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Infantile haemangioma: harmless 'strawberry' or life-threatening vascular anomaly?

Nerys Roberts, *Consultant Dermatologist, Chelsea and Westminster Hospital; Consultant Paediatric Dermatologist, Great Ormond Street Hospital, London*

Vascular birthmark classification was updated in 1996 (Table 1)[1,2] and has gained widespread recognition as a clinically useful framework. Haemangiomas are differentiated from vascular malformations by their clinical presentation, radiology and pathology, particularly by their immunohistochemistry.[3] Furthermore, it has now been established that the life-threatening coagulopathy seen in the Kasabach Merritt phenomenon (thrombocytopenic purpura due to consumption of platelets in association with a vascular lesion) is a complication of vascular tumours other than haemangiomas and does not occur with haemangiomas. Thus, the vast majority of patients with haemangiomas (10% of all neonates) can be spared a full blood count examination.[4]

Incidence

Strawberry marks (infantile haemangiomas) are the most common 'birthmark' recognised by the public, yet most are not present at birth but appear usually as a small red flat lesion in the first week of life. They are thought to occur in up to one in 10 infants but many do not come to medical attention. Factors increasing the risk include chorionic villus sampling, multiple births, low birth weight, prematurity, female sex and Caucasian ethnicity. The tumours proliferate for the first months, plateauing at about nine months of age. The natural history is for these lesions to regress gradually thereafter at an estimated rate of 10% per year (50% at 5 years, 70% at age 7), often leaving only minor, if any, abnormality.[5]

Pathogenesis

The pathogenesis of infantile haemangiomas is unclear but recent studies show they consist of endothelial cells which stain positively with glucose transporter protein-1 (GLUT-1) and share other properties of placental endothelial cells. This has led to speculation that they may originate from placental vascular endothelium. Some studies have shown clonality in the haemangioma endothelial cells with mutations in the vascular endothelial growth factor (VEGF) signalling pathway and Tie2.[3,6,7]

Clinical features

Clinically, the strawberry naevi represent the most common variant of infantile haemangioma – referred to as superficial haemangiomas. There are also deep (affecting the deep dermis and subcutis) and combined subtypes. Recent attention has focused on the different patterns of haemangiomas (focal and segmental); these appear to arise from embryonic prominences, suggesting a neuroectodermal derivation for their distribution. Lesions which do not conform to these patterns are known as indeterminate.[8] This distinction is thought to be important prognostically as segmental haemangiomas are more often associated with extracutaneous anomalies, including spinal dysraphism, genitourinary anomalies and PHACE syndrome (posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta and other cardiac defects, and eye abnormalities) (Table 2).[9–11]

Table 1. Modification of the Mulliken and Glowacki classification for vascular birthmarks[1] proposed by the International Society for the Study of Vascular Anomalies (1996).[2]

Vascular malformations: dysplastic, malformed vessels	**Vascular tumours:** cellular hyperplasia
Subcategories: • slow/fast flow • predominantly capillary, venous, lymphatic, arterial, AV – alone or in combination • local, segmental, diffuse, disseminated • isolated/familial/syndromic (eg stork mark – isolated local CM; port wine stain – CM – isolated or part of Sturge Weber and other syndromes)	Haemangioma Tufted angioma Kaposiform haemangioendothelioma

AV = arteriovenous; CM = capillary malformation.

Key Points

- **The classification of vascular anomalies has been modified to take into account knowledge of immunohistochemical staining**
- **Haemangiomas are common, but can have extracutaneous significance**
- **Kasabach Merritt phenomenon is not a complication of haemangiomas**
- **Active intervention can be medical or surgical and often requires a multidisciplinary approach**
- **With or without active intervention, the psychosocial impact of vascular anomalies should never be underestimated**

KEY WORDS: birthmarks, haemangioma, propranolol, vascular malformation

Table 2. PHACE syndrome (posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta and other cardiac defects, and eye abnormalities).

Posterior fossa brain malformations:
- Dandy Walker malformation
- Arachnoid cyst of post fossa
- Enlarged fourth ventricle
- Enlarged cisterna magna
- Cerebellar or vermian hypoplasia

Haemangiomas:
- Facial plaque-like or segmental haemangioma, often affecting several dermatomes
- Large, uni- or bilateral and often ulcerate
- ± laryngotracheal haemangioma

Arterial anomalies:
- Both intra- and extracranial arterial anomalies; can be complicated by cerebral infarction

Coarctation of the aorta and other anomalies including:
- Abnormalities of aortic arch, cortritiatum
- Tricuspid/aortic atresia
- Patent ductus arteriosus
- Ventricular septal defects

Eye abnormalities:
- Microphthalmia
- Optic nerve hypoplasia
- Cataracts
- Increased retinal vascularity

Sternal anomalies or supra-umbilical raphe

Other pointers to the possibility of extracutaneous lesions are multiple haemangiomas (diffuse neonatal haemangiomatosis)[12] or haemangiomas at a high-risk site. For instance, haemangiomas of the beard area are associated with airway and subglottic haemangiomas and often present with stridor, hoarse cry or airway obstruction,[13] while haemangiomas of the lumbosacral region sometimes herald anomalies of the genitourinary, gastrointestinal, skeletal or neurologic systems.[10]

The most common sites for internal symptomatic lesions are the liver and lung. Visceral haemangiomas occur in diffuse neonatal haemangiomatosis but lesions may also occur in the eyes, central nervous system and oral mucosa. Mortality can be as high as 80% in complex haemangiomas with extracutaneous features. It is recommended that children with more than five lesions should undergo screening as complications include:

- high output cardiac failure
- hydrocephalus
- ocular abnormalities
- visceral haemorrhage, and
- thyroid abnormalities – triiodothyronine hypothyroidism, sometimes occurring with a normal thyroxine, may be associated but not picked up by routine screening as it often develops after the neonatal period at the time of maximal proliferation of the haemangioma.[14]

Congenital haemangiomas

Rarely, haemangioma-like lesions appear to have undergone their proliferative phase *in utero* and do not develop further after birth. Two such congenital haemangioma variants are recognised:

- rapidly involuting congenital haemangioma (RICH), and
- non-involuting congenital haemangioma (NICH)

They are both more common on the limbs close to a joint or on the head and neck close to an ear. Unlike most haemangiomas, both these entities are GLUT-1 negative on immunohistochemical staining.

Rapidly involuting congenital haemangioma[15]

RICH can present as purple tumours with large radiating veins, a pink tumour with central red nodules or a hemispheric tumour with surrounding pallor and overlying telangiectasia. Hair growth and milia can occur rarely within the lesions and also ulceration, while haemorrhage and necrosis in the middle are complications. Most RICH undergo rapid involution within the first year of life, regressing by 14 months sometimes with atrophy.

Non-involuting congenital haemangioma[16]

NICH are usually flatter, well-circumscribed indurated or raised soft tissue lesions which are present at birth. They are also often purple or skin coloured, with superficial telangiectasia and a rim of pallor. They grow in proportion with the child but do not regress spontaneously.

Investigations

Most haemangiomas can be diagnosed clinically. The most useful investigations are Doppler ultrasound and sometimes magnetic resonance imaging (Table 3).[17]

Rarely, a biopsy may be necessary to distinguish the lesion from other vascular tumours or rapidly proliferating infantile tumours such as rhabdomyosarcoma, fibrosarcoma, neuroblastoma, nasal glioma, myofibromatosis, adrenal carcinoma or haemangiopericytoma. All haemangiomas show positive immunostaining with markers not seen in vascular malformations (Table 4).[3,6,7,15]

Treatment

One of the challenges of managing infants with haemangiomas is predicting the future behaviour of the lesions during

Table 3. Comparison of radiological characteristics of haemangiomas and vascular malformations.

	Doppler sonography	MRI	MRA
Haemangioma	Fast flow lesion	Tumoral mass with flow voids Bones generally normal, rarely distortion due to mass effect but no invasion	Lobular tumour
RICH/NICH	More frequently heterogeneous with visible vessels and calcification	Less well defined limits with increased fat stranding	RICH: inhomogeneous parenchymal staining, large and irregular feeding arteries in disorganised patterns, arterial aneurysms, direct AV shunts and intravascular thrombi – difficult to distinguish angiographically from AVM and congenital infantile fibrosarcoma
Vascular malformations	Fast or slow flow lesions	Slow flow: hypersignal on T2 Fast flow: flow voids on T1 and T2 Bones may show distortion, hypertrophy, invasion, lytic lesions or overgrowth	AV shunting in AVM

AVM = arteriovenous malformation; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NICH = non-involuting congenital haemangioma; RICH = rapidly involuting congenital haemangioma.

Table 4. Staining characteristics of haemangiomas.

	Phases		
	Proliferating	**Involuting**	**All**
Haemangioma	High expression of: • PCNA • PCNA • Type IV collagenase • VEGF • Urokinase	High expression of: • TIMP-1	High expression of: • bFGF • GLUT-1 • Merosin • Fc gamma RII • Lewis Y antigen
RICH/NICH			GLUT-1 negative High expression of VEGF-R, IGF-2 (levels comparable with involuting haemangioma)
Vascular malformation	Negative for all above markers		Negative for all above markers

bFGF = basic fibroblast growth factor; GLUT = glucose transporter protein; IGF = insulin-like growth factor; NICH = non-involuting congenital haemangioma; PCNA = proliferating cell nuclear antigen; RICH = rapidly involuting congenital haemangioma; TIMP = tissue inhibitor of metalloproteinase; VEGF = vascular endothelial growth factor.

the neonatal period. Many will not require active intervention, but prompt action is indicated if there is a threat to function. The risk versus the benefit of interventions which carry side effects and/or cause scarring (be it surgical or accidental) must be weighed up compared with the likely complication rate of natural progression and resolution.

In all children, whether or not undergoing investigations and treatment, the impact of vascular anomalies on the family cannot be underestimated. Many parents find haemangiomas distressing and waiting for natural resolution can be stressful and frightening. Some undergo a mourning reaction, while others find it difficult to cope socially.

Focal haemangiomas most frequently requiring intervention are those around the eye, nose, mouth and in the perineum as these lesions are most likely to cause functional problems or be complicated by ulceration or bleeding.

Earlier treatments

Historically, X-ray therapy was used, but it led to an increased risk of thyroid cancer, intracranial tumours and long-term cutaneous morbidity and is therefore no longer recommended.

In some circumstances, debulking or excisional surgery is life saving and/or becomes the treatment of choice, but for small lesions at sites of low risk of complications it is generally accepted that natural resolution leads to better cosmetic outcomes than surgical scars.

Laser therapy

Laser ablation has its place in some patients. Early promising results were reported with the argon laser and subsequently the Nd:Yag laser, but most operators feel that these lasers carry a greater risk of scarring than the pulsed dye laser (PDL). There is, however, no definitive evidence that PDL should be used for early, flat lesions. The concept that early intervention would prevent proliferation has not been borne out by a prospective trial, but the study design has been criticised.

It is now established that PDL does not influence the deeper dermal component of mixed haemangiomas. There is more widespread acceptance that PDL is the treatment of choice for ulcerated haemangiomas which fail to heal with conservative nursing measures, particularly in order to reduce the pain. It is also useful in reducing residual telangiectasia in resolved lesions.[18] The diode laser has been successfully deployed in subglotting haemangiomas.

Medical management of complex haemangiomas

Recent interest has focused on the medical management of complex haemangiomas. A few case reports have suggested a role for the topical immunomodulator imiquimod and, very recently, for the recombinant platelet-derived growth factor becaplermin. In some cases, intralesional treatment with corticosteroids or bleomycin has been sufficient, but many merit systemic treatment.

Oral corticosteroids[19] (1–3 mg/kg) have been the mainstay of treatment of proliferating haemangiomas since the 1960s. A meta-analysis in 2001 confirmed a response rate of 84% with a mean dose of 2.9 mg/kg over a mean of 1.8 months before tapering. Few serious adverse effects are reported, the most common being candida, gastric irritation and cushingoid facies. Steroid myopathy and hypertension are rare, though blood pressure monitoring is mandatory. There is often an effect on growth but the children undergo catch-up growth when treatment is stopped. These doses are immunosuppressive: a child has been reported to have developed *Pneumocystis carinii* pneumonia whilst undergoing treatment for an infantile haemangioma. Live vaccinations should be avoided during the treatment phase.

Interferon alpha (IFNα) is effective but is generally a treatment of last resort in the first year of life because it carries a risk of spastic diplegia. Neurotoxicity in the over one-year-olds seems to be less of an issue and IFN has a place in the management of difficult lesions which are still proliferating in this age group.

Vincristine[20] was trialled because it induces apoptosis in endothelial cells and has proven effective in some patients. A central line is needed and patients should be managed by a paediatric oncologist/haematologist.

Propranolol[21] has very recently been reported to have a rapid and sustained effect on the proliferative phase of complex haemangiomas. This is presumably due to decreased expression of VEGF and the b-fibroblast growth factor (bFGF) gene through the downregulation of the Raf mitogen-activated protein kinase pathway as well as inducing vasoconstriction and triggering apoptosis of endothelial cells. The dose required is high (2 mg/kg) and patients need both careful selection and cardiological surveillance.

Thalidomide is an antagonist of both VEGF and bFGF. It was used successfully in the management of a child with a life-threatening intracranial haemangioma.

Conclusions

Regardless of whether or not a vascular lesion has been actively treated or allowed to resolve spontaneously, these patients may have lasting disfigurement. Many children and adults with haemangiomas have contributed to the *Changing faces: face equality campaign.* As doctors, we must be sensitive to the fact that what one child will cope with easily will be a challenge to another. The objective size and sight of a lesion do not correlate well with the impact on quality of life.

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Address for correspondence:
Dr N Roberts, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH.
Email: Nerys.Roberts@chelwest.nhs.uk