Infantile haemangioma

Christine Léauté-Labrèze, John I Harper, Peter H Hoeger

With a prevalence of 4·5%, infantile haemangiomas are the most common benign tumours of infancy, arising in the first few weeks of life and exhibiting a characteristic sequence of growth and spontaneous involution. Most infantile haemangiomas do not require therapy. However, to identify at-risk haemangiomas, close follow-up is crucial in the first weeks of life; 80% of all haemangiomas reach their final size by 3 months of age. The main indications for treatment are life-threatening infantile haemangioma (causing heart failure or respiratory distress), tumours posing functional risks (eg, visual obstruction, amblyopia, or feeding difficulties), ulceration, and severe anatomic distortion, especially on the face. Oral propranolol is now the first-line treatment, which should be administered as early as possible to avoid potential complications. Haemangioma shrinkage is rapidly observed with oral propranolol, but a minimum of 6 months of therapy is recommended.

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Department of Dematology, Pellegrin Children's Hospital, Bordeaux, France (C Léauté-Labrèze MD); **Department of Paediatric Dermatology, Institute of Child Health and Great Ormond Street Hospital, London, UK** (Prof J I Harper MD); **Departments of Paediatrics and Paediatric Dermatology, Catholic Children´s Hospital Wilhelmstift, Hamburg, Germany** (Prof P H Hoeger MD)

Correspondence to: Dr Christine Léauté-Labrèze, Department of Dematology, Pellegrin Children's Hospital, Bordeaux 33076, France **christine.labreze@chu-bordeaux.fr**

Introduction

Infantile haemangiomas are the most common soft-tissue tumours of infancy. They arise in the first few weeks of life, then display a period of active growth followed by spontaneous involution. Most infantile haemangiomas do not require therapy and regress spontaneously; however, about 10–15% result in complications, such as obstruction, ulceration, or disfigurement, and require treatment. This Seminar provides an update on new insights into the pathogenesis and treatment of infantile haemangioma, which has arisen as a result of the discovery that β blockers are an effective treatment. It will cover the different clinical aspects of infantile haemangioma, their possible associated complications, and current approaches to management.

Epidemiology

The prevalence of infantile haemangioma in mature neonates is around 4·5%,[1] with a female (2·3–2·9 times higher) and white predominance. It increases with low birthweight and decreasing gestational age, and is as high as 23% in premature babies smaller than 1000 g birthweight.[2] Additionally, family history of infantile haemangioma, intrauterine complications such as eclampsia, and placental anomalies are also important risk factors.[1]

Pathogenesis

Infantile haemangioma is the result of dysregulation of both vasculogenesis and angiogenesis (figure 1); however, the triggers that initiate development of infantile haemangioma are still a matter of debate. No single hypothesis is sufficient to describe all features of infantile haemangioma. The most likely scenario would involve hypoxic stress as the triggering signal,[3] inducing overexpression of angiogenic factors such as VEGF via the HIFα pathway.[4] In response to VEGF overexpression, stem cells (expressing CD133), naturally present or recruited in fetal skin, proliferate and differentiate into immature endothelial cells (expressing CD31), but also pericytes (expressing SMA), dendritic cells (expressing factor XIIIa), and mesenchymal cells with an adipogenic potential.[5] During the growth phase of infantile haemangioma, endothelial cells predominate, with the formation of syncytial masses without a defined vascular architecture. Later, luminised capillary-like structures are organised with multilaminated basement membranes, involving endothelial cells and pericytes. After 3 years of age, in involuting lesions the lumina become narrower and blood vessels are replaced with a fibrofatty residuum. Throughout their development, endothelial cells in infantile haemangioma express a particular phenotype showing positive staining for glucose transporter (GLUT1), LYVE-1, merosin, and antigen Lewis Y. GLUT1 is also expressed on placental endothelial cells but is absent in other tumours and vascular malformations.[6] During the involution phase, endothelial cells express caspases, which are known markers of apoptosis. There is an increase in the expression of markers of maturation and activation of endothelial cells such as HLA-DR and ICAM1 (also known as CD54)

Additionally, the appearance, non-random distribution, and differences in potential growth of infantile haemangiomas probably result from a complex combination of genetic predisposition, dysregulation of VEGF receptor, and various environmental and local factors, such as abnormal underlying vascularisation and external trauma.

Clinical characteristics

Infantile haemangiomas exhibit a characteristic growth pattern (figure 2); precursor lesions (figure 3) are either present at birth or manifest during the early neonatal period (as a pale area of vasoconstriction or a telangiectatic

Search strategy and selection criteria

We searched PubMed with the term "infantile haemangioma" for articles published in English between Jan 1, 2010, to Dec 31, 2015. We also included highly cited older publications because of their relevance. For the sections on treatment we gave priority to randomised controlled studies, and meta-analyses or large series of patients in the absence of randomised controlled data.

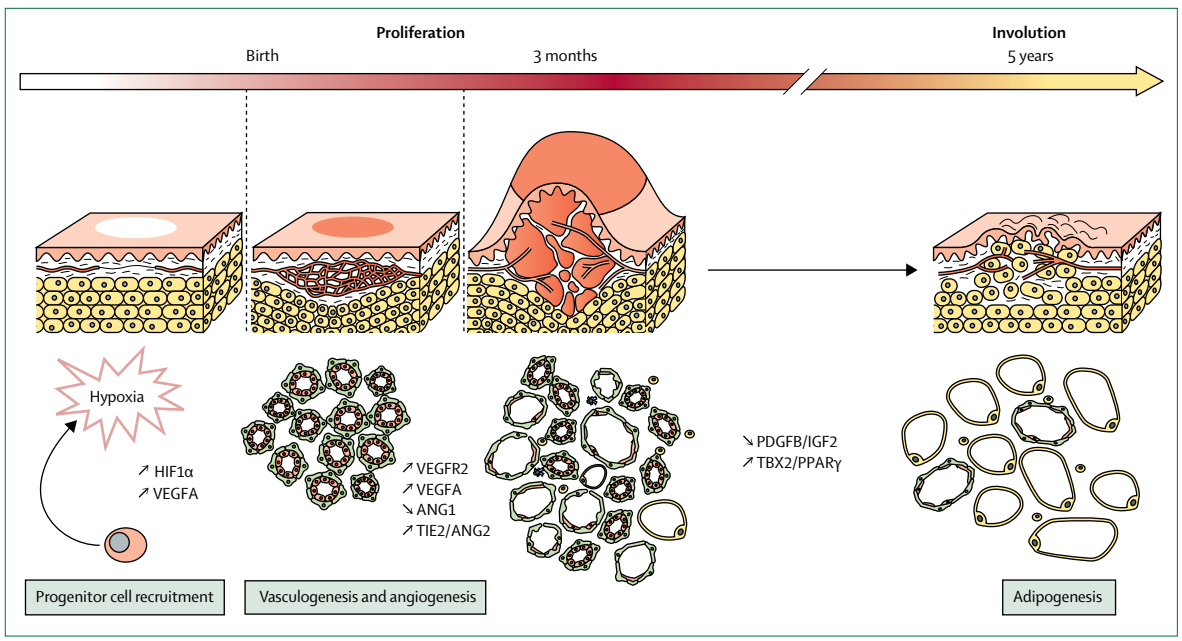

Figure 1: **Natural history of infantile haemangioma**
After birth, the proliferation and differentiation of progenitor cells are induced by angiogenic factors, such as VEGF. The most likely triggering factor is hypoxia responsible for the activation of the HIF1α pathway. During the growth phase, endothelial cells predominate, with the formation of syncytial masses without a defined vascular architecture. Later, luminised capillary-like structures appear with multilaminated basement membranes, involving endothelial cells and pericytes. Then, after 2–3 years of age, the infantile haemangioma involutes, the lumina become narrower, and blood vessels are replaced with a fibrofatty residuum due to the presence of mesenchymal cells with an adipogenic potential. HIFα=hypoxic inducible factor α. VEGF=vascular endothelial growth factor. VEGFR=vascular endothelial growth factor receptor. ANG=angiopoietin. TIE=angiopoietin receptor. PDGF=platelet-derived growth factor. IGF=insulin-like growth factor. TBX=T-box transcription factor. PPAR=peroxisome-proliferator activated receptor.

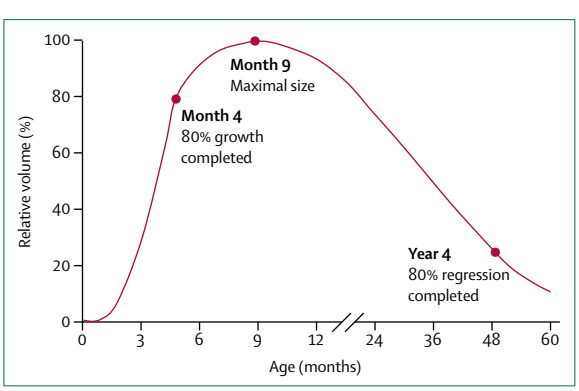

Figure 2: **Characteristic growth behaviour of infantile haemangiomas**

red macule. After a latent period of 1–3 weeks, the haemangiomas typically start to proliferate. Superficial infantile haemangiomas are located in the upper dermis and typically appear as elevated red papules, nodules, or plaques (figure 4). Deep infantile haemangiomas extend to the adipose tissue and can present as bluish tumours, with indistinct borders, as late as 2–3 months after birth. In a subset of patients, infantile haemangiomas exhibit only minimal or arrested growth;[7] these tumours are preferentially located on the lower extremities and can be confused with port wine stains.

The natural course of infantile haemangioma is similar for both full-term and premature babies; the growth is not linear, usually rapid during the first 3 months, especially between 5 and 8 weeks of life,[8] and about 80% of their absolute growth is completed by the age of 3 months.[9] Segmental infantile haemangioma and infantile haemangioma with a deep component can continue to grow until the 9th or 12th month of life, and in rare cases up to 24 months.[10] Usually a period of relative stabilisation is observed, followed by spontaneous regression over several months or years. Phases of growth and regression can overlap, and a pallor of the superficial component of the infantile haemangioma can be noted while the deep component still continues to grow. Regression is complete in 90% of cases by age 4 years,[11] although for deeper lesions it may be slower and continue to age 7 or 8 years. Without any treatment, residual consequences occur in 70% of cases,[11] namely telangiectasia (figure 5), excessive fibrofatty tissue (figure 6), and skin laxity due to the destruction of elastic tissue. Up to 12% of infantile haemangioma cases referred to paediatric centres are reported to be complex and prone to complications.[12] The type and extent of complications depend on localisation and size of the haemangioma, as well as the age of the infant. Previously ulcerated lesions usually leave scars.

Complications

Obstruction and functional impairment

Visual obstruction usually manifests during the early proliferation phase (ie, within the first 2–3 months of

life). Haemangiomas located on the eyelid or close to the eye can lead to permanent amblyopia, astigmatism, or strabismus (figure 7). Additional potential complications include proptosis, poor eyelid closure, and optic nerve injury.[13] Obstruction of the nostrils or auditory channel is less commonly observed. Paraglottic or intratracheal infantile haemangioma, often heralded by haemangiomas around the so-called beard area, can cause life-threatening upper airway obstruction.[14] Large infantile haemangioma of the neck can cause positional torticollis.

Ulceration

Ulceration, associated with pain and discomfort, is one of the most common complications of infantile haemangioma, occurring in 10 and 25% of patients presenting at referral centres.[12,15] It is most commonly observed between the 4th and 8th months of life. Early white discolouration at the margins of an infantile haemangioma is an early sign of impending ulceration.[15] Size, location, and type are determinants for ulceration,[16,17] with large, superficial, and segmental haemangiomas substantially more likely to ulcerate.[16] Predilection areas for ulceration are the lip, the head and neck area, and the intertriginous regions (figure 7). Constant exposure to moisture and maceration seem to promote ulceration.[15,17] In a prospective study, 50% of infantile haemangiomas located in the nappy area and 30% of those on the lower lip ulcerated.[15]

Disfigurement

Disfigurement is an issue with infantile haemangioma located in the centrofacial or parotid area, and large haemangiomas affecting the chest area in girls. Nose (figure 7) and lip haemangiomas frequently exhibit incomplete spontaneous regression. Subcutaneous haemangiomas around the parotid area are often large and tend to persist longer than other types.

Multifocal infantile haemangioma

The appearance of multiple small infantile haemangiomas (defined as either more than five[18] or at least ten[19] tumours) is formerly referred to either as benign or as diffuse neonatal haemangiomatosis, depending on whether or not there is visceral (typically hepatic) involvement (figure 8). Hepatic haemangiomas can be focal (27% of cases), multifocal (57%), or diffuse (16%).[20,21] Focal, solitary hepatic haemangiomas occur most often without cutaneous involvement; they are usually rapidly involuting congenital haemangiomas and tend to resolve rapidly within months. Multifocal and diffuse hepatic haemangiomas are classic infantile haemangiomas (positive staining for GLUT1), and are associated with cutaneous infantile haemangioma in 77% of multifocal cases and 55% of diffuse cases.[21] Hypothyroidism due to the expression of iodothyronine deiodinase[22] was found in all children with diffuse and 21% of those with multifocal infantile haemangioma.[21]

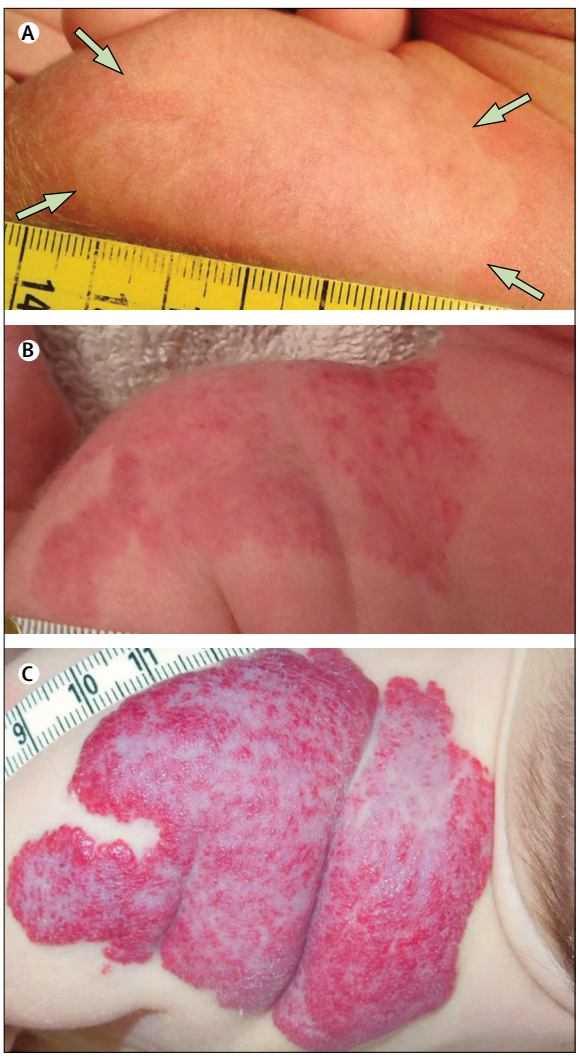

Figure 3: **Precursor lesions**
Figure shows a sharply demarcated, so-called anaemic spot on the left shoulder. (A) Day 3. (B) Day 21. (C) Day 90.

Children with diffuse hepatic infantile haemangioma (as well as those with large cutaneous infantile haemangioma) are at increased risk of developing high-output cardiac failure.[23] The high mortality rate previously reported in children with diffuse hepatic haemangiomas is probably attributable to a separate entity named multifocal lymphangioendotheliomatosis with thrombocytopenia.[24]

Segmental infantile haemangioma

Segmental infantile haemangioma of the face and the lumbosacral regions can be associated with various malformations. Large (>5 cm) facial infantile haemangiomas (figure 8) can be associated with various anomalies, which are summarised within the acronym PHACE(S): posterior fossa malformations; haemangiomas; arterial, cardiac, and eye anomalies; and

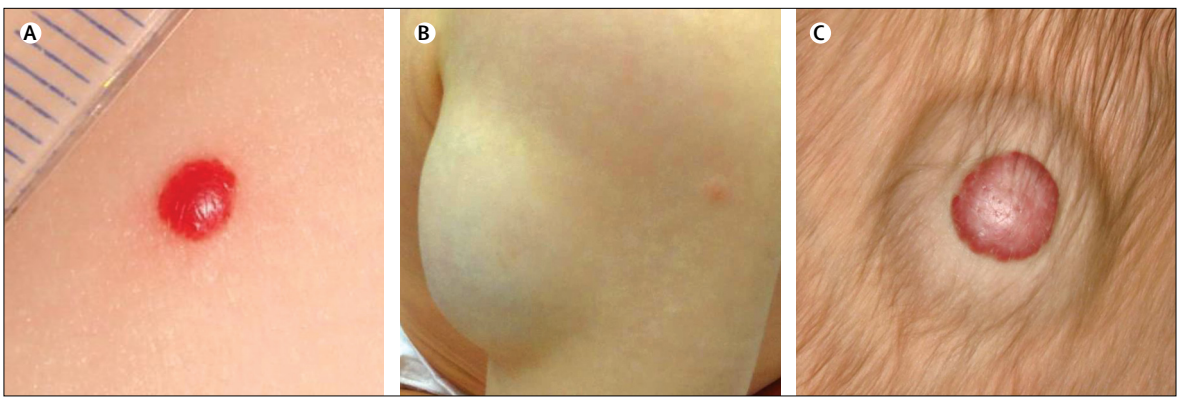

Figure 4: **Types of infantile haemangiomas according to anatomical location**
(A) Bright red, intracutaneous haemangioma. (B) Bluish, deep haemangioma. (C) Mixed type.

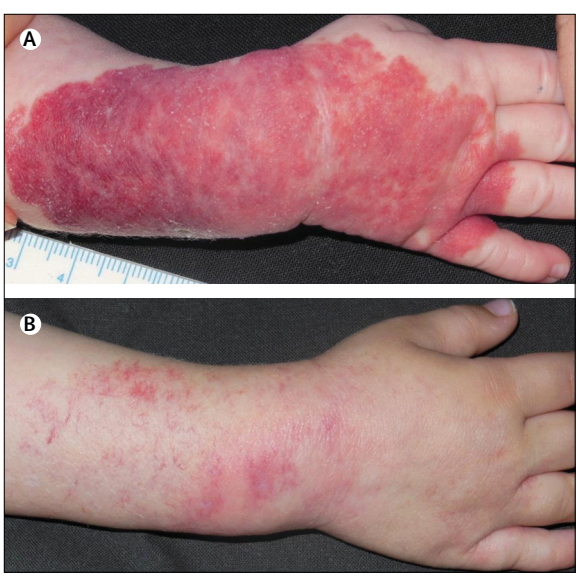

Figure 5: **Spontaneous regression**
(A) Haemangioma on right lower arm, age 14 weeks. (B) Residual telangiectasia at age 23 months.

sternal or umbilical raphe.[25] Although up to 30% of children with a large facial infantile haemangioma, particularly in the frontotemporal or mandibular segment, are affected by the PHACE syndrome, variants of the syndrome without facial infantile haemangioma (but with segmental infantile haemangioma on the upper torso or upper extremities) have been described.[26] The most common extracutaneous manifestations in PHACE are arterial anomalies (aplasia, anomalous origin or course, stenosis) of cerebral vessels, followed by anomalies of the aortic arch (aberrant subclavian artery, coarctation).[27,28] Several cases of arterial ischaemic stroke have been reported in children with PHACE.[29] Midline infantile haemangioma in the lumbosacral or perineal region, previously summarised under different acronyms (eg, PELVIS,[30] SACRAL,[31] or LUMBAR[32]), can be associated with urogenital (hypospadias, bladder extrophy, renal anomalies), anorectal (imperforate anus), and vascular anomalies (persistent sciatic artery, hypoplastic ileofemoral artery), as well as spinal defects (tethered cord, spinal dysraphism, lipomeningocele, diastematomyelia, anomalies of the os sacrum, scoliosis).

Diagnosis and assessment

Infantile haemangiomas are usually diagnosed clinically. Imaging studies and other investigations are required in the special situations listed in the table. Ideally, a patient with infantile haemangioma who is at risk of complications should be referred to a multidisciplinary team for evaluation and for specific diagnostic measures (eg, MRI, screening for hypothyroidism, or coagulation abnormalities) and initiation of specific treatment.

Several scores have been established to assess severity, particularly of complications (eg, the Hemangioma Severity Scale, the Hemangioma Dynamic Complication Scale), and are helpful in clinical studies. These scores have been evaluated for inter-rater and intra-rater reliability.[33] The Haemangioma Activity Score (HAS) assesses the proliferative activity of infantile haemangioma.[34,35]

Differential diagnoses

Vascular anomalies

Vascular anomalies are classically divided into vascular tumours and vascular malformations (panel 1), and both can resemble infantile haemangioma. Usually a vascular malformation (such as a port-wine stain or lymphatic malformation) is present at birth, does not grow (or grows very slowly over several years), and does not regress spontaneously. By contrast, a vascular tumour might or might not be present at birth, has a tendency to grow, and for infantile haemangioma has the ability to regress spontaneously.[36,37] In cases of an enlarging tumour in an infant, if the diagnosis of infantile haemangioma is not clinically obvious, a biopsy should be done and no treatment should be instituted without a definitive diagnosis.

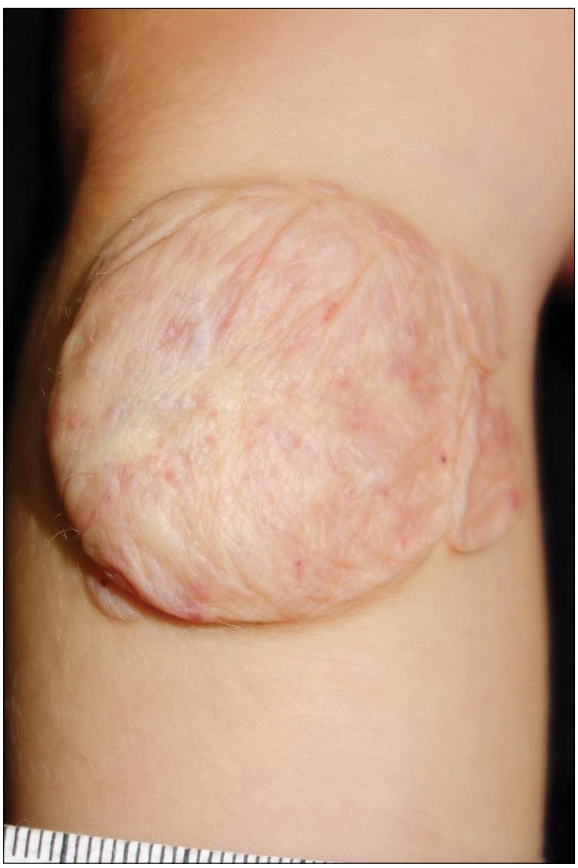

Figure 6: **Haemangioma residuum**
Fibrofattty haemangioma residuum on the arm of a 4-year-old child.

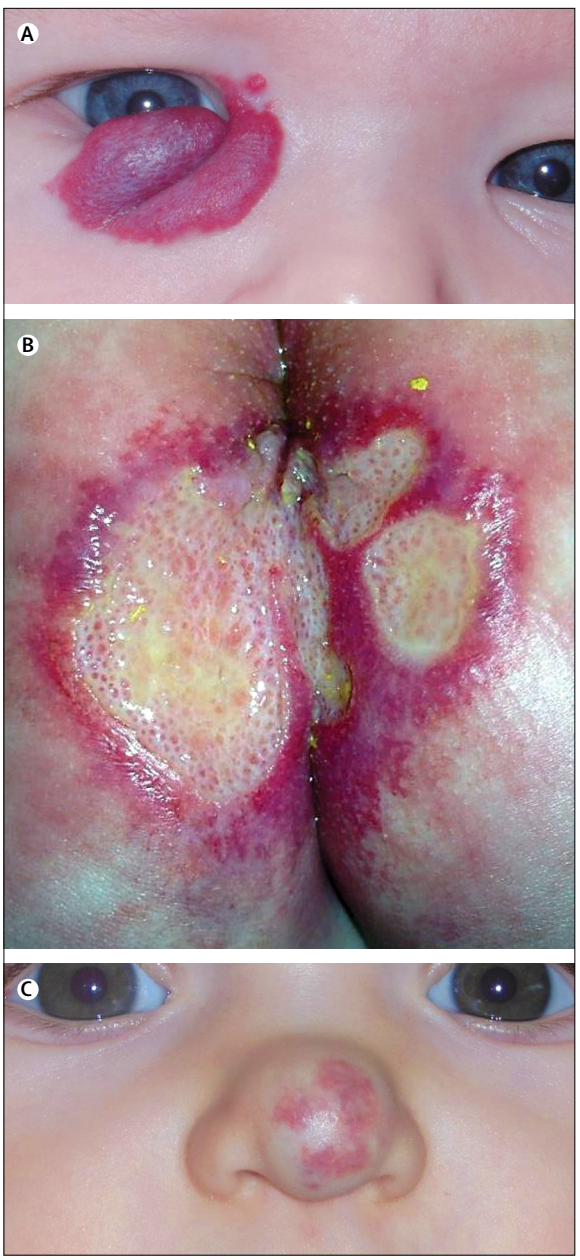

Figure 7: **Complications of infantile haemangiomas**
(A) Visual obstruction. (B) Ulceration. (C) Disfiguring facial haemangioma (so-called cyrano-nose).

Congenital haemangioma: rapidly involuting (RICH), partially involuting (PICH), or non-involuting (NICH)

Congenital haemangiomas resemble classic infantile haemangioma, but they are clearly different entities; although they also manifest at birth, congenital haemangiomas are negative for GLUT1, the immunohistological hallmark of infantile haemangioma. RICH are at or beyond their maximum size at birth and can be complicated by high-output cardiac failure and transient thrombocytopenia. Clinical signs of regression appear early (figure 9) and regression is usually complete within a year, often leaving behind an area of clinically significant lipoatrophy. By contrast, NICH persist without any sign of regression. The regression process of rapidly involuting haemangiomas can stop at any time, suggesting transformation into the PICH or NICH type.[38] Treatment is only required in case of persistence, for cosmetic reasons. These entities are rare.

Pyogenic granuloma

With an estimated prevalence of 0·5–1%, pyogenic granuloma is a common acquired vascular tumour. About 12% of all cases present in infants, but rarely before age 4 months.[39] After minor trauma (eg, insect bites, scratches), these exophytic, vascular papules with a diameter between 1 and 10 mm (figure 9) erupt, preferentially on the face and neck, and tend to bleed easily. They are characterised histologically by lobulated proliferation of capillaries and a neutrophilic infiltrate.[36,39] Pedunculated lesions can be ligated, but others are best treated surgically either by curettage and electrodesiccation or excision.

Kaposiform haemangioendothelioma

Kaposiform haemangioendothelioma is a fairly rare vascular tumour (prevalence of 0·9 cases per 100 000 population) which usually manifests within the

first 2 years of life; 60% of cases present during the neonatal period.[40] The lesions are either superficial plaques exhibiting local infiltration, or deep-seated bulky Vmasses (figure 9), often associated with purpura or ecchymoses. In 25% of cases, the lesions are confined to large body cavities or the retroperitoneum. Kaposiform haemangioendothelioma is associated with substantial thrombocytopenia caused by a disseminated coagulopathy, termed Kasabach-Merritt phenomenon. Vincristine is the first-line therapy, and although some reports suggest that this tumour is responsive to therapy with sirolimus, prospective studies have yet to be done.[41]

Therapy

Indications and timing

Because most infantile haemangiomas tend to regress spontaneously, treatment is only required for complicated cases. Indications for treatment include life-threatening infantile haemangioma (obstructive subglottic tumours, compression of neural structures, bleeding gastrointestinal tumours, large haemangiomas causing cardiac insufficiency or hepatic dysfunction), infantile haemangioma causing functional impairment (periocular haemangiomas causing [imminent] amblyopia, obstructive tumours of the nose or the external auditory channel, ulcerated infantile haemangioma), and infantile haemangioma likely to cause disfigurement (large facial tumours, particularly those involving the nose, lips, and preauricular regions, and large infantile haemangioma in the perimammary region in girls).[42]

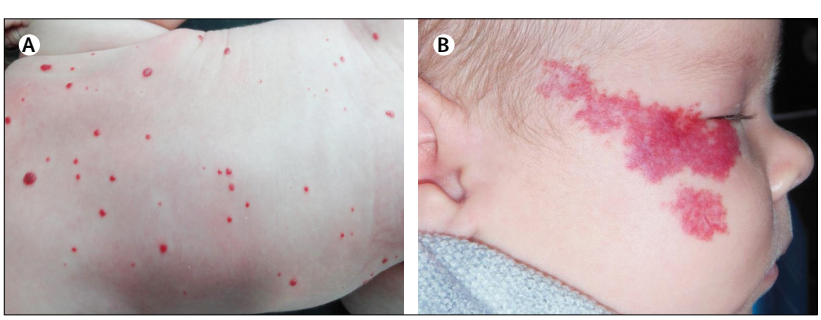

Figure 8: **Multifocal infantile haemangioma or haemangiomatosis (A) and segmental facial haemangiomas (B)**

Infantile haemangioma with manifest obstruction or ulceration obviously requires immediate therapy. Small infantile haemangiomas in critical areas (eg, periocular, anogenital) can frequently be handled by active non-intervention or watchful waiting—ie, close monitoring in intervals adapted to the growth velocity of infantile haemangioma, aided by sequential photographic documentation, with treatment intervention only if necessary.

The aims of therapy depend on the stage of the infantile haemangioma. In the proliferative phase, therapy is directed at the induction of growth arrest and remission. After incomplete regression, excessive fibrofatty tissue and scars can raise cosmetic concerns that need to be addressed.

Systemic treatment options

Propranolol

Within a few years of the serendipitous discovery of a new application for this old drug,[43] oral propranolol has become the treatment of choice for complicated infantile haemangioma (panel 2). As shown by findings of a randomised controlled trial,[44] a large cohort study,[45] and a meta-analysis of 1264 reported cases,[46] the response rate of oral propranolol at a dose of 2–3 mg/kg per day and after a mean of 6 months of therapy is 96–98%, with complete or nearly complete regression in 60% of cases. Propranolol has been shown to be effective for obstructive, life-threatening airway infantile haemangioma[47] and for ulcerated infantile haemangioma.[48] Its exact mechanisms of action are incompletely understood so far, but propranolol could regulate haemangioma cell proliferation via cathecholamines or the VEGF pathway.[49] Recurrence after discontinuation of therapy occurs in 10–15% of cases.[50] Recurrence is more common in segmental and deep infantile haemangioma,[51] and can probably be reduced by longer treatment in at-risk infants (age ≥12 months). Side-effects are reversible and mostly benign. The most common (20–25%) are sleep disorders, somnolence, and irritability. Others (>1%) include bronchospasm or bronchiolitis and asymptomatic hypotension. Rare but potentially serious side-effects include bradycardia, exposure of an undiagnosed atrioventricular block, and hypoglycaemia. Temporary discontinuation of oral propranolol therapy is

	Indication	Purpose
Ultrasound or doppler	Deep infantile haemangioma; multifocal or hepatic infantile haemangioma; segmental infantile haemangioma; midline infantile haemangioma of the lumbosacral area; differential diagnosis of vascular anomalies	Evaluate depth and size of infantile haemangioma; in intrahepatic infantile haemangioma, evaluate number and size of intrahepatic tumours and rule out renal and urogenital anomalies; rule out occult spinal dysraphism
Echocardiography	Large or multifocal infantile haemangioma; PHACE syndrome; lumbosacral infantile haemangioma	Rule out cardiac insufficiency, cardiac or aortic anomaly
MRI/MRA	Segmental infantile haemangioma	Rule out intracranial, cerebrovascular, or spinal anomalies
Ophthalmological consultation	Periorbital infantile haemangioma; PHACE syndrome	Rule out amblyopia or associated anomalies
Coagulation screening	Multifocal intrahepatic infantile haemangioma	Rule out DIC (platelets, fibrinogen, D-dimers) in MLT
TSH screening	Large or multifocal infantile haemangioma	Rule out secondary hypothyroidism

MRA=magnetic resonance angiography. DIC=disseminated intravascular coagulation. MLT=multifocal lymphangioendotheliomatosis with thrombocytopenia.

Table: **Indications for diagnostic procedures in infantile haemangioma**

recommended in cases of poor oral feeding, diarrhoea, and obstructive bronchitis. Because propranolol is a highly lipophilic β blocker and thus capable of crossing the blood–brain barrier, there are theoretical concerns regarding potentially relevant neurodevelopmental or cognitive side-effects of propranolol.[52]

Other β blockers

In small, non-controlled studies, nadolol,[53,54] atenolol,[55,56] and acebutolol[57] have been shown to be effective for the treatment of infantile haemangioma. Unlike propranolol, they are hydrophilic and do not cross the blood–brain barrier; they could therefore theoretically be associated with a lower risk of CNS side-effects (eg, disturbed sleep), bronchospasm, and hypoglycaemia. Additionally, atenolol is a β1-selective β blocker that acts neither on pulmonary nor pancreatic β2 receptors.[56] However, little data for either the efficacy or the safety of these drugs compared with propranolol is available.

Obsolete therapies

For decades, corticosteroids were the mainstay of therapy for proliferating, obstructive infantile haemangioma.[58] Findings from both retrospective[59] and prospective[60,61] studies comparing oral prednisolone with propranolol therapy suggest that prednisolone is less effective than propranolol and is associated with significantly more adverse events.[61] Interferon[62] and vincristine should be abandoned as treatments for infantile haemangioma due to their serious side-effects and the efficacy of propranolol.

Local treatment options

Topical or intralesional injections

Local injections of bleomycin or other antimitotic agents should be avoided in young children. These procedures are invasive and can cause severe systemic and local side-effects. However, proliferating infantile haemangioma can show some response to ultrapotent topical corticosteroids, particularly if the lesions are thin,[63] but there is concern about skin atrophy. The same holds true for intralesional triamcinolone injection,[64] which is painful and carries the additional risks of adrenal suppression and accidental embolisation.

Topical β blockers

Although efficacy and safety of topical timolol or propranolol has been claimed in several uncontrolled case reports and case series, so far only one randomised controlled trial comparing timolol (15 patients) with placebo (17 patients) has been reported.[65] No standardised preparation of topical β blocker for use in infantile haemangioma is available. There is concern about transcutaneous or transconjuctival resorption, which could lead to unforeseen systemic side-effects resulting from the first-pass effect (due to bypass of hepatic detoxification).[66] If safety and efficacy are confirmed, topical β blockers have the potential to become the first-line agent for the treatment of small and superficial infantile haemangiomas located in problematic regions such as eyelids or genital areas, thus obviating systemic treatment in this group of patients.

Imiquimod

Imiquimod is a topical antiangiogenic agent which has been shown to be moderately effective against superficial infantile haemangioma.[67] However, although apparently equally effective as timolol gel,[68] it is less well tolerated because of its high rate of skin irritation and risk of ulceration

Laser and surgical therapy

Laser

Although it is still widely propagated for infantile haemangioma, treatment with pulsed dye laser (wavelength 595 nm) is no better than spontaneous regression, as evidenced by a large prospective randomised controlled trial.[69] In the pre-propranolol era, pulsed dye laser was reported to have some efficacy in the treatment of superficial and ulcerated infantile haemangiomas.[70] In a small prospective study comparing pulsed dye laser or cryosurgery with oral propranolol, significantly more rapid involution was seen with propranolol.[71] Although propranolol is now the treatment of choice for proliferating or ulcerated infantile haemangioma, pulsed dye laser still plays a major part in the treatment of residual lesions (eg, erythematous patches and telangiectases).[72] Likewise, the previously established treatment of life-threatening airway haemangiomas with CO_2 laser or neodymium-doped yttrium aluminium garnet laser has now largely been replaced by oral propranolol therapy.[47]

Panel 1: **Main differential diagnoses of IH**

Present at or soon after birth

- Vascular tumour or anomaly
- Congenital haemangioma: rapidly, partially, or non-involuting type
- Kaposiform haemangioendothelioma or tufted angioma
- Capillary malformation (port-wine stain)
- Macrocystic lymphatic malformation
- Venous anomaly
- Others: myofibromatosis, dermoid cyst, teratoma, sarcoma (fibrosarcoma), neuroblastoma, leukaemia (so-called blueberry muffin baby)

Developed after birth

- Vascular tumour or anomaly
- Pyogenic granuloma
- Macrocystic lymphatic malformation
- Glomuvenous and venous anomalies
- Kaposiform haemangioendothelioma
- Malignant tumours (sarcoma, lymphoma, cutaneous localisation of neuroblastoma, or leukaemia)
- Others: haematoma, benign tumours (pilomatrixoma, Spitz naevus, myofibromatosis, neurofibroma, eosinophilic granuloma, myxoma, lipoblastoma, siloblastoma)

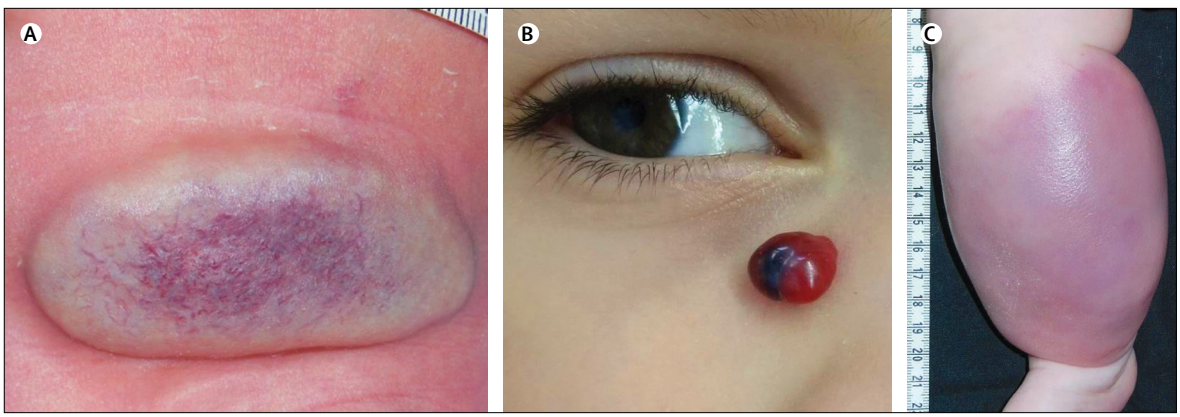

Figure 9: **Rapidly involuting congenital haemangioma (A), pyogenic granulma (B), and kaposiform haemangioendothelioma (C)**

Panel 2: **Oral propranolol in practice**

Previous therapy

- Search for contraindication: careful questioning and clinical examination
- Routine echocardiography and electrocardiogram (ECG) are not necessary if basic cardiology examination is normal
- ECG and cardiology visit required in case of bradycardia and/or arrhythmia at auscultation

Initiation and monitoring

- Treatment should be initiated only in clinical settings equipped and qualified for the safe and immediate management of any adverse event (bradycardia)
- Initiate as inpatient when corrected age younger than 2 months, weight less than 2000 g, infant with inadequate social support, or comorbidity affecting the cardiovascular or respiratory system or blood glucose maintenance
- Initial dose of 1 mg/kg per day in two divided doses* in the first week, then increase to 2–3 mg/kg per day the following weeks
- Monitoring for 2 h after the first intake and at each dose increase
- Maintain 2–3 mg/kg per day in two divided doses* for 6 months
- Monitor children monthly with clinical evaluation and pictures
- Tapering not necessary at end of treatment
- Parents should be informed of the risk of relapse (10–15% of cases)

Expected side-effects

- At each visit, parents should be educated concerning the risk of hypoglycaemia, and respiratory symptoms (wheezing)
- To avoid hypoglycaemia, be sure that the infant feeds regularly
- In case of poor food intake or wheezing, stop propranolol temporarily
- Do not alter dosing for minor side-effects such as cold hands and asymptomatic low diastolic blood pressure; to minimise nightmares, avoid giving the treatment after 1700 h, or reduce dose

*Three divided doses are recommended for children with PHACE syndrome. Recommendations taken from the European Expert Consensus.[42]

Surgery

Surgical treatment includes early and late interventions with different indications and outcomes. Early surgical removal of an obstructive infantile haemangioma (eg, in the periorbital area) is still an option[73] for special cases, particularly in the presence of contraindications to propranolol (ie, asthma or congenital heart block). Surgical intervention has the advantage of a rapid, permanent solution, but carries the disadvantages of requiring general anaesthesia and leaving a permanent scar. Late surgery after regression of infantile haemangioma could be necessary alone or in combination with a vascular laser to repair cutaneous sequelae (atrophic wrinkling, discolouration, redundant skin fibrofatty residual tissue) and sometimes anatomical distortions.

Conclusions

Despite the lack of satisfactory experimental models, knowledge of infantile haemangioma has made tremendous progress during the past decade. Risk factors are better identified, understanding of the pathophysiology has improved, and a wide variety of clinical presentations has been described. Additionally, the recognition that β blockers are an effective treatment for infantile haemangioma has opened up a new therapeutic area and given rise to research in the field of vascular biology. Propranolol has been approved by both the European Medicines Agency and the US Food and Drug Administration to treat complicated infantile haemangioma. Its efficacy has been clearly shown and it is well tolerated by most infants with few side-effects; long-term follow-up studies are planned to assess its safety with regard to neurodevelopment.

For the future, more education and research in this field are paramount. Early detection of at-risk infantile haemangioma is a major point, requiring an increased awareness by paediatricians, general practitioners, and health visitors to identify potentially problematic infantile haemangiomas within the first 2–3 weeks of life, so that they can be treated while in the early stage of proliferation.

Contributors

CL-L did the literature search, wrote sections on epidemiology, pathogenesis, differential diagnosis, and treatment, and prepared the figures, table, and panels. PHH did the literature search, wrote sections on clinical characteristics, differential diagnosis, and treatment, and prepared figures, table, and panels. JIH did the literature search,

overviewed all of the text, and wrote the introduction and conclusions. All authors contributed equally.

Declaration of interests

CL-L, PHH, and JIH have participated in expert panel meetings sponsored by Pierre Fabre Dermatologie. CL-L reports applying for a patent for the use of β-blockers in infantile capillary hemangiomas.

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