Infantile haemangioma: their presentation and management

Haemangiomas are the commonest type of vascular tumour in infancy. This article summarizes the pathophysiology and classification of the subtypes as early identification of high-risk lesions is essential for consideration of treatment to prevent short- and long-term complications from the condition.

Haemangiomas are the commonest type of vascular tumour in infancy (Restrepo et al, 2011). The classification of congenital vascular tumours and vascular malformations was first described by Mulliken and Glowacki (1982) based on endothelial characteristics and structural malformations. This classification has since been expanded by the International Society for The Study of Vascular Anomalies based on their clinical appearances, biological behaviour, radiological, pathological and haemodynamic features (Dasgupta and Fishman, 2014). Understanding the classification of vascular anomalies is essential as they differ in clinical and pathological behaviour and management (George et al, 2014).

Classification of vascular birthmarks

Haemangiomas occur as a result of endothelial hyperplasia and should be differentiated from vascular malformations which are localized defects of vascular morphogenesis secondary to dysfunctional embryogenesis and vasculogenesis (George et al, 2014) (*Table 1*). Haemangiomas are the most common benign vascular tumour of infancy and childhood with a prevalence of 12% in all newborns. They are more common in girls, caucasian families and multiple pregnancies, and are usually born to mothers of higher maternal age (Mulliken and Glowacki, 1982; Restrepo et al, 2011; George et al, 2014). Vascular tumours usually regress or persist depending on subtypes, whereas vascular malformations never regress and persist throughout life. Haemangiomas are grouped into infantile haemangioma and congenital haemangioma. A diagnostic algorithm is shown in *Figure 1*.

Infantile haemangioma

Infantile haemangioma affects up to 10% of children with a female:male ratio of 3:1. Potential predisposing factors include prematurity and low birth weight, where the incidence of infantile haemangioma increases with decreasing gestational age, from 1–4% in term infants to 23% in those of <1000 g birthweight (Goelz and Poets, 2015). It is characterized by a triphasic evolution with initial rapid growth (proliferative phase), followed by a plateau period (plateau phase), and then a slow spontaneous involution (involution phase) (Frieden et al, 2005). Infantile haem-

Table 1. Classification of vascular abnormalities according to the International Society for The Study of Vascular Anomalies

Vascular tumours	Infantile haemangioma	
	Congenital haemangioma	Rapidly involuting congenital haemangioma
		Non-involuting congenital haemangioma
	Tufted angioma	
	Kaposiform haemangioendothelioma	
	Haemangiopericytoma	
	Pyogenic granuloma	
	Spindle cell haemangioendothelioma	
	Others	
Vascular malformations	Low flow vascular malformations	Capillary malformations
		Port-wine stain
		Telangiectasia
		Angiokeratoma
	Venous malformations	Sporadic common venous malformation
		Glomangioma
		Familial cutaneous mucosal venous malformation
		Marfucci syndrome
	Lymphatic malformations	
	High flow vascular malformations	Arterial malformations
		Arteriovenous malformations
		Arteriovenous fistula
	Complex combined vascular malformations	Capillary venous malformations
		Capillary arteriovenous malformations

From Dasgupta and Fishman (2014)

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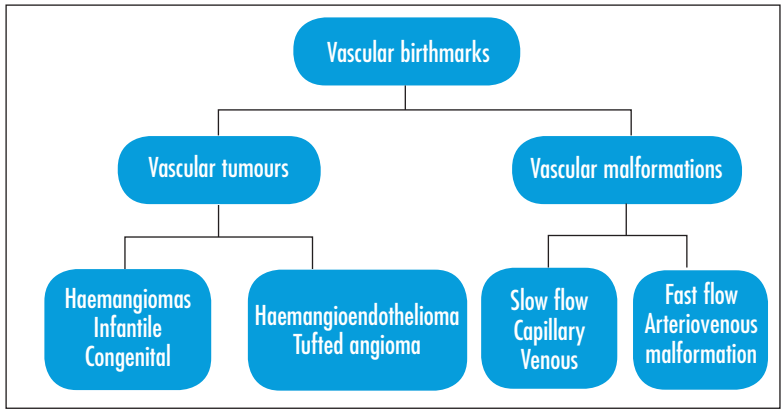

Figure 1. Diagnostic algorithm for vascular birthmarks.

angioma is usually not present at birth, but can present as an area of pallor, discolouration or telangiectasia. It exhibits a rapid proliferative phase in the first 6–12 months of life, followed by a gradual involution and usually spontaneous resolution by 5–9 years of age (*Figure 2*). Around 50% of all infantile haemangiomas will completely involute by the age of 5 years, while 90% will involute by 9 years of age (George et al, 2014). Approximately 15–30% of patients with infantile haemangioma have multiple lesions (Restrepo et al, 2011) with more than 60% of infantile haemangioma occur on the face, head and neck region (Goelz and Poets, 2015). Infantile haemangiomas are the only vascular tumour with positivity for a marker called glucose transporter isoform-1 (GLUT-1), independent of its evolutionary phase (Restrepo et al, 2011).

Figure 2. Haemangioma on the arm showing areas of pallor indicating that it is starting to resolve.

Figure 3. Haemangioma which could affect vision if it grows large. This is suitable for treatment with topical timolol.

Infantile haemangioma can be further classified into focal, segmental and intermediate infantile haemangioma depending on the distribution of the lesions or superficial, deep or mixed depending on the depth of the lesion from the skin surface (George et al, 2014). Occasionally, infantile haemangioma may affect the subcutaneous tissues only without affecting the skin surface, presenting as a bluish discolouration without disrupting the overlying skin.

Although infantile haemangioma is a benign growth, thorough clinical assessment is essential to guide management. Involvement of critical areas such as the eyelids (*Figure 3*), nasal tips, lips (*Figure 4*) and ears (*Figure 5*) may endanger eyesight, breathing, feeding, speech and developmental milestones. It also has the potential risk of resulting in irreversible disfigurement with significant psychosocial

Figure 4. Haemangioma seen in the upper lip of an infant.

Figure 5. Supra-auricular haemangioma. This needs monitoring as some displacement of the ear is occurring.

complications. Bleeding, ulceration and infection can also occur in up to 20% of cases (Chamlin et al, 2007). It is therefore crucial to identify critical lesions and provide treatment appropriately to prevent and minimize short- and long-term complications. Important details to ask when taking a history are shown in *Table 2* and anatomical sites with increased risk of morbidity in *Table 3*.

PHACE(S) syndrome

PHACE(S) syndrome is a neurocutaneous syndrome associated with large segmental haemangiomas on the face with one or more of the abnormalities shown in *Table 4* (Metry et al, 2006). A prospective study in 25 patients with PHACE syndrome revealed that 20% of infants with segmental facial haemangiomas had PHACE syndrome (Metry et al, 2006). There is also a higher risk of PHACE in female infants (Metry et al, 2006). All infants with large facial haemangiomas should be thoroughly assessed for PHACE – work up may include magnetic resonance imaging scans of the head and neck region as well as cardiac imaging, including of the aortic arch.

Lumbosacral and perineal haemangiomas

PELVIS syndrome is a rare association of lumbosacral and perineal haemangiomas with underlying abnormalities as outlined below.

- Perineal haemangioma
- External genital malformations
- Lipomyelomeningocele
- Vesicorenal abnormalities
- Imperforate anus
- Skin tag.

A prospective study revealed that infants and children with midline lumbosacral infantile haemangiomas are at increased risk of spinal anomalies, found in 35% (Drolet et al, 2010; De Graaf et al, 2012). Screening magnetic resonance imaging is advised in all such cases. LUMBAR syndrome is rare and is associated with segmental haemangioma in the lumbar and perineal region. SACRAL and PELVIS are alternative acronyms for LUMBAR syndrome (Johnson and Smidt, 2014).

Multifocal haemangiomas and visceral haemangiomatosis

Approximately 15% of infants will have more than one haemangioma. The most common sites for visceral involvement include the liver (43%), gastrointestinal (34%), brain (34%), mediastinum (19%) and lungs (15%) (Metry et al, 2004). Occasionally, congestive cardiac failure (as a result of high volume cardiac shunting) may complicate multifocal cutaneous haemangiomas on the skin (Metry et al, 2004). In diffuse eruptive neonatal haemangiomatosis with more than 10, usually small haemangiomas, a liver ultrasound scan should be arranged without delay to check for this complication. Thyroid function tests (thyroxine and thyroid-stimulating hormone) should also be performed. If an infantile hepatic haemangioma is present it is common to have secondary hypothyroidism because there is an increase in levels of type 3 iodothyronine deiodinase secreted by the haemangioma (Huang et al, 2000).

Table 2. Important clinical details from history

Birth history	Was the child premature?
	Multiple gestational birth?
	Any pregnancy or delivery complications?
Past medical history	Is the child feeding well?
	Is the child gaining weight well?
	Any hospitalizations or illness?
History of birthmark	Was it visible at birth?
	How has it changed since birth (evolution of lesion)?
	Photographs?
Complications	Bleeding
	Ulceration
	Recurrent infections
	How has the lesion affected the child?
Previous treatment	Duration?
	Efficacy
Family history	Family history of haemangiomas or other vascular birthmarks?

Table 3. Features of infantile haemangioma with risks of morbidity according to anatomical location

Anatomical location	Risks
Facial, large segmental Large facial lesions with prominent dermal component	PHACE Permanent disfiguring
Nasal tips	Breathing difficulties
Periorbital and retrobulbar	Occlusion of sight, astigmatism, amblyopia, tear duct occlusion
Perioral	Feeding difficulties, speech, developmental delay
Segmental chin, central neck	Airway obstruction
Segmental overlying lumbosacral	Tethered spinal cord, genitourinary anomalies
Multiple haemangiomas	Visceral involvement (liver, gastrointestinal tract)

Table 4. Clinical features of PHACE(S) syndrome

P	Posterior fossa brain malformations
H	Segmental cervico-facial Haemangioma
A	Arterial anomalies
C	Cardiac defects or Coarctation of the aorta
E	Eye abnormalities
S	Sternal defects

Congenital haemangioma

Congenital haemangiomas are rare, and differ from infantile haemangiomas in their clinical features, clinical behaviours, histopathology and immunohistological staining (Maguiness et al, 2015). Two types have been described in the literature: rapidly involuting congenital haemangioma and non-involuting congenital haemangioma (Restrepo et al, 2011; Maguiness et al, 2015). Unlike infantile haemangioma, congenital haemangioma is usually fully developed at birth. A rapidly involuting congenital haemangioma is characterized by spontaneous and complete resolution of the lesion soon after birth, usually within the first 14 months of life. If the lesions do not involute, or grow proportionate to the child's growth, they are classified as non-involuting congenital haemangiomas (Restrepo et al, 2011; Maguiness et al, 2015). Case series of congenital haemangioma regressing completely during fetal life have also been reported (Maguiness et al, 2015). In terms of immunohistochemistry, congenital haemangioma does not stain positive for GLUT-1. The differences between infantile haemangioma and congenital haemangioma are shown in *Table 5*.

Management and treatment

The prognosis of most infantile haemangiomas is excellent, with the majority undergoing spontaneous resolution and only a small minority of cases require treatment. Certain characteristics of infantile haemangioma are associated with increased risks of complications (*Table 6*) and should be identified early for consideration of treatment (Starkey and Shahidullah, 2011; Aly et al, 2015; Maguiness et al, 2015).

Table 5. Comparing infantile haemangioma and congenital haemangioma

Infantile haemangiomas	Congenital haemangiomas
Common lesions – 10% infants	Rare lesions
Presents after birth	Presents at birth
GLUT-1 positive	GLUT-1 negative
Triphasic course: proliferation, plateau, involution	Rapidly involuting congenital haemangioma – complete involution after birth
	Non-involuting congenital haemangioma – no involution after birth

GLUT = glucose transporter isoform

Table 6. Indications for treatment

Functional risks
Vital risks
Recurrent painful ulcerations or infections
Bleeding
Disfigurement

Propranolol

Propranolol is a non-selective beta-adrenergic receptor blocker. Since 2008, case reports, case series and clinical trials have established that propranolol is an effective and well-tolerated treatment for infantile haemangiomas (Starkey and Shahidullah, 2011). The National Institute of Arthritis and Musculoskeletal Skin Diseases published a consensus report on the initiation and use of propranolol for infantile haemangiomas (Biesbroeck and Brandling-Bennett, 2014). The dose of propranolol ranges from 1–3 mg/kg/day with the commonest dosage regimen being 2 mg/kg/day given in two divided doses at least 6 hours apart, although some units give this amount in three divided doses (Starkey and Shahidullah, 2011; Biesbroeck and Brandling-Bennett, 2014; Solman et al, 2014). Thorough examination of the patient is required before propranolol monitoring, and if a cardiac murmur is present an echocardiogram should be performed before treatment. Caution should be used if PHACE syndrome is suspected or confirmed. A starting dose of 0.5 mg/kg/day is recommended (Solman et al, 2014).

There is no absolute consensus on monitoring when initiating propranolol treatment but most UK units monitor blood pressure, pulse and glucose levels with the first dose. A case series of 174 patients treated with propranolol revealed that treatment was successful in 99.4% of cases, with immediate cessation of growth, softening, fading of the erythema and rapid induction of regression (Hermans et al, 2013). Propranolol is also safe with minimal side effects when used to treat patients with infantile haemangioma (Schupp et al, 2011; Hermans et al, 2013; Solman et al, 2014). Common side effects reported include wheezing, sleep disturbances, worsening of ulceration and asymptomatic bradycardia (Solman et al, 2014).

Corticosteroids

Corticosteroid monotherapy has now been replaced by systemic propranolol as the treatment of choice of infantile haemangiomas. A recent randomized controlled trial found that combining propranolol with corticosteroids provides a faster response and should be considered in treatment for high-risk infantile haemangiomas (Aly et al, 2015). A short course of prednisolone may be used when initiating treatment with propranolol with minimal side effects (Aly et al, 2015). Other systemic drugs such as vincristine, interferon-alpha and cyclophosphamide are normally reserved for high-risk haemangiomas not responsive to standard treatment and are only used in tertiary referral centres (Sethuraman et al, 2014).

Topical therapies

Topical therapies such as timolol, propranolol, corticosteroids and imiquimod can be considered in superficial infantile haemangiomas, especially when they are small and minimally raised. This is usually reserved for cosmetically sensitive areas or where there are concerns that the haemangioma may progress and affect a vital struc-

ture. They can also be used as an adjuvant therapy to other treatments such as the pulsed dye laser. Currently timolol is the commonest topical preparation used in the UK.

Lasers

Ulceration is the most frequent complication of haemangioma and occurs in approximately 5–13% of cases (David et al, 2003). It can cause pain and may result in haemorrhage and secondary infections. Pulsed dye laser is effective in treatment of complicated haemangiomas. A case series of 78 patients with ulcerated haemangiomas treated with pulsed dye laser revealed that pulsed dye laser is a safe and effective modality of resolving the complication of ulcerated haemangiomas (David et al, 2003). However, it is not proven to be more superior in treatment of uncomplicated haemangiomas in the literature so far but can be effective in removing residual telangiectasias (Sethuraman et al, 2014; Tawfik and Alsharnoubi, 2015). Use of the pulsed dye laser for haemangiomas has decreased since propranolol treatment was found to be an effective therapy for haemangiomas and is now widely used. A combination of propranolol and pulsed dye laser is more effective than using pulsed dye laser as treatment on its own (Reddy et al, 2013).

Conclusions

Haemangiomas are the commonest type of vascular tumour in infancy. Understanding the pathophysiology and classification of the subtypes is essential to allow for early identification of high-risk lesions. This allows consideration of treatment in order to prevent short- and long-term complications from the condition. However, it should be remembered that the overwhelming majority of infantile haemangiomas do not cause problems, require no treatment and resolve spontaneously. BJHM

Conflict of interest: none.

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KEY POINTS

- Haemangiomas are the commonest vascular tumour of infancy.
- Infantile haemangiomas are usually not present at birth, affect up to 10% of children and the majority require no treatment.
- Propanolol is a safe and effective treatment for infantile haemangiomas affecting vital structures or causing bleeding and ulceration but should be instituted with day case monitoring.
- Careful clinical assessment of patients is required before starting propranolol for associated syndromes especially as reduced doses should be used if PHACE syndrome is present.
- Diffuse neonatal haemangiomatosis with 10 or more lesions, usually small, may be associated with a liver haemangioma and liver ultrasound scan should be arranged.
- There are two types of congenital haemangiomas which are present at birth – rapidly involuting and non-involuting.