

Infantile hemangioma: which are the main risk factors?

Hemangioma infantil: quais são os principais fatores de risco?

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ABSTRACT

Introduction: Infantile hemangioma (IH) is a benign tumor of the vascular endothelium, characterized by early appearance, rapid growth, and slow involution. It is the most common tumor in the pediatric age group, and several risk factors are associated with its development. **Case Report:** Monozygotic twins, female, 29 weeks premature and with low birth weight, presenting reddish spots that after 15 days evolved into erythematous tumors, with a diagnosis of IH. **Conclusion:** This case report exemplifies simultaneously the main risk factors associated with the development of IH. Recognition of these factors by pediatricians is crucial for early diagnosis, appropriate follow-up, and management.

Keywords: Infantile hemangioma; Hemangioma; Vascular tumor; Neonatal; Twins; Probability; Risk factors.

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RESUMO

Introdução: O hemangioma da infância (HI) é um tumor benigno do endotélio vascular, caracterizado por aparecimento precoce, crescimento rápido e involução lenta. É o tumor mais comum da faixa etária pediátrica e diversos fatores de risco estão associados ao seu desenvolvimento.

Relato de Caso: Gêmeares monozigóticas, femininas, prematuras de 29 semanas e com baixo peso ao nascimento, apresentando manchas avermelhadas que após 15 dias evoluíram para tumorações eritematosas, com diagnóstico de HI. **Conclusão:** Este relato de caso exemplifica simultaneamente os principais fatores de risco para o desenvolvimento do HI, que devem ser reconhecidos por pediatras para seu diagnóstico precoce e acompanhamento/manejo adequado.

Palavras-chave: Hemangioma infantil; Hemangioma; Tumor vascular; Neonatal; Gêmeos; Probabilidade; Fatores de risco.

INTRODUCTION

Infantile hemangioma (IH) is the most common benign vascular tumor of childhood, with a prevalence estimated at 3 to 10% of the population and up to 20% of preterm infants¹. It may be present at birth as a precursor lesion and is characterized by a rapid proliferation phase, reaching its final volume in the first 3 months of life, followed by slow regression. The mechanisms that favor its emergence and evolution are not completely understood. Hypoxia has already been identified as one of those responsible for its pathogenesis, and recent evidence shows that the renin-angiotensin system can also act synergistically, creating a favorable environment for the emergence of IH². Several risk factors are associated with its development, as will be exemplified in this case report. Knowledge of these risk factors is essential for professionals who provide care to newborns for early diagnosis and appropriate management.

CASE REPORT

Female monozygotic twins, 29 weeks premature and with low birth weight.

Twin A: Newborn, weighing 1160 grams, with reddish spots on the upper eyelids, left inframandibular and inframammary areas, and right heel. After 15 days, the spots progressed into violet plaques, thus confirming the clinical diagnosis of superficial non-segmental infantile hemangioma (IH).

Twin B: Newborn, weighing 970 grams, with reddish spots on the left upper limb, upper back, and right lateral region of the chest. After 15 days, the lesions progressed into plaques and erythematous tumors, corroborating the hypothesis of superficial IH.

Figures 1 and 2 show the lesions in the first outpatient visit, at 4 months of age.

DISCUSSION

IH is a benign tumor that, in up to 65% of cases, presents at birth as a precursor lesion (telangiectasia, anemic spot, or reddish spot). Its incidence rate varies from 3 to 10% in the population but it can reach up to 20% in preterm infants^{1,2}. It is also more frequent in females than in males, at an approximate ratio of 2-3:1³. A meta-analysis conducted by Ding et al. (2020)⁴ evaluated seventeen potential risk factors for IH and showed that female gender, low birth weight, multiple gestation, premature delivery, progesterone therapy, and family history increased the risk of IH⁴. Low birth weight is one of the most relevant factors, with the risk for IH increasing by 40% for each 500 grams reduction in birth weight⁵.

The relationship between twins remains an uncertain factor in the occurrence of IH. While IH is not transmitted through direct mendelian inheritance, there exists a genetic influence, evidenced by the higher incidence in monozygotic twins compared to dizygotic twins. Multiple pregnancies are associated with a higher risk of prematurity and low birth weight. It is possible that several predisposing factors interact, leading to prematurity, low weight, and female sex appearing to be more influential than a single genetic predisposition⁶, as described in this case report. Moreover, the intrauterine-hypoxia theory, combined with the action of the renin-angiotensin system in IH's pathogenesis, could account for all these factors².

Recent studies suggest that IHs result from vasculogenesis (the formation of new blood vessels from stem cells) and angiogenesis (the creation of new blood vessels from existing vessels), with hypoxia appearing to trigger this dysregulation⁷.

Hypoxia has been identified as one of the factors responsible for IH's pathogenesis. Evidence is based on the pallor of IH precursors and possible associated



Figure 1. Ventral view. Twin A: Erythematous patches on the upper eyelid, inframandibular, and inframammary regions on the left side consistent with infantile hemangioma. Twin B: Nodular lesion on the left upper limb and a plaque on the right lateral thoracic region, indicative of infantile hemangioma.



Figure 2. Dorsal view. Twin A: Erythematous plaque on the right heel. Twin B: Erythematous plaque on the upper back. Both consistent with infantile hemangioma.

arteriopathies, the association between IH and conditions like placental insufficiency, preeclampsia, and low birth weight, as well as an increase in the expression of hypoxia-inducible factors^{2,4}. However, recent evidence suggests that the renin-angiotensin system may also act synergistically in this pathology. It is believed that angiotensin II promotes the secretion of endothelial growth factor and a protumor factor, contributing to vasculogenesis and anti-apoptosis².

The proposed origin of hemangioma via the placenta is supported by the fact that many molecular markers characteristic of hemangioma vessels are expressed in normal fetal microvessels of the placenta, including the erythrocyte-like glucose transporter-1 (GLUT-1). This suggests that IH likely originates from placental cells⁸. GLUT-1 positive cells have exhibited stem cell properties by demonstrating the ability to differentiate into endothelial, smooth muscle, or adipocyte cells, providing further evidence in support of the theory of vasculogenesis^{7,8}.

It is known that levels of placental proteins, such as human placental lactogen, differ in multiple pregnancies compared to singleton pregnancies. These enzymatic alterations also occur in conditions like preeclampsia, affecting placental growth factor (PIGF) and tyrosine kinase-1 values. PIGF has been discovered to be expressed in involuted hemangiomas, further supporting the idea that hemangiomas and the placenta are governed by similar angiogenic control mechanisms. Further studies are necessary to comprehend the role of these angiogenic growth factors concerning hemangioma and placental vessels⁹.

A case-control study conducted by Gong et al. (2022)¹⁰ analyzed maternal and perinatal risk factors for IH, demonstrating that a history of spontaneous abortion, anemia during pregnancy, premature rupture of membranes, placenta previa, preeclampsia, and abnormal volume of amniotic fluid are independent risk factors for IH.

The patients described in this case had the following risk factors: female gender, low birth weight, multiple pregnancy, and prematurity; all of which have been previously reported in the literature.

The diagnosis of IH relies on clinical evaluation, noting its characteristic evolutionary history marked by rapid growth, reaching approximately 80% of its final volume within the first 3 months of life, followed by a subsequent phase of slow involution at a rate of around 10% per year. In instances of diagnostic uncertainty, positive immunohistochemistry for GLUT-1 aids in distinguishing it from other vascular tumors or malformations². In the case in question, the clinical progression aligned with that typically observed in IH. Given the presence of multiple lesions, it is classified as hemangiomatosis, which can potentially involve internal organs such as the liver, warranting the recommendation for an ultrasound examination⁵.

The primary indications for treatment include large lesions, the risk of functional impairment (such as affecting vision, airways, or anogenital areas), aesthetic concerns, and ulcerations, which can have physical and emotional impacts

on both children and their families^{4,6}. When systemic treatment is necessary, the non-selective beta-blocker propranolol is the preferred initial choice¹¹. Although the twins shared similar risk factors, only twin A required systemic treatment with propranolol at a dosage of 2 mg/kg/day. This was due to lesions located in critical areas, such as the cervical region (posing a risk to the airway and potential for ulceration) and the eyelid region (affecting vision). Twin B received treatment with topical timolol. Both patients commenced treatment after reaching 5 weeks of corrected age, as recommended in the literature¹².

CONCLUSION

The presence of erythematous patches, telangiectasias, or anemic patches at birth may be the first sign of an IH. It is crucial for pediatricians to consider assessing risk factors such as female gender, low birth weight, multiple gestation, premature birth, progesterone therapy, and family history when diagnosing IH. Guiding parents regarding the observation of the lesion evolution is vital, as the prognosis is significantly influenced by the early introduction of beta-blocker treatment.

AUTHORS' CONTRIBUTIONS

We describe contributions to the papers using the taxonomy (CRediT) provide above:

Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing: Mariana Aparecida Pasa Morgan, Laura Serpa, Thaís Braga Cerqueira, Alice Andrade Gonçalves. Beatriz Carvalho, Aluhine Lopes Fatturi e Rafaela Moura de Oliveira. Project administration, Supervision & Writing – original draft: Mariana Aparecida Pasa Morgan, Laura Serpa, Thaís Braga Cerqueira e Alice Andrade Gonçalves. Validation & Software: Mariana Aparecida Pasa Morgan, Laura Serpa, Thaís Braga Cerqueira, Alice Andrade Gonçalves. Beatriz Carvalho, Aluhine Lopes Fatturi, Rafaela Moura de Oliveira, Vânia Oliveira de Carvalho e Kerstin Taniguchi Abagge. Data curation & Formal Analysis: Vânia Oliveira de Carvalho e Kerstin Taniguchi Abagge.

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