DOI: 10.15386/cjmed-781

INFANTILE HEMANGIOMAS: A 7-YEAR EXPERIENCE OF A SINGLE-CENTER

MĂDĂLINA BOTA[1], GHEORGHE POPA[1], CRISTINA LUCIA BLAG[1], DANIEL-CORNELIU LEUCUȚA[2], ALEXANDRU TĂTARU[3]

[1]Department of Pediatrics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Department of Medical Informatics and Biostatistics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]Department of Dermatology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Objectives. *The aim of the study was to describe the historical and clinical characteristics of hemangiomas in a series of cases of our clinic.*

Methods. *This is a retrospective study of 36 patients with infantile hemangiomas consulted in our clinic.*

Results. *We had 14 multiple hemangiomas, and 1 kaposiform hemangioendothelioma. Almost two-thirds involved the cephalic extremity, and 76% of the cases were treated. Pregnancy risk factors included prematurity, low-birth weight and respiratory distress syndrome. Propranolol was used in 22 cases, followed by prednisone in 3 cases. Vincristine and interferon were used as associated therapies or as second line therapies. Two hemangiomas had complications, one ulceration and a Kasabach-Merritt syndrome. All the patients had a good evolution.*

Conclusions. *Our study results regarding the involvement of pregnancy and birth risk factors in developing infantile hemangiomas is similar to literature data. The majority of patients had at least one risk factor suggesting that at least one trigger to develop an infantile hemangioma is necessary. Our study shows that the cephalic extremity is mostly involved, and because of its potential complications they are most likely to be treated. The study shows that propranolol is the leading treatment option with few and mild side effects.*

Keywords: infantile hemangioma, risk factors, treatment, evolution

Introduction

Infantile hemangiomas are benign vascular tumors of the infancy, occurring in 4-10% of infants [1,2]. It is known that they have 3 phases of evolution: a proliferative phase, an involuting phase and an involuted one. Hypoxia is considered to be the trigger of the angiogenesis that leads to the formation of hemangiomas; by increasing the secretion of VEGF (vascular endothelial growth factor). HIF1- alpha (hypoxia-inducible factor 1 alpha) induces the gene-transcription of VEGF, which is the most powerful angiogenic factor [3]. The tumors develop immediately after birth or at a few months, and are more frequent in the female gender, premature and low-birth-weight infants [1]. Maternal and pregnancy risk factors include older age, preeclampsia and placenta praevia [4,5]. The most affected area is the cephalic extremity [6], an intensely vascularized area during intrauterine life [7].

Most of the hemangiomas do not need therapy, but in about 10% this is necessary, either because of their complications, or life-threatening risks [8]. Areas

Manuscript received: 22.02.2017
Received in revised form: 09.05.2017
Accepted: 23.05.2017
Address for correspondence: Madalina.Bota@umfcluj.ro

associated with disfiguring or potentially serious sequealae are periocular, eyelid, lip area and airway areas [9]. Corticotherapy was the first-line treatment used until 2008, when propranolol efficacy was incidentally discovered by Leaute-Labreze and its use grew worldwide [10], being currently the first-line treatment for infantile hemangiomas [11]. In cases of problematic hemangiomas, other options are available, such as vincristine, interferon or laser therapy [12].

The purpose of this paper was to present our institutions experience with hemangiomas and to analyze the cases regarding risk factors, clinical characteristics, comorbidities and treatment approach of infantile hemangiomas.

Material and methods

After the approval of the institution's research ethics board, we conducted a retrospective study of 36 patients with infantile hemangiomas that have been consulted in the oncohematology department of the Second Pediatric Clinic in Cluj-Napoca, between January 2008 and December 2014.

Patients considered to be eligible for the study had to meet the inclusion criteria. The inclusion criteria were the clinical diagnosis of hemangioma in patients of any age under 18, with or without complications, with or without therapy requirement. We divided the low weight at birth into 3 grades Grade 1 (2500 g- 1500 g), Grade 2 (1500 g- 1000 g), Grade 3 (<1000 g). The maternal age was also divided into 3 groups of age, group 1 (under 25 years), group 2 (between 25-35 years), and group 3 (above 35 years).

We excluded patients that had other types of vascular malformations.

Data were collected from their medical charts or directly from the parents. Categorical data were presented as counts and percentages. Continuous data were presented by means and standard deviations or medians and interquartile ranges or ranges (for skewed data). Association between categorical variables was tested with Chi-square test or Fisher exact test, and quantified with odds ratios along with 95% confidence intervals. For all tests we used a statistical significance level of 0.05. All computations were made with R environment for statistical computing and graphics, version 3.2.1.

Results

Between 2008- 2014 there were 36 patients considered eligible for the study, a number of aspects were collected and analyzed regarding the pregnancy, birth and maternal risk factors, clinical characteristics and treatment options. There was a majority of 77.78 % females (28/36, 95% CI 60.85 - 89.88). The median age at the time of diagnosis was of 6 months (with a minimum of 3 months and a maximum of 30 months, 95% CI 3.75 - 9.25).

Pregnancy and birth data

Three quarters of patients had a physiological pregnancy evolution, the pathological causes of the other being listed in the table I. Data were not available in 2 cases.

Table I. Types of pathological pregnancy evolution.

Characteristic	Number (%) (n=36)
Imminent abortion	3/36 (8.33)
Cervical hemorrhagic polyp	1/36 (2.78)
Pregnancy hypertension	3/36 (8.33)
Urinary tract infection	1/36 (2.78)
Hyperemesis gravidarum	1/36 (2.78)

Of all patients, 11 (32.35%, 95% CI 17.39 - 50.53) were born by C-section, out of which 3 (8.33%) cases were with pregnancy hypertension but only 1 (2.94%) suffered from preeclampsia and 1 (2.94%) with placenta praevia. There were 6 (17.65 %, 95% 6.76 - 34.53) cases of birth suffering, all with respiratory distress syndrome.

The gestational age was with a minimum of 27 weeks and a maximum of 41 weeks. There were 7 (20.59%) cases with prematurity, out of which 3 (42.86%) had multiple hemangiomas. We found no statistical significance between the prematurity and the development of multiple hemangiomas. The Odds Ratio that premature infants develop multiple hemangiomas was of 1.48 (95% CI 0.18 - 11) higher than in those born at term, with p=0.677 (see table II).

Table II. Correlation between hemangiomas and prematurity.

Prematurity	MULTIPLE: no. (%)	SINGLE: no. (%)	Total (%)
yes	3 (42.86)	4 (57.14)	7 (100)
no	9 (33.33)	18 (66.67)	27 (100)

The weight at birth was with a median of 3360 grams (95% CI 2300-3800), with the minimum weight of 950 grams, and a maximum weight of 4350 grams. The low-birth weight was thereafter correlated with the development of multiple hemangiomas (p=0.303), listed in table III. There was one patient with third grade low birth weight, who developed multiple hemangiomas.

Table III. Correlation between birth weight and types of hemangiomas.

BIRTH WEIGHT	SINGLE: no. (%)	MULTIPLE: no. (%)	Total (%)
Low birth weight grade 1	1 (33.33)	2 (66.67)	3 (100)
Low birth weight grade 2	2 (100)	0 (0)	2 (100)
Low birth weight grade 3	0 (0)	1 (100)	1 (100)
Normal birth weight	19 (63.33)	11 (36.67)	30 (100)

The maternal age was also divided into 3 groups : under 25 years [7/34, 20.59%], between 25-35 years [24/34, 70.59%], over 35 years [3/34, 8.82%]. Hemangiomas occurred most frequently in women aged between 25-35 years. In 6 (17.64%) cases, mothers had treatment during pregnancy, 1 (2.94%) with anticoagulants, 3 (8.82%) with hormones and 2 (5.88%) cases with beta2 mimetics for asthma. None of the therapies showed any significant relation with either multiple hemangiomas, or therapy-resistant hemangiomas.

The pregnancy and maternal related risk factors mentioned above, were found in 19 cases (19/34, 55. 88%), with 8/19 (42.11%) cases of single risk factors and 11/19 (57.89%) cases with associated risk factors. We found no statistically significant association between multiple risk factors and multiple or big-sized hemangiomas.

Clinical data

There were 35 (97.22%) cases clinically diagnosed as being infantile hemangiomas, and 1 (2.78%) was diagnosed as a kaposiform hemangioendothelioma. There was a number of 14 multiple hemangiomas (38.89 % (95% CI 23.14 - 56.54). Almost two-thirds (69.44 % (95% CI 51.89 - 83.65) of the hemangioma involved the cephalic extremity.

The majority of cases (17/36, 47.22%) were small hemangiomas, but we didn't observe any relevant relation between the dimensions, the number and the treating decisions. Multiple therapy was used in 3 out of 4 cases (75%) with multiple hemangiomas. The Odds Ratio that multiple hemangiomas need multiple therapy approach is of 5.45 (95% CI 0.39 - 313.97) higher than in single hemangiomas. There were only 2 (5.56%) cases of hemangiomas larger than 3 cm, and both needed multiple therapy (see Table IV and Table V).

Table IV. Correlation between the types of hemangiomas and the need for multiple therapy.

Hemangioma:	multiple	single	P-value
	(n=14)	(n=22)	
Multiple therapy, no (%)	3 (21.43)	1 (4.55)	0.277

Table V. The correlation between the dimensions of the hemangioma and the need for multiple therapy

Dimensions:	Big (>5cm) (n=11)	Medium (3-5 cm) (n=8)	Small (<3cm) (n=17)	P-value
Multiple therapy, no (%)	1 (9.09)	1 (12.5)	2 (11.76)	1

There were 2 (5.56%) cases that had complications, one ulceration with the need of antibiotherapy, and one Kasabach Merritt syndrome (see figure 1 and 2).

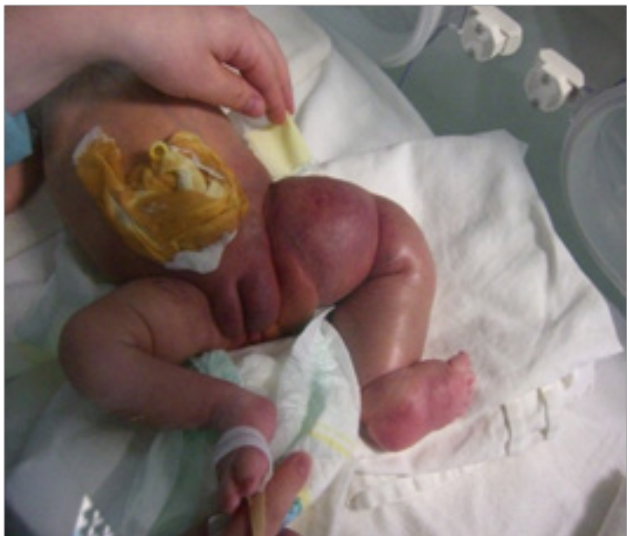

Figure 1. The aspect of the lesions of the Kasabach Merritt case at the diagnosis. The image shows the swelling of the lower left limb, with red-purple color and edema due to compression, a typical aspect of Kasabach-Merritt syndrome.

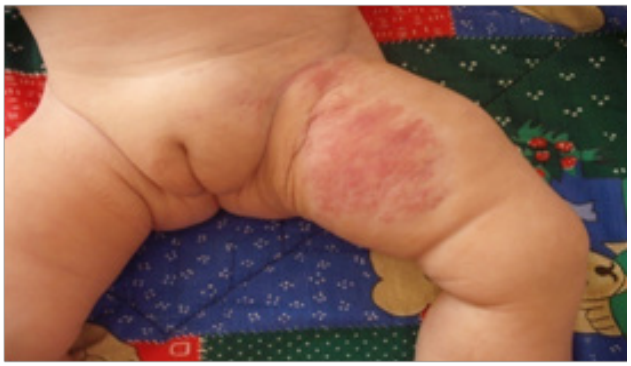

Figure 2. The aspect of lesions of the Kasabach Merritt after treatment. The image above outlines the improvement after 1 year of treatment of the infant with Kasabach Merritt syndrome. The swelling has withdrawn, there is no edema of the limb. A small area of residual lesions can still be seen on the interior side of the leg.

Comorbidites

We identified 19 (52.77%) cases with comorbidities, which included 16 (44.44%) cases of iron-deficiency anemia, 2 (5.55%) cases of congenital anomalies, spina bifida and labial coalescence, and 2 (5.55%) cases of other hematological diseases, such as major beta-thalassemia and hemophilia type A.

The mean value of hemoglobin in the anemia group was 11.25 g/dl (95% CI 10.5 - 11.93), with values ranging from 7.5 g/dl to 12.9 g/dl. We tested the association of anemia in multiple hemangiomas, according to which the odds ratio of having anemia in those with multiple hemangiomas compared to single hemangiomas is of 1.91 (95% CI 0.4-9.48), p-value 0.593.

Treatment data

We treated 25 (69.44%) patients, out of which a number of 4 (11.11%) cases needed multiple therapy approach. There were 19 (76%) patients of those who were treated that involved the cephalic extremity. There were various treatment options, including propranolol, corticotherapy, laser therapy, antiangiogenic agents (vincristine) and interferon. Propranolol was the leading treatment option, used in 22 patients, being associated in 2 cases with corticotherapy and in 4 cases with vincristine. Three cases were treated with prednisone, but only in one case it was used as a single therapy, in the other two being associated with propranolol and vincristine. Vincristine was used in all 4 cases as a second- or third-line therapy, after propranolol or prednisone. We had one case treated with laser therapy and two cases treated with interferon.

Therapy included the following: (1) propranolol in doses ranging from 0.5 mg/kg/day to 1.5 mg/kg/day, orally, (2) corticoids in doses of 1 mg/kg/day, orally, (3) vincristine 0.025 mg/kg/week, intravenously, and (4) interferon 1 million units/administration in 3 administrations/week, subcutaneously.

The median treatment period for propranolol was 23 weeks, with a minimum of 4 weeks and a maximum of 83 weeks. Corticotherapy was used as a single therapy in only one case, where the administration period was of 23 weeks. Vincristine was administered once a week with subsequent reduction to 1 administration/2 weeks, the maximum number of administration was of 23, with a median of 9 administrations. Interferon was used in two cases, one with 7 administrations and one with 13 administrations.

All cases had a good evolution, with the involution of hemangioma, in some cases with minimal residual lesions. There was only one case which developed hepatic toxicity to interferon and treatment was therefore stopped.

Discussion

The aim of this study was to analyze the cases regarding risk factors, clinical characteristics, comorbidities and treatment approach of infantile hemangiomas in our population, and to correlate the results with those seen in the literature.

Our population outlined a higher number of females with hemangiomas, such as seen in other studies as well [1], with a median age of 6 months at diagnosis.

Regarding the risks factors, our study shows their involvement in developing infantile hemangiomas, and even though there were no significant proportions in each risk group, the majority of patients had at least one risk factor and more than half of those had associated risks. This suggests that a trigger to develop an infantile hemangioma might be necessary. Vasculogenesis can be activated by multiple factors, this being an explanation to the variability of risk factors.

None of the risk factors has been shown to potentially influence the development of multiple or therapy-resistant hemangiomas. In our study half of the patients with extremely low-birth-weight have developed multiple hemangiomas, in comparison to the study of Drolet et al, where low birth weight was found to be the most significant risk factor [13]. This can be explained by the low number of patients in our study.

Pregnancy evolution was not a significant single risk factors in our population, but might have increased the risk as an associated factor [14]. In contrast to other studies, we couldn't confirm maternal age as a risk factor, in our study the majority of mothers were aged between 25-35 years [5].

Clinical aspects of the hemangiomas studied confirmed literature data, regarding to which the cephalic extremity is the most likely to be involved, due to increased intrauterine vascularization [7,14]. There was a majority of single and small hemangiomas. Cephalic hemangiomas were treated, as shown, in 76% of cases, the other remaining under supervision without treatment. This suggests that treatment was necessary in these cases, because of the risk of facial disfiguring, amblyopia in eyelid involvement and eating disorders in lip involvement. This confirms the fact that the decision to treat mostly regards the localization of the hemangioma and its potential risks rather than dimensions.

We had one case of Kasabach Merritt syndrome, which was firstly treated with corticotherapy and propranolol, and then switched to vincristine, with good evolution and regression of the hemangioma. In most cases Kasabach Merritt syndrome is associated to kaposiform hemangioendothelioma [15,16]. In our case the infiltrative trend on the imaging performed suggests a kaposiform hemangioendothelioma, no biopsy was performed, therefore we couldn't confirm its morphology. The first treatment options were cortisone, associated thereafter with propranolol. Therapy was later switched to vincristine for 3 months.

There was no significant association between comorbidities or congenital anomalies and infantile hemangiomas. Anemia was found to be the most frequent comorbidity, but this must be correlated to other comorbidities that can influence the level of hemoglobin, such as thalassemia and hemophilia A with subsequent posthemorrhage anemia.

The leading treatment option in our study was propranolol, being far apart followed by only 3 cases of prednisone-treated patients. Other treatment options, such as vincristine, laser therapy and interferon were elected only in situations in which more aggressive therapy was needed or other therapies have failed.

All patients had good evolution under treatment, with few side effects, with a good long-term prognosis, confirming the benign substrate of the tumor.

Conclusions

Our study results regarding the involvement of pregnancy and birth risk factors in developing infantile hemangiomas is similar to literature data. The majority of patients had at least one risk factor suggesting that at least one trigger to develop an infantile hemangioma is necessary. Our study shows that the cephalic extremity is mostly involved, and because of its potential complications they are the most likely to be treated. The study shows that propranolol is the leading treatment option with few and mild side effects.

Limitations of the study

The major limitation of the study is the small number of patients. Other limitations included the variability of the cases and the retrospective design.

References

1. Léauté-Labrèze C. [Infantile hemangioma: update and treatment]. Arch Pediatr. 2013;20(5):517-522.
2. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. Pediatr Dermatol. 2013;30(2):182-191.
3. Chen XD, Ma G, Huang JL, Chen H, Jin YB, Ye XX, et al. Serum-level changes of vascular endothelial growth factor in children with infantile hemangioma after oral propranolol therapy. Pediatr Dermatol. 2013;30(5):549-553.
4. Hemangioma Investigator Group, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, et al. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr. 2007;150(3):291-294.
5. Chen XD, Ma G, Chen H, Ye XX, Jin YB, Lin XX. Maternal and perinatal risk factors for infantile hemangioma: a case-control study. Pediatr Dermatol. 2013;30(4):457-461.
6. Léauté-Labrèze C, Sans-Martin V. [Infantile hemangioma]. Presse Med. 2010;39(4):499-510.
7. Sun ZY, Yi CG, Zhao H, Yin GQ, Gao M, Liu YB, et al. Infantile hemangioma is originated from placental trophoblast, fact or fiction? Med Hypotheses. 2008;71(3):444-448.
8. Ji Y, Li K, Xiao X, Zheng S, Xu T, Chen S. Effects of propranolol on the proliferation and apoptosis of hemangioma-derived endothelial cells. J Pediatr Surg. 2012;47(12):2216-2223.
9. Lee KC, Bercovitch L. Update on infantile hemangiomas. Semin Perinatol. 2013;37(1):49-58.
10. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649-2651.
11. Baselga Torres E, Bernabéu Wittel J, van Esso Arbolave DL, Febrer Bosch MI, Carrasco Sanz Á, de Lucas Laguna R, et al. [Spanish consensus on infantile haemangioma]. An Pediatr (Barc). 2016;85(5):256-265.
12. Xiao Q, Li Q, Zhang B, Yu W. Propranolol therapy of infantile hemangiomas: efficacy, adverse effects, and recurrence. Pediatr Surg Int. 2013;29(6):575-581.
13. Drolet BA, Swanson EA, Frieden IJ; Hemangioma Investigator Group. Infantile hemangiomas: an emerging health issue linked to an increased rate of low birth weight infants. J Pediatr. 2008;153(5):712-715, 5.e1.
14. Munden A, Butschek R, Tom WL, Marshall JS, Poeltler DM, Krohne SE, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. Br J Dermatol. 2014;170(4):907-913.
15. Ryan C, Price V, John P, Mahant S, Baruchel S, Brandão L, et al. Kasabach-Merritt phenomenon: a single centre experience. Eur J Haematol. 2010;84(2):97-104.
16. Kim JA, Choi YB, Yi ES, Lee JW, Sung KW, Koo HH, et al. Excellent outcome of medical treatment for Kasabach-Merritt syndrome: a single-center experience. Blood Res. 2016;51(4):256-260.