A Retrospective Study of Infantile Hemangiomas: Demographic and Clinical Characteristics at Hera General Hospital, Makkah, Saudi Arabia

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Abstract

Objective: The objective of this study is to provide the clinical features of infantile hemangiomas and their associated risk factors.

Method: The study included patients who have been diagnosed with infantile hemangiomas, who were identified from a logbook in the Dermatology Department of Hera General Hospital, Makkah, Saudi Arabia. Demographic, prenatal, perinatal, and clinical data, along with complications and treatment modalities, were included on the data sheet.

Result: The medical records of 61 patients were examined. Most of our patients were female (69.9%) and the maternal age of their mothers ranged from 22 to 43 years, with a mean maternal age of 28.8 years and a median age of 28 years. A positive family history of vascular anomalies in first-degree relatives was reported in 11.5% of patients. In 58 patients (95.1%), the age of onset for lesions was before two weeks (86.2%) and over two weeks (13.8%). Complications were noted in eight patients (13.3%). Most of our patients were treated by topical beta-blockers (39.7%), followed by pulsed-dye laser (10.3%) and systemic propranolol (10.3%). Observation of the hemangioma progression was seen in 57.6% of our patients.

Conclusion: Hemangiomas more commonly occur in premature, female infants, who are more likely to be born as a product of single gestation. Further studies are needed to define other risk factors and to understand the relationship between potentially confounding factors.

Keywords: Infantile hemangiomas; Makkah

Introduction

There are two main types of vascular lesion in an infant: vascular malformations and tumors [1]. Hemangiomas, also known as strawberry birthmarks, are the most common vascular tumors of infancy [2], yet surprisingly the actual incidence of infantile hemangiomas remains unknown [3]. Some studies have reported that the incidence of hemangiomas is up to 2.6% of neonates and up to 12% of children by the first year [4].

Hemangiomas are soft, bright, red marks over the skin [5] and are a type of benign endothelial cell neoplasm. They usually appear in the first few days to months of life [6]. Infantile hemangiomas are often characterized by two subsequent phases: a growth phase in the first year of life, followed by an involution phase over the next 5-7 years or more [4].

The cause is unknown but different factors are found to influence infantile hemangiomas, such as family history, gender, race, preterm status, and low birth weight, as well as whether an infant is the product of multiple gestations or born to older mothers. These factors have been explored in many studies [7] and may provide clues to their

pathogenesis. The role of genetics in IH is only partially understood. Most IHs occurs sporadically. Familial clustering has been reported, even though genetic predisposition is controversial [8]. Evidence exists that some IHs are inherited [9]. Walter et al reported 6 pedigrees with an autosomal dominant inheritance of high penetrance; for 3, linkage to chromosome 5q31-33 was proposed [10]. In a small number of patients, genetic variants were associated with germ line mutations in the VEGFR2, VEGFR3 and TEM8 genes; these genes regulate major angiogenesis-signaling pathways, suggesting hyper activation of VEGFR2 signaling in the pathogenesis of IH [11,12].

Infantile hemangiomas are often benign with a self-limited course [13]. However, in some cases they may cause complications such as permanent disfigurement and ulceration, which can lead to pain, bleeding, scarring, and infection [14]. The diagnosis of infantile hemangiomas is usually based on the clinical appearance of the lesions.

Although hemangiomas can appear on any part of the body, previous studies have demonstrated that they are more commonly located in the head and neck area [15]. Most are proliferate and involute without any functional impairment, but a minority require some form of intervention. Both the medical and psychological impact should be taken into consideration when a hemangioma is located on a patient's face [7]. This is because it will be more severe medically and

may require an intervention if it develops and compresses on the vital organ [13].

In the past, the treatment options for infantile hemangiomas were limited and their potential side effects were considerable. Now, however, there are many treatment options of infantile hemangioma, although debate continues about the best strategies for its management. In 2011, a Cochrane analysis of interventions for infantile hemangiomas showed that there is a limitation in the ability to identify the single best treatment due to non-availability of clinical trials and the absence of medication approved by the US Food and Drug Administration for the treatment of infantile hemangiomas [5].

Our objective for this study is to provide the clinical features of infantile hemangiomas and their associated risk factors in the Makkah region of Saudi Arabia, in order to advance our knowledge of it in our population.

Methodology

The study included patients who were diagnosed with infantile hemangiomas from a logbook in the Dermatology Department of Hera General Hospital. The datasheet included demographic, prenatal, perinatal and clinical data, along with information about complications and treatment modalities.

Statistical analysis was carried out using SPSS 13.0. The data were evaluated using descriptive statistical methods (mean $\pm$ standard deviation, median, frequencies and percentages). For all continuous factors, a univariable analysis was performed using chi-squared tests. A two-tailed P value less than 0.05 was considered statistically significant.

Results

The medical records of 61 patients were examined. Most of our patients were female (69.9%), and the female-to-male ratio was 2:1. The majority of our patients (47.5%) were the product of spontaneous vaginal delivery, whilst 32.8% were delivered by cesarean section and 3.3% by ventouse delivery.

Data on gestational age were available for 51 patients, 31.1% of whom were born prematurely (defined as younger than 37 weeks gestational age) and 49.2% who were full term. The mean birth weight was 2473 g and the median birth weight was 2550 g. Data on birth weight were available for 46 patients, 23.9% were very low birth weight (defined as 1500 g), 23.9% were low birth weight (defined as 1500-2499 g) and 52.2% were normal birth weight (defined as 2500 g and more). The correlation between prematurity and low birth weight was statistically significant (P-value 0.009).

Forty infants (65.6%) were products of single gestations and 19.7% of multiple gestations. A positive family history of vascular anomalies in first-degree relatives was reported in seven patients (11.5%). The age of the patients' mothers ranged from 22 to 43 years, with a mean maternal age of 28.8 years (SD $\pm$ 5.8) and a median age of 28 years. The average maternal age of first-time mothers was 26.5 years.

In 58 patients (95.1%), the age of onset for lesions usually occurred before two weeks (86.2%) but also could occur at two weeks and over (13.8%).

Among data available for 55 patients, the most common site of hemangioma was seen in the face (36.4%). Other locations included upper limbs (18.3%), lower limbs (12.7%), chest (12.7%), scalp (9.1%) and 3.6% for each neck, back, and buttock.

A total of 88.5% of our patients presented with a solitary lesion and 11.5% with multiple lesions. Complications were noted in eight patients (13.3%), including ulceration in 9.8% of patients, infection in 1.6%, and other complications in 1.6%.

Treatment was administered to 36 patients (62.1%), with five being treated with systemic steroids (8.2%), 23 with topical beta-blockers (39.7%), six with pulsed-dye laser (10.3%), and six with systemic propranolol (10.3%). Hemangioma progression was seen in 57.6% of our patients.

Discussion

Infantile hemangiomas are the most common vascular tumors of childhood, affecting about 5% of all infants. In this small group of patients, we systematically collected demographic, prenatal, perinatal, and clinical data on infants with hemangiomas to identify significant trends of the disease, including the different treatment modalities.

The female to male ratio was 2:1, which is comparable with the previously published ratio that ranges from 1.4:1 to 3:1 [16-19]. The reason for female predominance is unclear. Kindred studies have suggested that a subset of hemangiomas may be inheritable and linked to genes on chromosome 5 [20]; no genetic mutations on the X chromosome have been reported. Historically, some researchers have argued that parents perceive hemangiomas to pose a greater cosmetic concern when females are affected, which could be a reason why girls are over-represented in dermatology clinics.

Most of our patients (47.5%) were the product of spontaneous vaginal delivery, although 32.8% were delivered via cesarean section and 3.3% by ventouse delivery, which is less than the published data, which showed 20% in the population study [15].

The correlation between prematurity and low birth weight was statistically significant (P-value 0.009) for our patients, which is comparable with one published study [21]. It is unclear whether the presence of hemangioma places the infants at risk of prematurity or vice versa. It is possible that an imbalance of angiogenic control mechanisms may result from prematurely removing a developing fetus from maternal and placental influences [21].

In our study, 47.8% of the patients were low birth weight, defined as $\leq$ 2500 g, which is more than one population-based study (12%) [15]. This could be explained by the fact that our research is a hospital-based study, in which the number of patients included is expected to be more than in a population-based study.

Most of our patients (65.6%) were the product of a single gestation, and 19.7% were the product of multiple gestations. This finding is comparable with another study in which the number of infants of multiple gestations was 10.6% [21].

Infantile hemangioma lesions range from a few millimeters to several centimeters in diameter. Most of our patients presented with solitary lesions (88.5%), with only 11.5% of them suffering multiple lesions, which is less than the data published in one study [21]. This may be due to a limited number of cases in our study.

In one published study [22], the authors found that 51% of their patients had complications, including ulceration (13%) and infections (11%). This is a greater amount of incidences than we found, as 9.8% and 1.6% of our patients suffered ulceration and infection, respectively. This difference could be explained by the fact that the aim of the other research was to identify complications in hemangioma patients.

In our study, the majority of hemangiomas were located on the face (36.4%), which differs from the findings of another study [17] that reported the trunk as the most frequent site in a population-based study [15].

Systemic corticosteroids have become a mainstay in the treatment of hemangiomas, yet their mechanism of action is not well understood [23,24]. Daily doses of 2-3 mg of prednisolone or prednisone per kilogram of body weight are usual and were prescribed to our patients, although some investigators have recommended even higher doses (5 mg/kg daily).

Systemic steroid treatment results in dramatic shrinkage of the hemangioma, usually within days, in an estimated one-third of infants. In another third, stabilization of the growth without measurable shrinkage is observed and minimal or no response is similarly found in a further third [24], which also applied to our cases. Despite many potential side effects, including irritability, gastrointestinal upset, immunosuppression, hypertension, and growth retardation, systemic steroid treatment remains useful in some instances of hemangioma, particularly in patients who cannot tolerate other therapeutic options.

Propranolol therapy has become increasingly more helpful in the management of infantile hemangioma. Leaute-Labreze et al. [25] fortuitously discovered the efficacy of beta-blockers for the treatment of infantile hemangioma in 2008. A few of our patients (10.3%) used this medication, which led to stabilization of the hemangioma. The usefulness of this drug is shown in more than 170 reports and studies [26,27].

Topical agents are an appropriate therapy for use on small, thin lesions, but whilst the side effects are less than systemic agents, there is limited data about the efficacy. Twenty three of our patients (39.7%) used topical beta-blockers. Timolol maleate is a non-selective topical beta-blocker that has been approved for the treatment of ocular glaucoma and hypertension in children and infants by the Food and Drug Administration [28]. For our patients, we selected the ophthalmic preparation of timolol maleate, which has been used in other studies as a topical treatment of infantile hemangioma. To date, the only adverse effect reported in association with this treatment is a single episode of severe sleep disturbance. Nonetheless, experts urge caution with the drug and recommend using no more than one drop twice a day on affected lesions [29].

Several laser systems have been used to treat hemangiomas. The flash lamp-pumped pulsed-dye laser, though extremely useful in treating port-wine stains, is less efficient for hemangiomas. Only 10.3% of our patients were treated with a pulsed-dye laser, which showed only mild improvement. This is because of the limited depth of penetration (approximately 1 mm), meaning that this laser works better for thin superficial hemangiomas than for those that are destined to be both superficial and deep [30]. However, the laser can be used to improve residual telangiectasia after involution and is useful in treating ulcerated hemangiomas, resulting in decreased pain and prompt re-epithelialization [31].

Conclusion

We find that hemangiomas more commonly occur in premature, female infants who are the product of single gestation. More studies are needed to define further the risk factors and complications for hemangiomas and to understand the relationship between potentially confounding factors.

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