Actas Dermosifiliogr. 2009;100:Supl. 1:73-6

Infantile Hemangiomas: A Look Back and Future Directions

S.M. Maguiness and I.J. Frieden
Department of Dermatology. University of California. San Francisco. United States of America.

Abstract. Over the past 10 years, there have been significant advancements in our understanding of the biology and natural history of infantile hemangiomas (IH). Research into their pathogenesis has led to many new discoveries including the first mouse model recapitulating hemangioma growth and genes such as the vascular Endothelial Growth Factor Receptor (VEGFR) which may be intimately involved in their proliferation. Large prospective studies have born out important data on the natural history, complications and structural associations of these fascinating vascular tumors. In addition, new therapies have emerged which appear to be very effective. In the following article, a summary of major contributions over the past decade is outlined.

Key words: hemangioma, infantile hemangioma, hemangioma of infancy, vascular tumors.

HEMANGIOMAS INFANTILES: UNA VISTA ATRÁS Y DIRECCIONES FUTURAS

Resumen. En los últimos 10 años se han producido importantes avances en el conocimiento de la biología y la historia natural de los hemangiomas infantiles. La investigación sobre la patogenia ha dado lugar a nuevos descubrimientos, incluyendo el primer modelo murino que resume el crecimiento de los hemangiomas y los genes, como el receptor del factor de crecimiento endotelial vascular, que pueden estar estrechamente relacionados con su proliferación.

Amplios estudios prospectivos han aportado importantes datos sobre la historia natural, las complicaciones y las asociaciones estructurales de estos tumores vasculares. Además, se han desarrollado nuevas terapias que parecen ser muy efectivas. En el siguiente artículo se esboza un resumen de las principales contribuciones durante la última década.

Palabras clave: hemangioma, hemangioma infantil, hemangioma de la infancia, tumores vasculares.

The 21st century is an exciting time to be interested in infantile hemangiomas (IH). Over the past 10 years there have been numerous important advances in our understanding of the pathogenesis, growth characteristics, risk factors, complications and treatments for these common vascular tumors. Many observations have been made by basic scientists and clinicians that have helped to increase our understanding of IH, and several of these stand out as important advances.

Nosology

The study of vascular anomalies as a whole has also advanced significantly over the last several decades. Among the most important of these advances was the development and wide acceptance of a framework for classifying vascular anomalies which was pioneered by Mulliken and Glowacki, and formally adopted in 1996 by the International Society for the Study of Vascular Anomalies (ISSVA). This classification provides a simple schema differentiating vascular tumors from malformations based on their unique biology and growth characteristics which helped to clarify confusion between IH and, vascular malformations, such as port-wine stains and venous malformations, which were previously often erroneously referred to as "capillary" or "cavernous" hemangiomas[1,2]. It also led to the recognition of important distinctions between a number of benign of vascular tumors presenting during infancy. An example are fully-formed congenital hemangiomas as being distinct from IH. Non-involuting congenital hemangioma (NICH) and rapidly involution congenital hemangioma (RICH) differ from IH with respect to clinical presentation, growth characteristics and immunohistochemical properties[3-5]. Another example is the understanding that Kasabach-Merritt syndrome is *not* cause by

Correspondence:
Ilona J. Frieden.
Professor of Clinical Dermatology and Pediatrics.
University of California. San Francisco.
Department of Dermatology, Box 0316, San Francisco, CA 94143-0316.
friedeni@derm.ucsf.edu

infantile hemangioma but rather by other vascular tumors, Kaposiform hemangioendothelioma and tufted angioma[6,7]. More recently, distinctions have been made among certain multifocal vascular tumors wich help to better characterize these rare presentations. Whereas virtually all were previously called either "benign neonatal hemangiomatosis"and "disseminated neonatal hemangiomatosis" we now have recognized at least 2 other diagnoses, multifocal lymphangioendotheliomatosis and multifocal pyogenic granulomas presenting as multifocal tumors. Likely others will be identified over time[8,9].

Immunophenotype and Pathophysiology

The discovery (published in 2000) that the erythrocyte-type glucose transporter protein GLUT1 is a specific immunohistochemical marker for IH was a hallmark event, as it provided a diagnostic test which could distinguish IH from other vascular tumors and malformations[10]. It also led to a rapid increase in research attempting to further delineate the cells of origin of hemangiomas and the implications thereof. For example, a possible relationship between IH and placental tissue became evident: GLUT-1 as well as other markers such as merosin, Lewis Y antigen, and the low-affinity Fc receptor (FcYRII) have also been found to be present on placental blood vessels. This has led to further studies which have shown genomic identity between hemangioma and placental blood vessels[11,12]. It is not known if IH (either some or all) might represent embolization from the placenta, but other possible explanations for the similarities, such as an immature vascular phenotype shared by both the placenta and IH might also explain these findings[11].

Recent evidence suggests that vasculogenesis, de novo formation of new blood vessels rather than angiogenesis, may play an important role in hemangioma growth. Until recently vasculogenesis had been thought to occur only during fetal life. This new concept is based on several lines of evidence including the presence of immature progenitor endothelial cells in patients with hemangiomas, both circulating and within IH themselves[13]. The recent development of an animal model which demonstrates this phenotype is a particularly important advancement. This model uses multipotential stem cells derived from IH tissue to generate hemangioma-like neoplasms in immunodeficient mice and over time these cells involute and some form adipocytes, similar to natural involution of IH which often results in a fibrofatty residua[14]. New evidence also demonstrates the potential role of mutations in Vascular Endothelial Growth Factor Receptors (VEGFR) in the proliferation of IH. Mutations in VEGFR1 have been demonstrated in IH tissue have been demonstrated. VEGFR1 is a so-called decoy receptor which blunts the action of VEGFR2 and these mutations apparently lead to uncontrolled activation of VEGFR2, with subsequent increased hemangioma cell growth[15,16]. In addition to providing clues to the basis of hemangioma pathogenesis, VEGF receptors may also indicate a potential future therapeutic target.

Natural History

Several studies spanning a period from the 1930s to 1960s including those by Lister and Jacobs provided evidence of the involutionary capacity of infantile hemangiomas, leading to a better understanding of the unique natural history of this common tumor[17,18]. IH are either absent or present as precursor lesions at birth, and proliferate rapidly during the first few months of life, followed by slow involution over several years. These observations had major implications for patient care. Prior to this understanding, many patients with IH were treated with radical surgery or radiation therapy. However, once this natural history was well established a 'hands-off' approach was advocated by most clinicians. Today, the potential complications of IH are better recognized and there are more treatment options. While most IH do not need treatment, a significant minority do, due to life or function-threatening complications or risk of permanent scarring. In most cases infants at risk for these complications can be identified early in order to get treated, but treatment must always be based on the individual patient and site and characteristics of their hemangioma - there is no "one size fits all" approach (see *Advances in therapy* below). The understanding of which hemangiomas can cause these complications has been greatly increased by via the collaborative research of the Hemangioma Investigator Group (HIG), founded in 2001, which prospectively enrolled a cohort of more than 1000 infants. This large cohort resulted in the confirmation of many previously identified demographic factors associated with an increased risk for having a hemangioma including female gender and Caucasian race, but also found significant associations with premature birth, low birth weight, multiple gestation pregnancies, and advanced maternal age. A subsequent case-control study using multivariate analysis found that low birth-weight was the most strongly associated pregnancy-related risk factor[19,20]. HIG investigations have also led to a better understanding of hemangioma growth characteristics[21], and clinical features, such as large size and segmental distribution, which are most predictive of morbidity and associated structural anomalies[20].

Associations and Complications

An important advance was the delineation of a specific neurocutaneous syndrome, PHACE syndrome

(OMIM #606519), an acronym that refers to a constellation of structural anomalies reported in association with segmental hemangiomas: posterior fossa abnormalities, hemangiomas, arterial abnormalities, cardiac anomalies, eye abnormalities. PHACE syndrome has subsequently been shown to be an uncommon but not rare syndrome, with more than 200 cases reported[22]. Prospective studies on high risk infantile hemangiomas are currently underway and are sure to help answer many more questions regarding what size and location carry the highest risk of associated anomalies which will undoubtedly help clinicians to stratify the risk of patients which large facial hemangiomas as well as guide which evaluations are needed to look for these structure anomalies.

Analagous to PHACE syndrome, anomalies of the genitourinary system and spinal cord have been increasingly recognized in association with IH of the lumbosacral area. Two acronyms have recently been proposed: PELVIS syndrome (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) or SACRAL syndrome (spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization)[23,24]; Segmental IH in the lumbosacral area should prompt investigations to rule out underlying structural anomalies.

Therapy

Systemic corticosteroids, first used in the 1960s were an important step in applying medical therapies for IH requiring treatment[25,26]. Topical corticosteroids are often used to treat superficial IH in cosmetically sensitive areas such as the face/periorbitally. Intralesional steroids have also played a role in the treatment of nasal tip or mucosal (lip) IH causing aesthetic or other complications. Other topical therapies such as 5% imiquimod cream and timolol gel have recently been reported, however, controlled trials are lacking[27,28].

After decades of use of steroids as a mainstay, a new treatment for IH, alfa-interferon 2a was reported on in 1992[29]. Unfortunately, though initially quite promising, subsequent reports of neurotoxicity, specifically spastic diplegia, led most clinicians to reserve it only for severe morbidity in patients. Alfa-interferon 2b is still used in severe cases. Neurotoxicity may be minimized by using it in older children, ideally over age 1 year, who have not responded to corticosteroids or continue to have late growth as they are being tapered, with close neurologic monitoring is necessary[30].

Vincristine, a vinca alkaloid chemotherapeutic agent has also shown promise as a potential agent in the treatment of life and function threatening IH[31,32]. A randomized clinical trial looking at Vincristine in the management of high risk airway hemangioma is currently underway (see: www.clinicaltrials.gov for more information).

Another medication which holds great promise for treatment is propranolol. Propranolol was serendipitously found to be effective in shrinking infantile hemangiomas by Leaute-Labreze et al in 2009[33]. It has subsequently been used by many pediatric specialists including pediatric dermatologists and otolaryngologists for a variety of problematic hemangiomas including for periocular and airway hemangiomas with impressive results[34,35]. Most reports are at a dose of 2-3mg/kg/day divided twice or three times per day. Rigorous studies are currently lacking, but are planned in the near future.

Quality of Life and Aesthetic Impairment

The past has taught us a great deal about the natural history, biologic activity, complications and treatments of infantile hemangioma. However, it is only recently that clinicians have begun to focus on the dramatic impact of IH on the lives of patients and their parents; specifically, the impact on quality of life. In keeping with an increased understanding that quality of life of both parents and children is an important outcome, physicians have become increasingly aware that even those hemangiomas which do not cause medical morbidities can be problematic to parents. Their rapid growth can cause tremendous parental stress, particularly those located in a "public" site such as the face or hands. Those which leave permanent scarring, even if not life-threatening, can be truly life-altering[36]. Because of this, we must abandon the strategy of blanket reassurance, and rather be proactive in our management, both in providing photographs and information about natural history to help support parents if watchful waiting is the best approach period. In those patients whose hemangiomas are considered high-risk, weighing risks and benefits of a variety of therapeutic modalities and instituting the therapy which seems best for a particular patient. While we do not currently have rigorous evidence-based approaches to management of problematic hemangiomas, we have made progress, particularly in the past decade, and these and future advances hold great promise for the future.

Conflict of interests
Dr. Maguiness has no conflict of interests to declare.
Dr. Frieden has proffessional relationship as a consultant with Pierre Fabre Dermatology.

References

1. Mulliken JB, Glowacki J. Classification of pediatric vascular lesions. Plast Reconstr Surg. 1982;70:120-1.

2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69: 412-22.
3. Berenguer B, Mulliken JB, Enjolras O, Boon LM, Wassef M, Josset P, et al. Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol. 2003;6:495-510.
4. Browning JC, Metry DW. Rapidly involuting congenital hemangioma: case report and review of the literature. Dermatol Online J. 2008;14:11.
5. Krol A, MacArthur CJ. Congenital hemangiomas: rapidly involuting and noninvoluting congenital hemangiomas. Arch Facial Plast Surg. 2005;7:307-11.
6. Enjolras O, Wassef M, Mazoyer E, Frieden IJ, Rieu PN, Drouet L, et al. Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. J Pediatr. 1997;130:631-40.
7. Sarkar M, Mulliken JB, Kozakewich HP, Robertson RL, Burrows PE. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. Plast Reconstr Surg. 1997;100:1377-86.
8. Maronn M, Catrine K, North P, Browning MB, Kerschner JE, Noel R, et al. Expanding the phenotype of multifocal lymphangioendotheliomatosis with thrombocytopenia. Pediatr Blood Cancer. 2009;52:531-4.
9. Nappi O, Wick MR. Disseminated lobular capillary hemangioma (pyogenic granuloma). A clinicopathologic study of two cases. Am J Dermatopathol. 1986;8:379-85.
10. North PE, Waner M, Mizeracki A, Mihm MC Jr. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000;31:11-22.
11. North PE, Waner M, Mizeracki A, Mrak RE, Nicholas R, Kincannon J, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol. 2001;137:559-70.
12. Barnes CM, Christison-Lagay EA, Folkman J. The placenta theory and the origin of infantile hemangioma. Lymphat Res Biol. 2007;5:245-55.
13. Kleinman ME, Greives MR, Churgin SS, Blechman KM, Chang EI, Ceradini DJ, et al. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. Arterioscler Thromb Vasc Biol. 2007;27: 2664-70.
14. Khan ZA, Boscolo E, Picard A, Psutka S, Melero-Martin JM, Bartch TC, et al. Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. J Clin Invest. 2008;118:2592-9.
15. Claesson-Welsh L. Healing Hemangiomas. Nat Med. 2008; 14:1147-816.
16. Jinnin M, Medici D, Park L, Limaye N, Liu Y, Boscolo E, et al. Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. Nat Med. 2008;14:1236-46.
17. Jacobs AH. Strawberry hemangiomas; the natural history of the untreated lesion. Calif Med. 1957;86:8-10.
18. Lister WA. The natural history of strawberry nevi. Lancet. 1938;1429-34.
19. 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;153:712-5, 715.e1.
20. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics. 2006;118:882-7.
21. Chang LC, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, et al. Hemangioma Investigator Group. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics. 2008;122:360-7.
22. Metry DW, Haggstrom AN, Drolet BA, Baselga E, Chamlin S, Garzon M, et al. A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings, and complications. Am J Med Genet A. 2006;140: 975-86.
23. Girard C, Bigorre M, Guillot B, Bessis D. PELVIS syndrome. Arch Dermatol. 2006;142:884-8.
24. Stockman A, Boralevi F, Taïeb A, Léauté-Labrèze C. SACRAL syndrome: spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization. Dermatology. 2007;214: 40-5.
25. Fost NC, Esterly NB. Successful treatment of juvenile hemangiomas with prednisone. J Pediatr. 1968;72:351-7.
26. Edgerton MT. The treatment of hemangiomas: with special reference to the role of steroid therapy. Ann Surg. 1976;183: 517-32.
27. Ho NT, Lansang P, Pope E. Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. J Am Acad Dermatol. 2007;56:63-8.
28. Pope E, Ajith C. Timolol Gel for Infantile Hemangiomas - a Pilot study. Abstract 35. Philadelphia: Society for Pediatric Dermatology; 2009.
29. Ezekowitz RA, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. NEJM. 1992;326:1456-63.
30. Barlow CF, Priebe CJ, Mulliken JB, Barnes PD, Mac Donald D, Folkman J, et al. Spastic diplegia as a complication of interferon Alfa-2a treatment of hemangiomas of infancy. J Pediatr. 1998;132 3 Pt 1:527-30.
31. Enjolras O, Brevière GM, Roger G, Tovi M, Pellegrino B, Varotti E, et al. Vincristine treatment for function- and life-threatening infantile hemangioma. Arch Pediatr. 2004;11: 99-107.
32. Fawcett SL, Grant I, Hall PN, Kelsall AW, Nicholson JC. Vincristine as a treatment for a large haemangioma threatening vital functions. Br Plast Surg. 2004;57:168-71.
33. 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;358:2649-51.
34. Al Dhaybi R, Milet A, McCuaig C, Ospina L, Powell J. Treatment of periocular infantile hemangioma with Propranolol: review of 17 cases. Abstract 36. Philadelphia: Society for Pediatric Dermatology; 2009.
35. Denoyelle F, Leboulanger N, Enjolras O, Harris R, Roger G, Garabedian EN. Role of Propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma. Int J Pediatr Otorhinolaryngol. 2009;73:1168-72.
36. Tanner JL, Dechert MP, Frieden IJ. Growing up with a facial hemangioma: parent and child coping and adaptation. Pediatrics. 1998;101 3 Pt 1:446-52.