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Infantile Hemangiomas with Minimal or Arrested Growth – Do They Occur More Often in Premature Infants Than It Seemed?

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ABSTRACT Infantile hemangiomas with minimal or arrested growth (IH-MAGs) are a subtype of infantile hemangiomas (IHs), characterized by absent or minimal (equal or less than 25% of the total IH surface area) proliferation. They are less conspicuous than classical IHs, but can also be complicated by ulceration or can be misdiagnosed as capillary malformations. The literature on IH-MAGs is scarce, but with increasing interest in the literature. We investigated the clinical and epidemiological characteristics of IH-MAGs in a retrospective series of cases found in a regional tertiary-care pediatric clinic during a 7-year period. Eleven infants with 14 IH-MAGs were included in the analysis. There were 7 girls and 4 boys. Unlike the majority of other authors, we have found 7 premature and 4 full-term infants in our case series. Most of the IH-MAGs were classified as focal (78.57%), were present at birth (72.72%), and were located on the lower body, below the waist line (71.42%). In almost all infants, erythematous background as well as vasoconstricted patches and/or halos were present, while fine or coarse telangiectasias were observed mainly in full-term infants. A subtle proliferative component was observed in only one case on follow-ups. There were no ulcerations. The therapy – topical and oral beta-blocker – was introduced in two cases of IH-MAGs in the face region. Clinical characteristics of IH-MAGs in our case series were similar to those found in other studies on this subject. However, we found a significantly higher percentage of premature infants with IH-MAGs than in any available reference.

KEY WORDS: hemangioma, infant, premature, telangiectasia

INTRODUCTION

Infantile hemangiomas (IHs) are common benign vascular tumors of infancy. Most IHs are not present at birth but usually appear at the age of several weeks to three months (1), on unaltered skin or with some precursor lesions. IH growth has two distinct phases – proliferation and involution. The proliferative phase begins shortly after IH appearance. In most IHs, involution starts between 6 and 12 months of age and can last for years (2). Growth followed by involution is one of the most prominent characteristics of IHs.

Infantile hemangiomas with minimal or arrested growth (IH-MAGs) (also known as abortive hemangiomas) are a less frequent variant of IH. Nevertheless, in the literature one can observe increasing interest for this specific subset of IH. The most important feature of IH-MAGs is the absence of proliferation or minimal proliferation (restricted to up to 25% of total IH surface area) (3-6). Unlike classical IHs, they are usually present at birth and thus sometimes misdiagnosed as capillary malformations. But certain clinical and

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Table 1. Summary of demographic and clinical characteristics of patients with IH-MAGs

Number of Patients	11
Total number of IH-MAG	14
Boy:girl ratio	4:7 (36.37:63.63%)
<37 weeks	7 (63.63%)
Birth-weight (g) average	**Total**: 2258 *Premature infants*: 1785 *Full-term infants*: 3085
Gestation (weeks) average	**Total**: 34.63 *Premature infants*: 32.14 *Full-term infants*: 39
Age of onset	Present at birth 8 (72.73%) During first 2 months: 3 (28.27%)
Type	Focal: 11 (78.57%) Segmental: 3 (21.43%)
Location	Head/neck: 2 (14.29%) Arms and trunk: 2 (14.29%) Lower body: 10 (71.42%)

histological aspects, as well as presence of glucose transporter (GLUT-1) protein on endothelial cells help us establish a clear distinction and classify these skin lesions correctly as forms of IHs (5). In most IH-MAGs cases, clinical characteristics and absent or minimal proliferation are sufficient parameters for a correct diagnosis. Determination of presence of GLUT-1 requires a skin biopsy, and in clinical practice it is thus reserved for specific, unclear cases.

PATIENTS AND METHODS

A search was performed during the period of January 2014 – December 2020 in a single tertiary-care university Pediatrics clinic, at the neonatology department as well as at the outpatient facility for follow-up of neonates/infants. A photo archive database and medical records were evaluated. After careful analysis in which at least 2 neonatologists and/or dermatologists took part, those infants with skin lesions indubitably corresponding to IH-MAGs were included in our case series. IH-MAGs were defined as IH with a proliferative component equal or less than 25% of their surface. For each patient, data about sex, gestation, and birth-weight, age at onset of IH-MAG, description of their clinical characteristics, evolution on follow-up visits, and on therapy were collected from their medical records. According to written description of skin lesions and analysis of photo archives, the following characteristics of individual lesions were noted:

Location – head/neck; arms and trunk; lower body (trunk below the waist and on the legs).

Morphological type – segmental or focal IH-MAG; larger than 5 cm in diameter was considered segmental (7).

Clinical characteristics – erythematous background; fine or coarse telangiectasias; bright red papules; vasoconstricted patches; vasoconstricted halos; ulceration; additional hemangiomas.

Subsequent photographs and written descriptions recorded on follow-up visits were used to evaluate the evolution of individual lesions.

RESULTS

A total of 14 IH-MAGs in 11 patients were identified in our study. The mean birth-weight of participants was 2258 g. There were 4 infants born full-term, while 7 (63.63%) were premature infants. Average birth-weight in premature infants was 1785 g, while it was 3085 g in full-term infants. Gestation of premature infant ranged from 28 to 36 gestational weeks; 3 of them were born with very low gestational age (less than 32 weeks of gestation).

The female to male ratio in the whole case series was 1.75:1 (7 girls and 4 boys). Mean birth-weight was 2162 g for female and 2425 g for male newborns. This

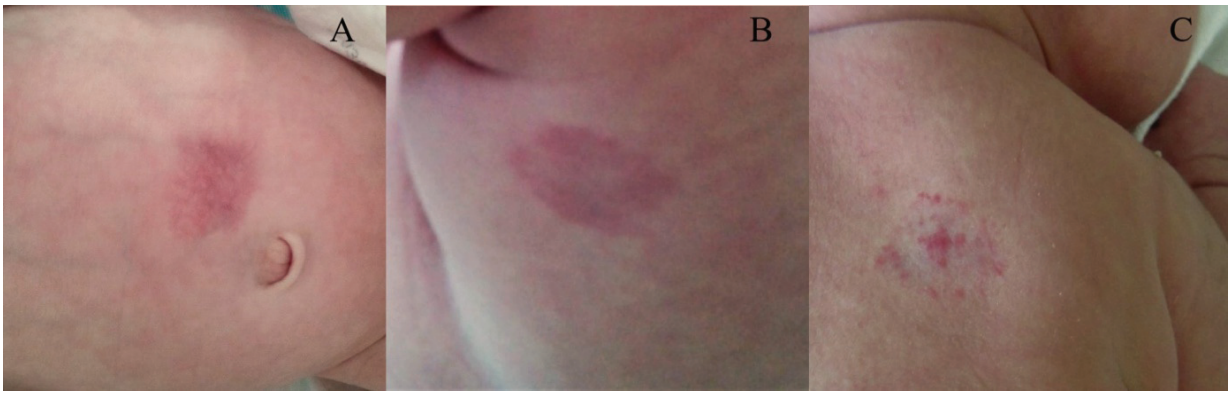

Figure 1. Clinical characteristics of IH-MAGs. (A) Telangiectasias; (B) erythematous background; vasoconstricted patches; (C) bright red papules.

Table 2. Characteristics of IH-MAGs in group of preterm infants

Patient	Number of IH-MAGs	Sex	Birth-weight (g)	Gestation (weeks)	Age of onset	Type	Location	Clinical characteristics	Evolution	Therapy	Follow-up
1	4	Female	1540	28	At birth	Focal	Lower body	Vasoconstricted patches; Erythematous background	Complete regression by the age of 8 months	No	8 months
2	1	Female	1780g	32	Second month	Focal	Lower body	Telangiectasias; Vasoconstricted patches; Erythematous background	Partial regression	No	3 months
3	1	Male	1500	34	At birth	Focal	Head/ neck	Bright red papules; Vasoconstricted halo; Erythematous background	Significant regression by the age of 20 months	Topical timolol	20 months
4	1	Female	2100	36	Second month	Focal	Arms and trunk	Bright red papules; Vasoconstricted halos	Partial regression	No	3 months
5	1	Female	2700	35	At birth	Focal	Lower body	Vasoconstricted patches; Erythematous background	Partial regression	No	6 Months
6	1	Female	1350	30	At birth	Segmental	Lower body	Fine Telangiectasias; Erythematous background	Partial regression	No	12 months
7	1	Male	1530	30	2 weeks after birth	Focal	Head/ neck	Fine Telangiectasias; Vasoconstricted patches and halos; Erythematous background	Partial regression	Propranolol oral	6 months
Σ or average (as appropriate)	**10**	**M:F 5:2**	**1785**	**32.14**	**At birth (4) 7 By second month 3**	**9:1**	**Head/ neck: 2 Arms and trunk: 1 Lower body: 7**	**- Telangiectasias: 3 (30%) - Vasoconstricted patches or halos: 9 (90%) - Bright red papules: 2 (20%) - Erythematous background: 9 (90%)**			**8.29 months**

sex ratio was similar between full-term and premature infants.

Out of 11 patients with IH-MAGs, lesions were noticed at birth (72.72%) in 8 infants. The other IH-MAGs were observed during the first two months after birth. All three infants who did not have IH-MAGs present at birth but developed them later were prematurely born.

Out of 14 IH-MAGs, 11 (78.57%) were classified as focal, while 3 were segmental (21.43%). Segmental IH-MAGs were observed in 2 premature and 1 full-term infant.

A great majority of lesions were on the lower body (71.42%), followed by the arms and trunk (14.29%) and the head and neck regions (14.29%). Similar distribution was observed in premature and full-term infants.

An erythematous background as well as vasoconstricted patches and/or halos were present in almost all infants in our case series. Fine telangiectasias were more often present in full-term infants, while coarse telangiectasias were present only in one full-term infant. Bright-red papules were the least frequently observed clinical characteristic described in IH-MAGs. All IH-MAGs from our case-series were at the level of the surrounding skin (Figure 1).

All of the presented infants had subsequent follow-up visits for 3-20 months. During the follow-up period, all of the IH-MAGs stayed flat and at the level of the surrounding skin, including those with bright-red papules. In only one IH-MAG case there were subtle signs of initial proliferation in the form of a more pronounced red color of the hemangioma.

The most important epidemiological and clinical data of our case series are summarized in Tables 1 to 3.

We did not observe any IH-MAG-associated complications in our patients. We also did not find any

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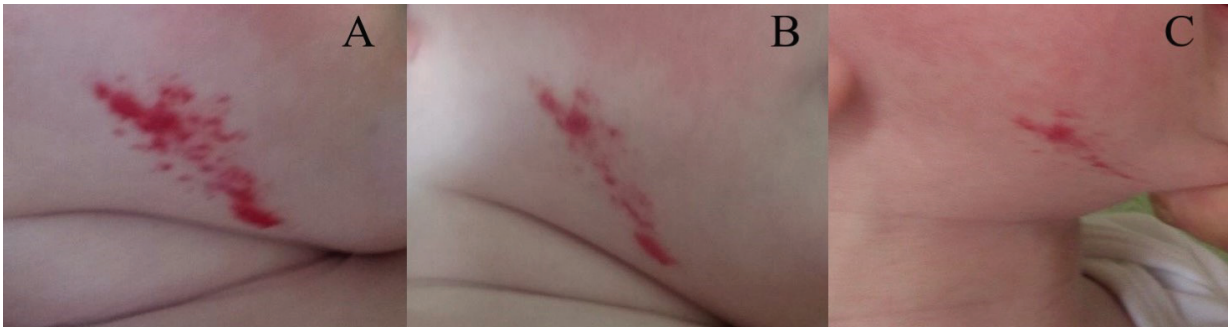

Figure 2. Patient with IH-MAG on the lower part of the face: (A) at the age of 2 months; (B) at the age of 6 months; (C) at the age of 15 months.

soft-tissue hypertrophy or atrophy or presence of other types of IH. However, some congenital abnormalities were evident in 2 patients: one premature infant had a cleft palate and bilateral partial syndactyly of the 2nd and 3rd toes, while one full-term infant had right hand polydactyly.

There was no need for IH-MAG therapy in most of our patients. However, the therapy was introduced in two of them: in an infant with IH-MAG on the lower parts of the face (topical timolol) and in an infant with IH-MAG on the upper eyelid (oral propranolol). On follow-up visits, substantial partial to almost complete resolution was observed in all patients (Figure 2).

DISCUSSION

IH-MAGs are usually present and completely formed at birth or appear soon after. They have certain characteristics that can distinguish them from other types of IH or capillary malformations (CM). Classical IHs are usually absent at birth or present with some precursor lesions. As previously mentioned, they are distinctly characterized by two evolutionary phases: proliferation and involution. CM are present at birth, but grow in size commensurate with the child and have no tendency toward involution.

Anatomical distribution of IH-MAGs differs significantly from distribution of classical IHs. IH-MAGs

Table 3. Characteristics of IH-MAGs in the group of full-term infants

Patient	Number of IH-MAGs	Sex	Birth-weight (g)	Gestation (weeks)	Age of onset	Type	Location	Clinical characteristics	Evolution	Ther-apy	Follow up
1	1	Female	2390	38	At birth	Focal	Arms and trunk	Coarse Telangiectasias; Vasoconstricted halo; Erythematous back-ground	Partial regression	No	5 months
2	1	Female	3280	39	At birth	Focal	Lower body	Bright red papules; Va-soconstricted patches and halos; Erythematous background	Partial regression	No	4 months
3	1	Male	3520	39	At birth	Segmen-tal	Lower body	Fine Telangiectasias; Vasoconstricted patches; Erythematous back-ground	Partial regression	No	4
4	1	Male	3150	40	At birth	Segmen-tal	Lower body	Fine Telangiectasias; Vasoconstricted patches; Erythematous back-ground	Partial regression	No	3 months
Σ or average as ap-propriate	**4**	**M:F** **2:2**	**3085**	**39**	**At birth 4/4**	**2:2**	**Head/ neck: 0** **Arms and trunk: 1** **Lower body: 3**	**- Telangiectasias: 3 (75%)** **- Vasoconstricted patches or halos: 4 (100%)** **- Bright red papules: 1 (25%)** **- Erythematous back-ground: 4 (100%)**			**4 months**

are usually located on the lower half of the body (the trunk below the waist and legs). In their case series, Suh *et al.* found that 32 of 47 IH-MAGs (68%) were placed below the waist, while 32% appeared on upper body parts (3). In a paper which compared 8 more significant case series, it was found that the incidence of lower body IH-MAGs was 60% (66/110) (4). In our study, this percentage was even higher, and we found that IH-MAGs were located below the waist in 71.43% of cases. Interestingly, none of our patients had changes in the anogenital area.

In a large prospective study that involved 1058 patients with a total number of 1915 IHs, Haggstrom *et al.* found that 62% of classical IHs involve the head and neck region (8). This anatomical distribution of classical IHs has, however, come under question recently, given that the majority of studies on this subject were not population-based, but comprised only children with IHs who were referred to a specialist.

A study by Martin *et al.* found a predominance of female sex in patients with IH-MAGs, with a female to male ratio of 3.3:1.0. The same authors analyzed all previously published series of IH-MAG cases and confirmed predominance of female patients (63.8%) (4). We obtained a very similar result in our study. Namely, 7 out of 11 (63.64%) patients were female, and sex distribution was similar in full-term and premature infants. Classical IHs also occurs at a much higher frequency in female infants. Girls are 2-5 times more likely to have IHs than boys, which is similar to the female-to-male ratio for IH-MAGs detected in most studies (9-11).

In our case series of IH-MAGs, we found a very high percentage of premature infants (63%). Furthermore, out of 7 premature infants, 3 were of very low gestational age (<32 weeks, VLGA). This is significantly higher than in other IH-MAGs studies where the frequency of premature infants ranged from 0 to 20% (average 7.4%) (4). Although our case series is rather small, we believe that these data are important given that we did not find data on the occurrence of IH-MAGs in neonates with such a low gestation in the available literature. Consequently, mean birth-weight in our patients was significantly lower than in other reports on this subject. In literature data, this characteristic (mean birth-weight) does not differ significantly between patients with IH-MAGs and classical IHs and is about 3000 g (3).

Such a high percentage of premature infants among those diagnosed with IH-MAGs in our series of patients may be explained by the fact that our research was conducted in a regional tertiary care pediatric clinic. All very preterm infants, as well as a significant number of newborns born over 32 weeks of gestation from the entire province comprising 2 million inhabitants are referred to this clinic. We thus had access to a large number of preterm infants, in whom the presence of any kind of IHs was actively looked for. In contrast, most research published so far on IH-MAG has included patients who were referred to a dermatologist or a plastic surgeon. Given that premature infants, especially those of very low gestation and/or birth-weight, have a number of other medical and developmental problems that require multidisciplinary monitoring and intervention, they are unlikely to consult a specialist due to clinically less significant skin lesions.

It is known that the incidence of classical IHs increases with decreasing gestational age and can be as high as 23% in preterm infants with <1000 g birth-weight (12). There is a 40% increased risk of IH for every 500 g decrease in birth-weight (13). Despite some clinical differences between classical IHs and IH-MAGs, such a difference in appearance of these two types of skin lesions in the population of premature infants does not have a clear explanation. It is reasonable to assume that the percentage of IH-MAGs could be significantly higher in premature infants than has been observed so far and that the frequency probably increases with decreasing gestational age, similar to classical IHs. In general, the frequency of IH-MAGs is probably significantly higher than generally thought, but given their clinical characteristics – they appear at a very early age; they usually disappear spontaneously during the first year of life; are mostly small in size and without any symptoms – they are very often simply not noticed. In order to determine their real frequency, it would be necessary to conduct a screening study in the health-care facilities where both premature and full-term infants are treated and examined. Some differences in clinical characteristics of IH-MAGs between premature and term infants that we have found – delayed occurrence of hemangioma in premature infants, or presence of telangiectasias more often in term infants – could not be confirmed in such a small study group.

Ulceration is the most common complication of IH-MAGs (average 16.3%), as well as classical IHs (10-30%). It is believed that ulceration occurs more commonly during the late proliferative phase of IH. But the fact that ulceration can also occur in IH-MAGs suggests that there are other mechanisms such as hypoxia or local environmental factors (3,4,14). This complication most often occurs in IHs that are segmental in type and located in the anogenital area. One study showed that over 50% of perineal localized IHs develop ulcerations. Additionally, segmental hemangiomas were 11 times more likely to develop

complications, including ulceration (8). These characteristics are similar in IH-MAGs. The vast majority of ulcerated IH-MAGs were in the perineal region and of the segmental type (3 4). In our study, we did not find any IH-MAG located in the perineal region, and this at least partially explains why there were no ulcerations in our series of IH-MAGs. Furthermore, we found no ulcerations in segmental IH-MAGs either. The absence of any proliferative component in all but one of our patients with IH-MAGs of any type is probably the main reason for the lack of this complication (15).

Active therapy of IH-MAGs is usually not necessary, except in cases where complications occur (primarily ulcerations), or if they are located on the face. If active treatment is required, therapy options are usually oral propranolol or topical timolol, the same as for classical IH. Therapy response is usually prompt, and progressive fading of the lesion can be observed; this was the case with treated IH-MAGs from our case series, especially the one treated with oral propranolol (4).

The natural history of IH-MAGs seems similar to that of classical IHs. It has been stated that hemangioma reach eighty percent of their maximum size during the early proliferative stage at a mean age of 3 months (16). Follow-up of IHs of any type is important for prevention or early treatment of the main complication, ulceration. All of the presented patients were followed-up at least during the first three months of life, which is enough time to establish a clinical diagnosis as well as to confirm the presence or absence of the proliferative component. Furthermore, the parents of all patients were educated about the nature and potential complications of IH-MAGs. We acknowledge that one of the limitations of our study was that not all the patients had follow-up visits for a sufficiently long period. However, since these are skin changes that generally do not cause any symptoms and resolve spontaneously over time, a number of parents chose to stop bringing the child to follow-up visits for IH-MAG. Among those that had regular follow-up, considerable fading of their IH-MAGs was noticed in almost all cases.

For classical IHs, it is recommended to monitor them once a month for at least a year (17). We are of the opinion that for most IH-MAGs (especially those without complications) the protocol does not have to be so strict, given their restricted or absent growth and usually spontaneous regression.

CONCLUSION

Although IH-MAGs are usually asymptomatic and uncomplicated, with slow but complete resolution, they should be noted and followed-up, and in some cases treated as well. Their presence should be actively searched for in premature infants, since there is no clear reason for such rare occurrence in this population group.

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