with a greater number of patients are necessary to validate these findings.

Acknowledgements

We acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Center, Wakayama Medical University.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ding Y, Zhang JZ, Yu SR, Xiang F, Kang XJ. Risk factors for infantile hemangioma: a meta-analysis. World

J Pediatr. 2020; 16:377-384.
2. Jinnin M, Ishihara T, Boye E, Olsen BR. Recent progress in studies of infantile hemangioma. J. Dermatol. 2010; 37:283-298.
3. Khan ZA, Boscolo E, Picard A, Psutka S, Melero-Martin JM, Bartch TC, Mulliken JB, Bischoff J. Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. J Clin Invest. 2008; 118:2592-2599.
4. Jinnin M, Medici D, Park L, Limaye N, Liu Y, Boscolo E, Bischoff J, Vikkula M, Boye E, Olsen BR. Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. Nat Med. 2008; 14:1236-1246.
5. Kawaguchi A, Kunimoto K, Inaba Y, Mikita N, Kaminaka C, Kanazawa N, Yamamoto Y, Kakimoto N, Suenaga T, Takeuchi T, Suzuki H, Baba N, Jinnin M. Distribution analysis of infantile hemangioma or capillary malformation on the head and face in Japanese patients. J Dermatol. 2019; 46:849-852.
6. Anderson KR, Schoch JJ, Lohse CM, Hand JL, Davis DM, Tollefson MM. Increasing incidence of infantile hemangiomas (IH) over the past 35 years: Correlation with decreasing gestational age at birth and birth weight. J Am Acad Dermatol. 2016; 74:120-126.
7. Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. Curr Probl Surg. 2000; 37:517-584.
8. Chang LC, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, Lucky AW, Mancini AJ, Metry DW, Nopper AJ, Frieden IJ, Group HI. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics. 2008; 122:360-367.

Received July 9, 2021; Revised August 4, 2021; Accepted August 13, 2021

Address correspondence to:
Kayo Kunimoto, Department of Dermatology, Wakayama Medical University, 811-1 Kimiidera, Wakayama-shi, Wakayama 641-0012, Japan.
E-mail: k-jigen@wakayama-med.ac.jp

Released online in J-STAGE as advance publication August 26, 2021.