Ref: Ro J Med Pract. 2022;17(3)
DOI: 10.37897/RJMP.2022.3.1

The prevalence and risk factors for visceral hemangiomas in children with infantile cutaneous hemangiomas

Mirela-Elena RITIVOIU[1,2], Ioana Florentina CODREANU[1,2], Valentina-Daniela COMANICI[1,2], Anca BALANESCU[1], Paul BALANESCU[1], Dumitru MATEI[1,2], Alina Angelica CIOLPAN[1,2], Alina-Maria ROBU[2], Iustina Violeta STAN[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]"Alessandrescu-Rusescu" National Institute for Mother and Child Health, Bucharest, Romania

Abstract

One of the most frequent benign tumor pathology in children is represented by infantile hemangiomas (IHs). Although they are mostly cutaneous, sometimes they can develop at visceral level, the liver being the most common localization.

Objectives. *Estimating visceral hemangiomas (VHs) prevalence, and identification of risk factors for VHs in patients with infantile cutaneous hemangiomas (ICHs).*

Materials and methods. *6 years cross-sectional study (2012-2017) including children diagnosed with ICHs, admitted in I.N.S.M.C "Alfred-Rusescu". All patients underwent an ultrasound screening for the detection of VHs. In order to identify possible risk factors, we collected demographic and perinatal data.*

Outcomes. *138 patients diagnosed with infantile cutaneous hemangiomas (ICHs) were included, with a slight predominance of girls (58%). The prevalence of the VHs in our study was 7,24% (10 patients). The liver was the most common visceral localization (7 patients).*

Conclusions. *Female gender, preterm birth, low birth weight, and multiple gestations were described as potential risk factors for IHs. In our study, only multiple gestations tend to be associated with visceral hemangiomas, but without a significant statistical correlation.*

Keywords: infantile cutaneous hemangiomas, visceral hemangiomas, prevalence, risk factor

Abbreviations:
IHs – infantile hemangiomas
ICHs – infantile cutaneous hemangioma
VHs – infantile visceral hemangioma
I.N.S.M.C. – "Alessandrescu-Rusescu" – National Institute for Mother and Child Health "Alessandrescu-Rusescu", Department of Pediatrics

INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign tumor pathology described in children. The true incidence of childhood hemangiomas is difficult to establish, and it varies between 4.5% [1] up to 9.9% [2]. Although they are mostly cutaneous, lesions can arise at any visceral level. Among visceral localization, liver is the most common site, followed by parotids, central

Corresponding authors:
Ioana Florentina Codreanu
E-mail: dr.ioanacodreanu@gmail.com

Article History:
Received: 20 September 2022
Accepted: 27 September 2022

nervous system, and the gastrointestinal tract [3]. The association of visceral hemangiomas (VHs) with infantile cutaneous hemangiomas (ICHs) may raise problems in terms of diagnosis, therapeutic approach, and evolution [4].

MATERIAL AND METHODS

In order to achieve the desired objectives, we conducted a cross-sectional study, for a period of 6 years (2012-2017), including children with ICHs admitted to I.N.S.M.C "Alessandrescu-Rusescu". In this cohort are included patients that were already described in our previous studies [5,6] and we decided to conduct a secondary analysis of the patients' group in order to determine the prevalence of VHs and secondary to identify possible risk factors for the occurrence of VHs in children with ICHs. In order to achieve the latter objective, demographic and perinatal characteristics of the patients included in the study group were analyzed (sex, gestational age, birth weight, single/multiple pregnancy, mode of delivery, pathology associated with pregnancy). The following data were also analyzed: type of hemangiomas (focal, multiple, segmental) and their number, type of cutaneous hemangiomas according to depth of involvement (superficial, mixed or deep hemangiomas), localization, size and presence of ulcerations/bleeding/infections. Inclusion criteria: all children admitted to I.N.S.M.C "Alessandrescu-Rusescu" with an ICHs diagnosis and who did not received any treatment.

For all subjects a signed parental informed consent was obtained prior enrollment. Enrolled patients underwent a well-established protocol-based evaluation (anamnestic, clinical and ultrasonographic).

Patients with ICHs were examined by the pediatrician and also by a dermatologist. Some of them required interdisciplinary evaluations. For a greater accuracy, in selected cases of ICHs, an ultrasonography of the skin lesions was performed, with determination of the size and vascularity. All the subjects diagnosed with ICHs underwent an ultrasound screening (abdominal ± head ultrasound) for detection of possible associated VHs. In selected patients, additional investigations such as MRI examination and bronchoscopy were performed.

The present study was conducted following the recommendations of the Declaration of Helsinki upon ethical principles guiding medical research involving human subjects and was also approved by the local Ethical Committee of the Hospital (INSMC "Alessandrescu-Rusescu").

STATISTICAL ANALYSIS

The first part of the statistical processing of the data was represented by the descriptive analysis of the study group, i.e. the variables analyzed in the study. For the statistical analysis of the association between different factors, two types of tests were applied: the Chi-square test and Spearman's rho non-parametric correlation coefficient. Statistical processing of the data from the study group was carried out using SPSS software version 16 for Windows.

RESULTS

A total of 138 children diagnosed with ICHs were enrolled in the study. The prevalence of VHs in patients with ICHs was 7.24% (10 patients). The descriptive analysis data are presented in table 1.

Their localizations were as follows:

Subglottic: 1 patient

Parotid: 2 patients

Hepatic: 7 patients

TABLE 1. *Descriptive statistical analysis of the study group*

Variable	**Value (n=138)**
Female gender (%)	80 (58%)
Gestational age – gestational weeks	38 (26-42)
Infants born from multiple pregnancies	11 (8%)
Number of cutaneous hemangiomas	1 (1-9)
Single IH	98 (71%)
Multiple IH	34 (24,6%)
Segmental IH	9 (6,5%)
Superficial IH	126 (91,3)
Mixt IH	15 (10,9)
IH which lead to functional impairement	15 (10,9%)
Ulcerative IH	20 (14,5%)
VHs	10 (7,2%)

In the subgroup of patients with hepatic hemangiomas, 5 patients had solitary hepatic hemangiomas and 2 patients were diagnosed with multifocal hepatic type. A significant percentage of patients included in the study were born at term (62.3%), although literature presenting premature birth as a risk factor for the development of ICHs.

90% of patients who were identified with VHs were term-born children. Thus, patients with VHs had statistically significantly higher gestational age than those without VHs, p=0.04 with Mann Whitney test 39 week (37-40) compared to 38 week (26-42) (Figure 2).

Related to gestational age, patients with hepatic hemangiomas had a statistically significant higher gestational age compared with children who had only cutaneous lesions (p=0.02 with Mann Whitney test), 39 weeks (37-40) for children with hepatic hemangiomas compared to 38 weeks (26-42) for children without hepatic hemangiomas. There was no statistically significant correlation regarding birth weight or female gender and the occurrence of visceral hemangiomas.

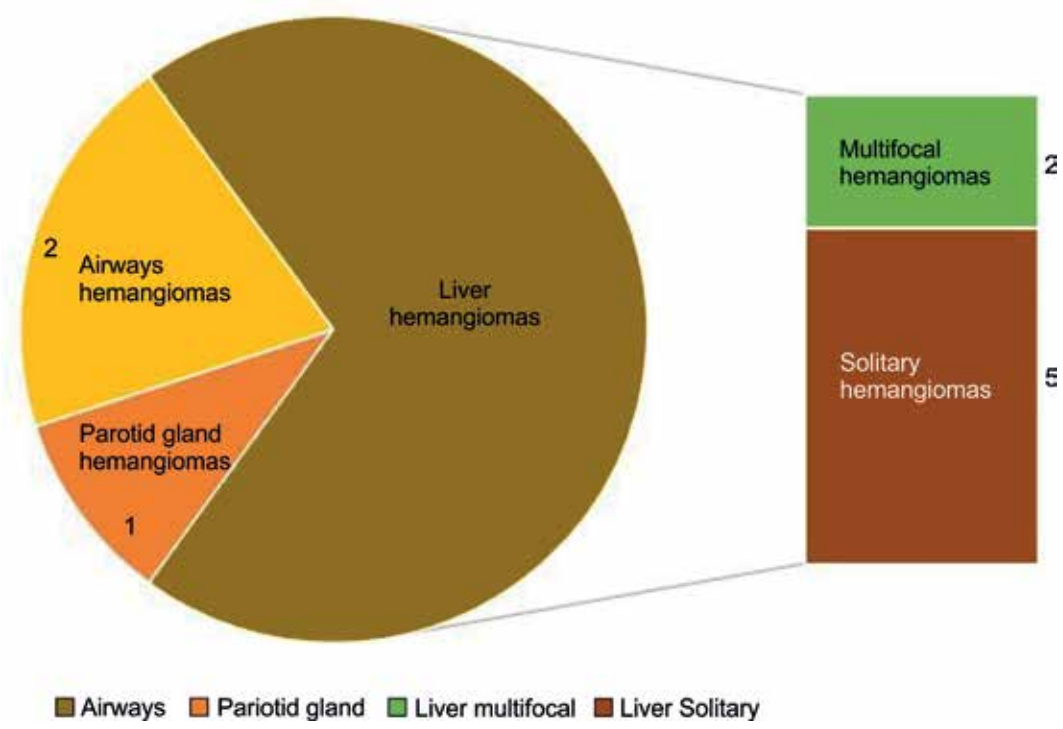

FIGURE 1. *Localization of visceral hemangiomas*

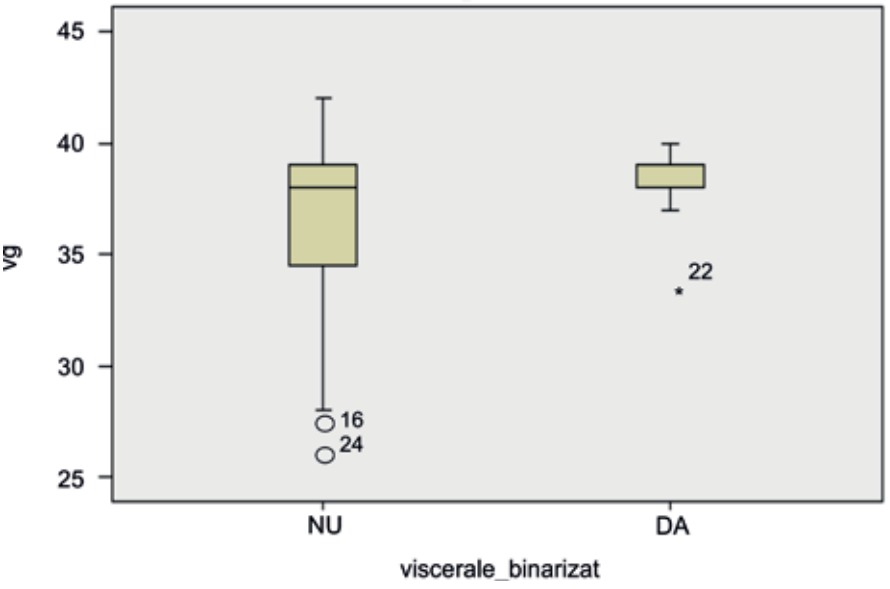

FIGURE 2. *Comparison of gestational age in patients with and without visceral hemangiomas (VG = gestational age, NU = without VHs, DA = with VHs)*

Statistical analysis of the data revealed a tendency in patients from multiple pregnancies to also have visceral hemangiomas, 2 patients (18.2%) from multiple pregnancies versus 8 patients (6.3%) from single pregnancies (p=0.18 with Fischer test).

The presence of superficial hemangiomas was identified as a statistically significant risk factor for the occurrence of visceral hemangiomas (p=0.02 with Fischer test, OR=5.66%, CI=95%).

No statistically significant correlation was identified between the presence of mixed-type hemangiomas and the occurrence of visceral hemangiomas. In addition, there was no significant correlation in patients with segmental hemangiomas.

Statistical analysis of the study group revealed no statistically significant difference between the number of ICHs in patients with visceral hemangiomas versus those without visceral hemangiomas 1 patient (1-9) vs 1 patient (1-4), p=0.21 with Mann Whitney test.

DISCUSSION

IHs are one of the most common benign vascular tumors found in children. Their increased incidence in the general population makes this vascular tumor pathology a common occurrence in the current medical practice. The natural history of hemangiomas is characterised by an early proliferative phase, followed by an involuting phase that starts at the age of 1 year [6,7]. The proliferative phase associates different morbidities (ulcerations, intereference with a vital function) [8,9]. The pathogenesis of IHs is complex and not entirely understood [10]. Risk factors are represented by female gender, preterm birth, low birthweight, multiple gestations, and preeclampsia [11]. Clinical observations suggest that perinatal hypoxia may trigger the occurrence of IHs and this could explain the correlation between prematurity anh IHs [12].

Generally, hemangiomas are self-limited. Most of them spontaneously regress, and do not require any treatment, but approximately 10% require therapheutic intervention [13]. Commonly IHs are localised in the region of the head and neck [14,15].

In some cases they can lead to significant complications, including disfigurement, pain, and functional impairment (periocular, oral cavity hemangiomas), even life-threatening complications (hepatic or airways hemangiomas) [9,16-18].

Life-threatening complications are associated with ''beard-area'' localization (preauricular skin, chin, anterior neck, and/or lower lip, bilaterally), the risk factor being the association of an obstructive airways hemangiomas. A feature of VHs is represented by possible life-threatening complications such as cardiac failure and hypothyroidism for hepatic hemangioma, especially in the case of multiple or diffuse liver hemangiomas [16].

Ultrasounds screening is recomended for the cases when the diagnosis is uncertain, or when there are ≥ 5 ICHs, or associated anatomic abnormalitis are suspected [19]. Multifocal ICHs (≥ 5 noncontiguous lesion) are not rare and may be associated with visceral hemangiomas [20], especially with hepatic hemangiomas. In our study we found 2 patients with multifocal liver hemangiomas but less than 5 cutaneous lesions. Segmental ICHs, a less common type of IHs have an associated risk of visceral hemangiomas and a higher risk of being life-threatening or causing functional impairment. These types of hemangiomas may associate structural anomalies such those that occur in PHACE(S) syndrome or LUMBAR syndrome [21-24].

The prevalence of visceral hemangiomas in our study was 7.24%. We could not compare this value with values from other studies, because these data are missing. There was found no statistically significant correlation between prematurity or the type or extension of ICHs (presence of mixt or segmental hemangiomas) and visceral hemangiomas. Multifocal ICHs has not been identified as a risk factor for VHs. A rare case on VHs has been found among our patients - subglottic hemangioma, a high-risk lesion because its potential to determine obstruction of the airways.

CONCLUSION

Our study revealed a number of 10 patients presenting with visceral hemangiomas associated with cutaneous hemagiomas. As previously seen in the literature, the most common visceral hemangiomas in the analyzed group were hepatic hemangiomas, followed by parotid hemangiomas, but there was also a rare form of hemangioma, the subglottic hemangioma. In our study, preterm birth and female gender were not identified as risk factors. There was no significant association between multifocal ICHs and VHs.

Although rare, VHs may be associated with higher rates of morbidity and often patients may be asymptomatic. Taken this into consideration, even if the current indication for ultrasound screening in patients with ICHs refers to those who present more than 5 hemangiomas, we consider that ultrasound screening can be useful for detection of visceral localization also in patients with a fewer number of tumors.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Munden A, Butschek R, Tom WL, et.al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. *Br J Dermatol*. 2014 Apr;170(4):907-913. doi:10.1111/bjd.12804
2. Hoornweg MJ, Smeulders MJC, Ubbink DT, van der Horst CMAM. The prevalence and risk factors of infantile haemangiomas: a case-control study in the Dutch population: Prevalence of infantile haemangiomas. *Paediatric and Perinatal Epidemiology*. 2012 Mar;26(2):156-162. doi:10.1111/j.1365-3016.2011.01214.x
3. Cura-Esquivel I, Velasquez-Palacios C, Núñez-Ku M. Gastrointestinal infantile hemangioma: A rare cause of digestive tract bleeding in children to consider. *Clin Case Rep*. 2021 Sep;9(9). doi:10.1002/ccr3.4722
4. Okuno T, Tokuriki S, Yoshino T, Tanaka N, Ohshima Y. Diffuse neonatal hemangiomatosis in a very low-birthweight infant treated

with erythropoietin: DNH and erythropoietin treatment. *Pediatr Int*. 2015 Apr;57(2):e34-e36. doi:10.1111/ped.12517
5. Codreanu IF, Comanici VD, Stan IV, Balanescu A, Acs B, Ritivoiu M. Hemangiomatoza cutanată infantilă asociată cu hemangiomatoză hepatică multifocală - prezentare de caz. *Romanian Journal of Medical Practice*. 2018;13(2):p114-116. 3p.
6. Codreanu IF, Comănici VD, Stan IV, Balănescu A, Ritivoiu M. Role of ultrasound in diagnosis and follow up of parotid gland infantile hemangioma – case series presentation. *Ro J Med Pract*. 2018 Sep;13(3):217-221. doi:10.37897/RJMP.2018.3.9
7. Callahan AB, Yoon MK. Infantile hemangiomas: A review. *Saudi Journal of Ophthalmology*. 2012 Jul;26(3):283-291. doi:10.1016/j.sjopt.2012.05.004
8. Couto RA, Maclellan RA, Zurakowski D, Greene AK. Infantile Hemangioma: Clinical Assessment of the Involuting Phase and Implications for Management. *Plastic & Reconstructive Surgery*. 2012 Sep;130(3):619-624. doi:10.1097/PRS.0b013e31825dc129
9. Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. *The Lancet*. 2017 Jul;390(10089):85-94. doi:10.1016/S0140-6736(16)00645-0
10. Grzesik P, Wu J. Current perspectives on the optimal management of infantile hemangioma. *PHMT*. 2017 Dec;Volume 8:107-116. doi:10.2147/PHMT.S115528
11. Smith CJF, Friedlander SF, Guma M, Kavanaugh A, Chambers CD. Infantile Hemangiomas: An Updated Review on Risk Factors, Pathogenesis, and Treatment: Updated Review of Infantile Hemangioma. *Birth Defects Research*. 2017 Jul;109(11):809-815. doi:10.1002/bdr2.1023
12. Metry DW, Hawrot A, Altman C, Frieden IJ. Association of Solitary, Segmental Hemangiomas of the Skin With Visceral Hemangiomatosis. *Arch Dermatol*. 2004 May;140(5). doi:10.1001/archderm.140.5.591
13. de Jong S, Itinteang T, Withers AHJ, Davis PF, Tan ST. Does hypoxia play a role in infantile hemangioma? *Arch Dermatol Res*. 2016 May;308(4):219-227. doi:10.1007/s00403-016-1635-x
14. Macca L, Altavilla D, Di Bartolomeo L, et al. Update on Treatment of Infantile Hemangiomas: What's New in the Last Five Years? *Front Pharmacol*. 2022 May;13:879602. doi:10.3389/fphar.2022.879602
15. Sethuraman G, Yenamandra V, Gupta V. Management of infantile hemangiomas: Current trends. *J Cutan Aesthet Surg*. 2014;7(2):75. doi:10.4103/0974-2077.138324
16. Kowalska M, Dębek W, Matuszczak E. Infantile Hemangiomas: An Update on Pathogenesis and Treatment. *JCM*. 2021 Oct;10(20):4631. doi:10.3390/jcm10204631
17. Darrow DH, Greene AK, Mancini AJ, Nopper AJ, the SECTION ON DERMATOLOGY, SECTION ON OTOLARYNGOLOGY–HEAD & NECK SURGERY, AND SECTION ON PLASTIC SURGERY. Diagnosis and Management of Infantile Hemangioma: Executive Summary. *Pediatrics*. 2015 Oct;136(4):786-791. doi:10.1542/peds.2015-2482
18. Jung HL. Update on infantile hemangioma. *Clin Exp Pediatr*. 2021 Nov;64(11):559-572. doi:10.3345/cep.2020.02061
19. Corbeddu M, Meucci D, Diociaiuti A, Giancristoforo S, et.al. Management of Upper Airway Infantile Hemangiomas: Experience of One Italian Multidisciplinary Center. *Front Pediatr*. 2021;9:717232. doi:10.3389/fped.2021.717232
20. Chang LC, Haggstrom AN, Drolet BA, Baselga E, et.al. Growth Characteristics of Infantile Hemangiomas: Implications for Management. *Pediatrics*. 2008 Aug;122(2):360-367. doi:10.1542/peds.2007-2767
21. Sebaratnam DF, Rodríguez Bandera A I., Wong LCF, Wargon O. Infantile hemangioma. Part 2: Management. *Journal of the American Academy of Dermatology*. 2021 Dec;85(6):1395-1404. doi:10.1016/j.jaad.2021.08.020
22. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, SUBCOMMITTEE ON THE MANAGEMENT OF INFANTILE HEMANGIOMAS, et.al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. *Pediatrics*. 2019 Jan;143(1):e20183475. doi:10.1542/peds.2018-3475
23. Rotter A, Samorano LP, Rivitti-Machado MC, Oliveira ZNP, Gontijo B. PHACE syndrome: clinical manifestations, diagnostic criteria, and management. *An Bras Dermatol*. 2018 Jun;93(3):405-411. doi:10.1590/abd1806-4841.20187693
24. Yu X, Zhang J, Wu Z, Liu M, Gu Y, et.al. LUMBAR syndrome: A case manifesting as cutaneous infantile hemangiomas of the lower extremity, perineum and gluteal region, and a review of published work. *J Dermatol*. 2017 Jul;44(7):808-812. doi:10.1111/1346-8138.13763