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

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
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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (%)</td>
<td>80 (58%)</td>
</tr>
<tr>
<td>Gestational age – gestational weeks</td>
<td>38 (26-42)</td>
</tr>
<tr>
<td>Infants born from multiple pregnancies</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Number of cutaneous hemangiomas</td>
<td>1 (1-9)</td>
</tr>
<tr>
<td>Single IH</td>
<td>98 (71%)</td>
</tr>
<tr>
<td>Multiple IH</td>
<td>34 (24.6%)</td>
</tr>
<tr>
<td>Segmental IH</td>
<td>9 (6.5%)</td>
</tr>
<tr>
<td>Superficial IH</td>
<td>126 (91.3)</td>
</tr>
<tr>
<td>Mixt IH</td>
<td>15 (10.9)</td>
</tr>
<tr>
<td>IH which lead to functional impairment</td>
<td>15 (10.9%)</td>
</tr>
<tr>
<td>Ulcerative IH</td>
<td>20 (14.5%)</td>
</tr>
<tr>
<td>VHs</td>
<td>10 (7.2%)</td>
</tr>
</tbody>
</table>

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.
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 characterized 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, interference 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 and IHs [12].

Generally, hemangiomas are self-limited. Most of them spontaneously regress, and do not require any treatment, but approximately 10% require therapeutic intervention [13]. Commonly IHs are localized 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 recommended for the cases when the diagnosis is uncertain, or when there are ≥ 5 ICHs, or associated anatomic abnormalities are suspected [19]. Multifocal ICHs (≥ 5 noncontiguous lesions) 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 hemangiomas. 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
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Conflicts of interest: none declared
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