

## Vascular anomalies in children (Part 2): Vascular tumours

### Key points

- Infantile haemangiomas (IH) are not present fully formed at birth but often a premonitory mark is noted.
- The natural history of IH is rapid proliferation over weeks to months, then slow involution over months to years.
- Large segmental haemangiomas on the head and neck may be associated with structural brain, cerebrovascular, cardiac or ocular anomalies
- Large segmental haemangiomas of the perineal skin, or over the lower back and sacrum may be associated with spinal, renal, genital or lower gastrointestinal tract anomalies.
- Most IHs require no active treatment but should be actively reviewed during the proliferative phase
- Oral propranolol is indicated for IHs which are ulcerating, disfiguring or affecting function
- An infant with a haemangioma should be referred for assessment within 4 weeks of onset of the lesion.

## Vascular tumours

These are due to proliferation of cells forming blood vessels. The most important lesion is the infantile haemangioma (IH), which is not present fully formed at birth. Congenital haemangiomas are less common. They are fully formed at birth, and sometimes can be detected by fetal ultrasound at about 20 weeks gestation. They may either rapidly involute or persist. Rarer tumours include tufted angiomas and Kaposiform haemangioendothelioma which are thought to form a spectrum and may be associated with coagulopathy (Kasabach-Merritt phenomenon).

### Infantile haemangioma

This is the most common tumour of infancy, being found in at least 4% of children at 1 year of age. It is more common in females at a ratio of 2-5:1.

Infantile haemangiomas may occur anywhere on the body. They are more common on the head and neck. In certain locations IH are at higher risk for complications.

#### Aetiology and pathogenesis

Risk factors (five times increase in incidence) include prematurity, low birth weight and multiple gestation pregnancy. A history of placenta praevia and maternal preeclampsia is more common in babies with IH. Chorionic venous sampling is now not thought to be a risk factor for IH.

Most IH are sporadic and no mutations have been identified. The cause has not been elucidated. Theories about placental cell embolisation which would explain natural history of IH have not been proven.

IHs originate from the proliferation of benign endothelial CD133+ progenitor cells with the immunohistochemical marker GLUT-1 (a glucose transporter protein). The presence of GLUT-1 differentiates IHs from other vascular tumours. GLUT-1 is also present on placental blood vessels. It is an important sensor for hypoxia.

A current reasonable theory is that hypoxia, either systemic (due to placental insufficiency), or local (in a specific niche area of poorly perfused tissue) stimulates endothelial cells to proliferate inappropriately, in a homeostatic attempt to [normalise](#) hypoxic tissue.

#### Classification

IHs are broadly classified as focal or segmental types. Focal IH are papules or nodules. They can be superficial (bright red), deep (bluish) or mixed. Segmental IH, which are much less common, are plaques which occupy a broader area of skin.

Diagnosis is clinical and biopsy not necessary unless lesions are atypical.

#### Natural history

IH are either absent at birth or manifest as a premonitory mark (pallor, telangiectases or dusky macule). They become clinically apparent by the first month of life.

IH demonstrate a characteristic natural history. Proliferation starts in week 2-3 of life. There is an early rapid proliferative phase with the most rapid growth occurring between 5- 8 weeks of life. Eighty per cent of final growth is complete by 3 months within the territory marked out in the early phase. Growth is volumetric rather than radial. In the later proliferative phase, up to 6-9 months of age, growth is at a slower rate.

Deeper lesions may have later apparent onset (up to 16 weeks of age).

In 3% of cases IH have a prolonged proliferative phase which extends beyond 9 months of age. Most of these are deep or mixed IH, or segmental IH; growth may continue for 18 months.

Sometimes IH are atypical, with minimal or arrested proliferation. These are referred to as reticular or abortive haemangiomas. By definition less than 25% of their area proliferates. They are characterized by fine or coarse telangiectasia within a zone of vasoconstriction. They are more common on the lower body.

Following proliferation there is a slow involution phase. The onset of this is heralded by a colour change from bright to dull red with streaks of grey on the surface. The tumour becomes paler, flattens and softens. This occurs earlier for small lesions than large ones. Involution commences after 6-9 months, and usually by the end of the first year, and continues gradually. Most IHs cease to improve significantly after 3-5 years.

Residual signs are common. Telangiectases, atrophy, fibrofatty tissue or scarring persist once involution is completed. In the case of very small lesions, there may be no residual signs.

#### Multifocal IHs

If more than 5 IH are present this may be a marker for the presence of extracutaneous haemangiomas, particularly in the liver. Hepatic IH are usually asymptomatic, but can cause high output cardiac failure. Very rarely haemangiomas diffusely involve the liver.

Multifocal IHs can be associated with consumptive hypothyroidism due to deiodination of thyroid hormones by the tumours. These infants need monitoring of thyroid function and if indicated, thyroid hormone supplementation.

If more than 5 cutaneous haemangiomas are present ultrasound of the liver should be arranged. Serial hepatic ultrasound is needed if haemangioma are identified.

### **Higher risk locations**

#### **Cervicofacial segmental IH (figure 2)**

Large segmental haemangiomas on the head and neck (more than 5cm in diameter) may be associated with malformations and vascular anomalies of the brain and heart. This is known by the acronym "PHACES" (P,osterior fossa, h,aeangioma, a,rtial, c,ardiac, e,ye, s,ternal).

One or more of these anomalies are found in up to one third of large haemangiomas of the head and neck, especially those located on frontotemporal and mandibular segments.

Females are affected more than males in a ratio of 9:1.

Diagnostic criteria are listed in Table 1.

Table 1: Diagnostic criteria for PHACES syndrome:

Haemangioma of head or neck > 5cm diameter

And 1 Major or 2 Minor features

<p><b>MAJOR</b></p> <p><b>Cerebrovascular anomaly</b> – absence, dysplasia, hypoplasia, aneurysm of major cerebral artery</p> <p><b>Structural brain anomaly</b> – posterior cranial fossa malformation, Dandy Walker malformation</p> <p><b>Cardiovascular anomaly</b> - aortic arch, coarctation of aorta, aneurysm</p> <p><b>Ocular</b> – posterior segment, retinal vascular</p> <p><b>Ventral</b> – sternal, supra-umbilical raphe</p>
<p><b>MINOR</b> –</p> <p><b>Cerebrovascular</b> – minor anomaly</p> <p><b>Structural brain</b> – midline anomaly, neuronal migration disorder, pituitary, intracranial haemangioma</p> <p><b>Cardiovascular</b> – VSD, double or right aortic arch, aberrant origin of subclavian artery</p> <p><b>Ocular</b> – anterior segment, cataract, coloboma, microphthalmia</p> <p><b>Ventral</b> – ectopic thyroid</p>

If an infant presents with a segmental cervicofacial IH which is greater than 5cm diameter, urgent referral to a paediatric dermatologist or paediatrician should be arranged. Brain MRI and MRA and echocardiography need to be performed before commencement of active treatment. Eye examination is also needed.

The child will require ongoing developmental and neurological assessment and monitoring of thyroid function.

#### **Periocular IH**

Haemangioma, even small focal lesions, in this site can be vision endangering. They may cause obstruction of the visual axis and compression of ocular structures leading to amblyopia, astigmatism, myopia and strabismus. This is also a site where presence of a haemangioma may cause significant cosmetic disfigurement with consequent psychological effects for the family and child when older.

Urgent referral should be made to an ophthalmologist with a paediatric interest. Frequent review is needed during the proliferative phase.

#### **Beard area IH**

IHs of the pre-auricular, mandibular, chin and neck areas have a high risk of airway involvement. If this is the case, stridor or noisy breathing develops at 4-12 weeks of age, or the baby's cry becomes hoarse. This possibility should be suspected even with small haemangiomas in the beard area but especially if there is bilateral mandibular involvement even without airway compromise. Early referral to an ENT surgeon needs to be arranged if an IH is located in this site. If the baby develops upper respiratory symptoms, urgent referral should be arranged to a paediatric ENT surgeon and early active treatment should be commenced.

#### **Lumbosacral spine/perineal segmental IH**

Segmental haemangiomas on the lower back or perineum may be associated with structural malformations of the spine (dysraphism, lipomyelomeningocele, tethered cord) and other bony structures of the pelvis and sacrum, genitourinary and anorectal anomalies (renal, abnormal external genitalia, imperforate anus).

Urgent referral for assessment and investigation should be arranged for an infant with a segmental haemangioma in this site. If the infant is less than 3 months old, ultrasound of the lower spine can be performed, followed by MRI spine with contrast at 4-6 months. Ultrasound of kidney, ureter and bladder should also be arranged.

### **Complications of IH**

#### **Ulceration**

Ulceration may occur during the proliferative phase especially in larger lesions (segmental, deep or mixed), or in lesions exposed to friction and moisture such as those located in flexures, neck, lip, perineum, or perianal skin. The highest risk is about the age of 4 months and is heralded by the development of grey-white colour on the surface of the haemangioma. Ulceration causes pain, bleeding and sometimes secondary infection, and heals with scarring.

#### **Impairment of vital structures**

IHs may be complicated by vision threatening complications if periocular, and airway obstruction in beard area lesions, as discussed previously.

#### **Disfigurement**

IHs, even small lesions of the face, especially on or around eyes, nose, mouth and ears may have significant cosmetic and therefore psychological consequences. This is more likely if the lesion ulcerates resulting in scarring which can be devastating on eyelid margins, nasal septum, vermilion of the lip or pinna of the ear.

IHs are not associated with coagulopathy.

Large segmental haemangiomas may be associated with hypothyroidism, as mentioned with respect to multifocal haemangiomas.

### **Management**

Most IHs undergo gradual spontaneous involution resulting in no permanent sequelae. For this reason most IH do not need active treatment. Consideration needs to be given to the location and size of the IH, as well as psychological consequences of residual scars and structural [deformities](#) both for the child and parents, which may be significant if the lesion is facial.

Small lesions which are determined to be of minor significance are managed with active non-intervention. They need close observation and frequent review during the proliferative phase. The child can be seen in person, or serial photographs viewed by email. It is important to educate the parents about expected course and potential complications. Decision to treat actively is determined by considering the risk of complications, including cosmetic (ulceration and scarring), impairment of function, or effect on vital structures. Early treatment may prevent complications

Ulceration is managed with saline cleansing and barrier protection with sterile petrolatum ointment or zinc oxide paste. Suitable dressings are non adhesive, including vaseline impregnated gauze. Cleansing and dressing should be performed at least once per day. Regular analgesia is important as ulceration is painful. If secondary infection is suspected topical (mupirocin ointment or metronidazole gel) or oral antibiotics should be prescribed. Active treatment of ulcerated IHs (excision, or oral propranolol, laser) will be discussed below.

Active treatment should be considered for deforming, endangering or life threatening lesions. (Table [2](#)).

If there is uncertainty about whether to commence active treatment, arrange weekly review of the infant, with photographs.

For any IH you consider might need active treatment early referral of the infant (before 4 weeks of age) needs to be [organised](#). If treatment is needed it should be commenced early in order to have optimum impact.

Referral should be to a paediatric dermatologist, paediatrician or to a multidisciplinary vascular anomaly clinic in a children's hospital.

As discussed previously, certain IH have a risk of associated structural anomalies which need to be excluded by assessment and investigation before oral treatment is commenced.

**Table 2: High risk IH where early active treatment should be considered**

Segmental > 5cm face – vision or airway compromise, ulceration NB investigation for PHACES syndrome prior to treatment)
Segmental > 5cm lumbosacral/perineal – ulceration, associated structural anomalies
Bulky lesion – volume, steep ascent from normal to involved skin, dermal thickening; tissue distortion; risk of scarring or disfigurement
Early white discolouration
Central face location
Periorbital, perinasal, perioral location

### **Topical treatment**

This may be suitable for small focal superficial lesions where the risk of serious complications is not considered to be high.

Options include potent topical corticosteroid ointment (such as betamethasone dipropionate 0.1% or compounded clobetasol propionate 0.5%). There is a risk of cutaneous atrophy and glaucoma with extended periocular use of these agents.

Intralesional corticosteroid injection can be a useful option for focal lesions such as on the nasal tip or lip, especially if there is a deeper component. This would require sedation of the infant. It may need to be repeated after 3-4 weeks.

Recently timolol maleate (a non-selective beta blocker approved for glaucoma) as 0.5% Gel Forming Solution has been used to treat small superficial lesions in cosmetically sensitive sites. One drop is applied twice daily to intact skin. Caution is needed not to apply a larger amount because of significant systemic absorption and bioavailability. Theoretically side effects are similar to propranolol (see below). This mode of treatment is still under investigation.

### **Oral treatment**

[Propranolol](#), a non-selective beta blocker, is now first line treatment of significant IHs. The first report of its serendipitous use for this indication was made in 2008, and since then it has become widely used and has mostly replaced the use of oral glucocorticoids.

Propranolol is more effective with response rates up to 97%, and less toxic than corticosteroids. Treatment results in cessation of growth and regression during proliferative phase AND later in the involution phase: propranolol is also effective for fully formed IH.

Mechanism of action is still being elucidated but includes initial vasoconstriction, inhibition of angiogenesis by suppression of growth factors, and induction of apoptosis of endothelial cells.

Urgent referral should be arranged if you think an infant with a significant IH may need treatment. Treatment protocols, particularly for initiation, vary between institutions and practitioners. There is still lack of standardisation with respect to optimal dosing, frequency of dosing, duration of therapy, age of initiation, timing and method of tapering. Some infants need admission to hospital, usually for a short day stay admission, to commence treatment. This includes infants less than 2 months of age, particularly if premature or low birth weight, with any comorbidities (history of apnoea, bradycardia or congenital cardiac disease).

Propranolol has to be compounded extemporaneously into a solution. A proprietary product may soon be available. At the time of writing propranolol is still an 'off label' treatment. This should be taken into account when obtaining and informed consent for treatment.

Propranolol is given in doses ranging from 0.5-2 mg/kg/day in 2 or 3 divided doses.

Treatment is usually initiated at half dose and the dose increased if tolerated and no side effects occur. If the IH is considered to be high risk or complicated propranolol should be commenced at a lower dose with slower upward titration. Treatment is continued for focal lesion until at least 6-9 months of age, more often until the first birthday. Earlier cessation has a higher rate of rebound growth. Segmental lesions need treatment for longer.

#### Side effects

The most common side effects are cold hands, sleep disturbance and constipation. The most serious, but fortunately rare adverse effects are hypotension, bradycardia, bronchial hyperreactivity and hypoglycaemia.

It is important that infants treated with propranolol are fed frequently, and that propranolol is given after a feed. It should be ceased if oral intake is poor. The last dose of the day should be given by about 6pm to avoid overnight hypoglycaemia.

High risk infants (small, premature, failure to thrive, comorbidities) need close monitoring. In addition to large haemangiomas, propranolol should be considered for treatment of airway, peri-ocular, lip, nose, ear and multiple hepatic haemangiomas causing sequelae, and lesions likely to leave a cosmetic defect not easily corrected surgically. It is also effective for cases where the haemangioma ulcerates, however it does not then prevent the associated scarring.

If an infant has a large segmental IH of the head and neck, it is important to exclude PHACES syndrome before commencement of propranolol. If a cerebrovascular anomaly is present, propranolol may precipitate stroke due to poor cerebral perfusion secondary to abnormal vessels.

If there are risk factors such as comorbidities, PHACES syndrome or ulceration propranolol should be given as three times daily (rather than twice daily) dosing, at a lower starting dose, with slower titration, and the minimum effective dose to prevent complications.

Adrenalin for anaphylaxis might be ineffective on beta blocker therapy. Careful consideration needs to be given to the risk/benefit equation if such children are prescribed propranolol.

There has been some concern about effects of propranolol on long term cognitive function because propranolol can cross the blood brain barrier. However to date there is no definite evidence of this, and studies involving ongoing longer term follow up of infants treated with propranolol are in progress.

Glucocorticoids were the mainstay of treatment for haemangiomas requiring intervention prior to propranolol.

Corticosteroids stabilise and slow growth but do not cause involution.

Usual dosing is 2-3mg/kg/day of prednisolone orally for 4-8 weeks, then slow taper is commenced over several months.

Side effects include cushingoid facies, gastrointestinal irritation, slowing of growth, hypertension and adrenal insufficiency. Live vaccines should not be administered during treatment, and blood pressure needs to be monitored.

Vincristine is sometime used for treatment of complicated IH unresponsive to propranolol or prednisolone

### Laser

Treatment of IH with laser is controversial in the proliferative phase because of the risk of inducing ulceration. Depth of penetration of the laser beam into the skin is superficial (1 mm), making laser an inappropriate option anyway for an IH with a deeper component. Laser is effective for residual telangiectases and erythema.

Laser treatment may diminish pain and hasten healing in ulcerated lesions.

The gold standard vascular laser is the pulsed dye laser (585nm, 595nm), with treatment administered every 2-4 weeks. General anaesthetic is needed for young children (see earlier comments relating to treatment of capillary malformations about the safety of GA in this age group).

Nd-Yag or alexandrite lasers (which have a longer wavelength and penetrate more deeply into the skin) are sometimes used for refractory lesions.

Fractionated carbon dioxide lasers have been used for residual scarring.

### Surgery

Excision may be appropriate for small lesions of nasal tip and lip, pedunculated IHs and for ulcerating small lesions in any site. Surgery can be considered if the lesion is in a site where a surgical scar will not be noticeable.

Surgery is appropriate for removal of residual fibrofatty tissue.

If reconstruction is needed this is best done at the age of 3-4 years of age when involution is expected to be completed and to minimize psychosocial impact prior to starting school.

A child with an IH should be re-evaluated at the age of 3-4 years regarding permanent skin changes requiring laser or surgery.

### **Other vascular tumours**

Pyogenic granuloma (lobulated capillary haemangioma)

Figure 3 : <http://www.hemangiomaeducation.org/images.html>

This is a common vascular lesion which will be familiar to most general practitioners. It is acquired, arising spontaneously or more commonly after irritation of the skin due to minor trauma. Pyogenic granulomas can also arise within a capillary malformation. It presents as a solitary red growing papule or nodule with a collarette of scale. It is usually eroded and bleeding. They can occur on any site but especially the head and neck. They may occur in the oral mucosa or on periungual skin. They do not involute spontaneously and require active treatment with either cautery or excision. This may be problematic particularly in facial lesions in young children, requiring referral for treatment under sedation or general anaesthetic. They may recur in the same site after treatment.

Vascular laser if available is effective.

Imiquimod cream has been used successfully (off-label) but caution needs to be used as this can cause irritation, and diagnosis needs to be certain. The differential diagnosis includes a

melanocytic lesion such as an atypical Spitz naevus or melanoma. If there is any doubt about diagnosis, referral is indicated before imiquimod cream is prescribed.

Congenital haemangiomas are fully formed at birth and do not proliferate in post natal life. They are rare. The risk factors for IH are not relevant for congenital haemangiomas. They are GLUT-1 negative. Doppler ultrasound shows fast flow characteristics in both RICH and NICH. They are broadly divided into two types, although these can overlap.

Rapidly involuting congenital haemangiomas (RICH) are violaceous tumours with overlying telangiectases, radiating veins, surrounded by a halo of pallor. They are warmer than the surrounding skin, and occasionally a bruit or thrill can be heard or felt. They are more commonly located on the head and neck, or lower limbs. Involution begins in first days or weeks of life and is usually complete by the end of the first year of life or soon after (by 14-15 months). They sometimes ulcerate and heal with atrophy, redundant skin, and telangiectases.

They can be associated with thrombocytopaenia (usually mild and self-resolving) coagulopathy, hypofibrinogenemia and anaemia.

Non involuting congenital haemangiomas (NICH) are flatter and more indurated than RICH. They also have overlying telangiectases, and are surrounded by a rim of pallor. Enlarged draining veins are seen in the surrounding skin. They never regress, grow in proportion with the child and need eventual excision. Ulceration is uncommon.

#### Tufted angioma

These are rare, benign, vascular tumours that are usually acquired and present in early childhood as a firm, infiltrated and sometimes tender plaque. There may be associated localised hyperhidrosis or hypertrichosis overlying the lesion. They are usually solitary and more common on the trunk and limbs.

Tufted angioma may be complicated by the Kasabach-Merritt phenomenon (see below) in 10% of cases. They can either persist or regress.

It is thought that tufted angioma may be a milder, superficial form of Kaposiform haemangioendothelioma, and that these tumours form part of a spectrum.

#### Kaposiform haemangioendothelioma

This is a rare vascular tumour that is congenital in 15% of cases, but usually acquired. Most cases present before the age of 5 years as a brown red stain which evolves into a tender purpuric plaque or indurated nodule. These tumours are locally aggressive, and may involve skin muscle, retroperitoneal space, [mediastinum](#) or viscera. Regional lymph nodes may be enlarged.

Assessment and treatment should occur in a tertiary referral children's hospital.

Biopsy is indicated for confirmation of diagnosis and MRI should be performed to identify the location and extent of the lesion.

Kasabach-Merritt phenomenon may develop in 70% of cases of KHE. If this occurs the lesion enlarges and becomes painful, indurated and purpuric. Patients can become profoundly thrombocytopaenic. Early diagnosis and treatment is important. Platelet transfusions or cryoprecipitate lead to further enlargement of the tumour.

Options for treatment include prednisolone, vincristine, and sirolimus (rapamycin). Excision, embolisation and radiotherapy might also be considered.

The tumour usually persists but coagulopathy abates, usually by 1 year or sooner with treatment. Occasionally KHEs can regress spontaneously.



The differential diagnosis of paediatric vascular tumours includes rare entities such as infantile myofibromatosis, lipoblastoma and malignant tumours including fibrosarcoma, rhabdomyosarcoma and neuroblastoma. Suspect malignancy if the lesion is firm, fixed, growing or ulcerating.

#### **Tips for GPs**

- If IH is suspected, refer early (less than 4 weeks of age) for diagnosis and decision about management.
- If IH is > 5cm and involves the face, suspect PHACES syndrome.
- If PHACES syndrome suspected, MRI and MRA of the brain, echocardiogram and eye examination need to be arranged.
- Propranolol should be prescribed by doctors experienced in its use.

#### **Future directions**

- Elucidation of the pathogenesis of infantile haemangioma.
- Understanding of the mechanism of action of propranolol.
- Propranolol: availability of a proprietary preparation, approval for this indication by regulatory bodies; standardised initiation of treatment and dosing regimens based on randomised controlled trials.
- Use of other beta blockers and other anti angiogenic agents for the treatment of IH.

#### **Further reading**

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