Congenital vascular anomalies of the liver

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Congenital vascular anomalies of the liver include a range of malformations of the portal venous, hepatic arterial and venous systems. Congenital portosystemic shunts and arteriovenous malformations make up the two most frequent such malformations. While infantile haemangiomas of the liver, endothelial tumours characterised by vascular proliferation should also be considered, as a proportion of them form prenatally. Evidence to support treatment strategies for these infants and children has been mainly based on small case series. In this review, we explore classification, clinical presentation, investigation and treatment strategies.

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Congenital vascular anomalies of the liver refer to abnormal connections between the three vascular entities, i.e. the incoming portal vein, hepatic artery, and the outgoing hepatic veins (i.e. the systemic circulation) and their respective branches. The clinical implications of such anomalies can be diverse or silent and depend on alteration of blood flow and direction. In addition, we will consider actual parenchymal lesions composed mainly of blood vessels – haemangiomas – as many have their origins in prenatal life.

As there are 3 vascular systems within the liver there are 3 possible anomalous connections:

- portosystemic shunts
- arteriovenous shunts
- arterioportal shunts.

Congenital portosystemic shunt

Congenital portosystemic shunts (CPSs) are vascular malformations resulting in the diversion of portal venous blood from the liver sinusoids and into the systemic circulation. The first reported case was by John Abernethy, a surgeon at St Bartholomew's Hospital, London, who described an abnormal venous connection between the portal vein as it entered the liver and the inferior vena cava (IVC) in its intrahepatic course.[1] Howard and Davenport presented one of the first case series in the literature in 1997 and suggested that such portosystemic shunts be given the eponym of 'Abernethy malformation' in recognition.[2] Experience with other types of portosystemic shunts highlighted the variation in anatomy in these patients. The most frequent CPS is an 'H' type venous connection from the back of the bifurcation of the portal vein directly into the IVC as it enters the liver. This may be associated with an intrahepatic portal venous system of varying size. The caudate lobe is often smaller than usual and is usually traversed by the shunt.

Originally CPSs were felt to be very rare, with only 15 clinical cases reported up to the 1990s;[2] however, widespread use of abdominal ultrasound (US) scanning has shown them to be much more common than was initially thought, with 316 cases identified in the most recent systematic review of the literature.[3] Data on the actual incidence of CPSs are limited. The only estimate has been extrapolated from studies of hypergalactosaemia screening. One study of 145 000 infants in which 5 cases of CPSs were found with hypergalactosaemia, thus yielding an approximate incidence of 1 in 30 000 live births.[4] However, two factors may indicate that this figure is unreliable. Firstly, the cases identified in this study resolved spontaneously and were likely portohepatic shunts; thus this calculation may overestimate the clinically significant CPSs. Secondly, the majority of patients with CPSs do not present with hypergalactosaemia and may have normal blood galactose. The study may have missed a significant number of patients with CPSs in their cohort. Further epidemiological studies are required for an accurate estimate of the incidence of CPSs.

Together with the overall increase in reported cases, multiple classification systems have also emerged. Differences between classification methods are based on small variations in anatomy or alternate prespectives of the same shunts (e.g. classifying based on the origin of the shunt in the portal system v. based on the insertion of the shunt in the systemic circulation). The two most widely used classification systems are summarised in Table 1. The Chicago Classification's latest iteration[5] divides CPSs broadly into type I – end-to-side implying little or no intrahepatic portal venous system, and type II – side-to-side with preservation of a variable amount of intrahepatic flow (Fig. 1). Our current understanding suggests

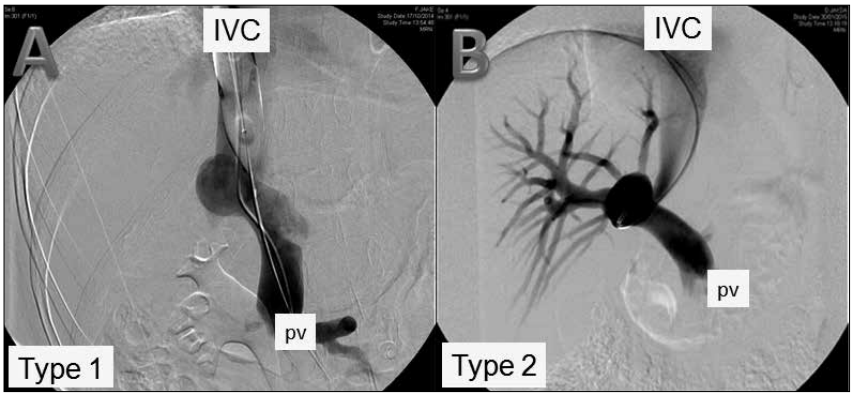

Fig. 1. Radiological portocavograms with balloon occlusion of the shunt showing (A) no evidence of an intrahepatic portal venous system (Type I) and (B) re-opening of an apparently normal portal venous system (Type II).

more of a continuum – severe hypoplasia of the intrahepatic portal tree may render it invisible on imaging but complete absence is highly unlikely. The other noteworthy classification is that of Blanc *et al.*[6] from Bicêtre, Paris, who proposed a complex surgical classification focusing on the subtle differences of the insertion of the shunt onto the IVC or hepatic veins. However, the Blanc classification was formed using both radiology and intraoperative findings for each individual patient, thus limiting its accuracy preoperatively when only radiological investigations are available.

Persistence of the ductus venosus is a CPS in which the normal prenatal connection between the left portal vein and hepatic veins fails to close spontaneously and involute. This 'shunt' circumvents the liver sinusoids, thereby directing oxygenated blood from the placental circulation via the left hepatic vein to the right heart.

Clinical features

An incidental ultrasound abnormality is probably the most common form of presentation these days – often as part of an investigation into persistent jaundice. Otherwise, CPS becomes apparent in infants with other congenital, particularly cardiac, abnormalities. Table 2 outlines the most frequent associations and complications of CPS.

Most symptoms of CPS can be attributed to either the effects of shunted mesenteric blood directly into the circulation – measurement of serum ammonia is the best surrogate of this – or from the development of tumours within the liver, probably as a result of an increased arterial contribution to the sinusoidal circulation.

Loss of the hepatic 'filter' causes neuro-psychological symptoms ranging from frank encephalopathy through drowsiness, poor attention span and, in infants and children, developmental delay in up to 25% of cases. Up to 15% of cases develop hypoxia, platypnoea (breathlessness which worsens on sitting up) or dyspnoea due to hepatopulmonary syndrome or pulmonary hypertension. The actual mechanism at the molecular level in either symptom complex is not known. While hyperammonaemia is certainly reflective of the shunt, it is probably not the specific agent of pathology.

The other main presentation of CPSs is with a liver tumour (Fig. 2).[2,5,7] Such patients develop abdominal pain and/or a palpable mass prompting investigation, with the finding of a tumour and a co-incident CPS. The most common tumours are benign, such as focal nodular hyperplasia and adenomas,[7,8] but malignancy is also possible – typically hepatoblastomas[5] and hepatocellular carcinomas.[3]

Table 1. Classifications of congenital portosystemic shunts

Lautz *et al.* 2010[8] – The Chicago Classification

Type I – end-to-side with apparent absence of the portal vein
- Ia – SMV and splenic vein do not join prior to implanting into systemic circulation
- Ib – SMV and splenic vein join prior to implanting into the systemic circulation

Type II – partial shunt with preserved portal flow
- IIa – arising from the left or right portal vein
- IIb – arising from the main portal vein, its bifurcation or the splenomesenteric confluence
- IIc – arising from the mesenteric, gastric, or splenic vein

Blanc *et al.* 2013[6] –The Paris Classification

Extrahepatic
- End-to-side shunt – with no apparent portal venous flow (similar to Lautz *et al.*[8] Type I)
- Side-to-side shunt – similar in appearance but with preserved portal flow
- H-type – shunt going through the caudate lobe with preserved portal flow

Intrahepatic
- Portohepatic – any communication from a portal venous branch to a hepatic venous branch
- Persistent ductus venosus

SMV = superior mesenteric vein.

Table 2. Associations and complications in infants and children with infantile hepatic haemangiomas (Adapted from Kulungowski *et al.*[16])

	Focal, %	Multifocal, %	Diffuse, %
Cutaneous lesions	15	77	53
Prenatal detection	30	0	0
Hypothyroidism	0	21	100
Heart failure	27	18	56
Shunt	38	16	39

Investigations and management

Laboratory investigations should include a full blood count, serum biochemistry, albumin, coagulation screen, and of course ammonia levels (Fig. 3).

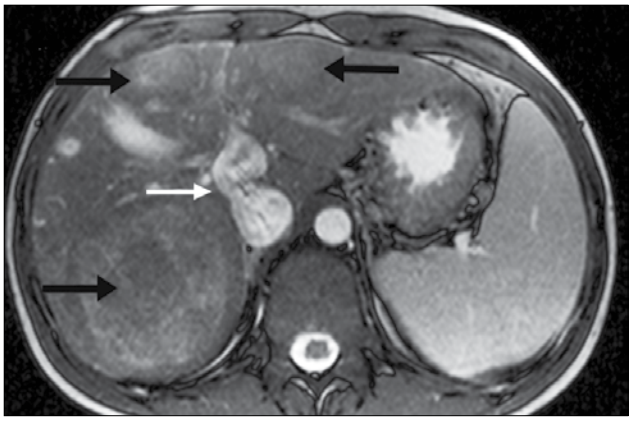

Fig. 2. Axial view of liver magnetic resonance imaging scan showing the shunt (white arrow) and associated hepatic tumours (black arrows).

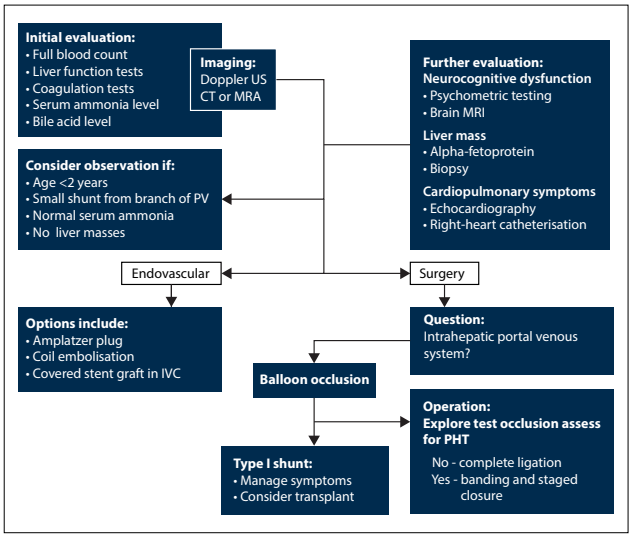

Fig. 3. Clinical algorithm for the investigation and management of a suspected congenital portosystemic shunt. (US = ultrasonography; CT = computed tomography, MRA = magnetic resonance arteriography; MRI = magnetic resonance imaging; IVC = inferior vena cava; PHT = portal hypertension.)

Cross-sectional imaging (computed tomography (CT) scan or magnetic resonance imaging (MRI)) is required to define the anatomy and caval or portal venography and is essential prior to any form of direct intervention. The latter defines the size of the connection and in the event of temporary occlusion it shows whether the latent intrahepatic portal venous system can handle the restored mesenteric blood flow without clinically significant portal hypertension.

Intrahepatic CPS and patent ductus venosus do have the potential for spontaneous closure within the first 2 years of life.[3] CPSs with shunts persisting beyond 2 years of age should be treated, even if apparently asymptomatic. Options for closure are dependent on available expertise and the anatomy of the shunt but radiological endovascular closure is typically used for those CPSs with a long intrahepatic course (Fig. 4). CPSs such as the Abernethy shunt, with a short and wide connection, usually require open surgical ligation, either in one stage or following partial closure by banding if on-table measured mesenteric pressures are too high to be sustainable, e.g. >20 mmHg, with normal portal venous pressure being <5 mmHg.

Those who have already developed tumours will require resections but should still be closely monitored for the development of other tumours after surgery. Shunt closure in itself has also been reported to have led to regression of benign tumours.[10]

For those CPSs considered to be uncorrectable by conventional surgical or radiological means, or through the development of unresectable or multiple malignancy, liver transplant may still have a role. This had been used for up to 25% of CPSs in one recent systematic review.[3]

Arterioportal fistulas

Congenital arterioportal fistulas (APFs) are rare[11] and usually present with features and complications of portal hypertension due to increased 'arterialisation' of the portal venous system. Rarely, if flow is sufficient and a ductus venosus remains patent, high-output cardiac failure may result. Congenital APFs are less common than the acquired version, which usually follows penetrating liver trauma or iatrogenically with a core liver biopsy needle. Protein-losing enteropathy and malabsorption have also been observed but are not common findings. Ultrasound and Doppler flow studies are key in the assessment of patients in whom pulsatile and often reversed portal flow is observed. Cross-sectional imaging supplements the anatomical definition and hepatic angiography can be followed by endovascular treatment. Congenital APFs have not been reported to close spontaneously and should be treated to limit the effects of portal vein arterialisation, which can become irreversible. Treatment is aimed at closure of the shunt via an endovascular or an open surgical approach involving ligation of the hepatic artery. Rarely, a patient with complex multiple bilobar APFs can be challenging to treat by embolisation and thus a partial hepatectomy or even liver transplantation may be considered. The outcome is largely favourable but perhaps 10% of patients can be shown to have persistent portal hypertension but now owing to portal vein thrombosis secondary to abrupt withdrawal of the arterial input.

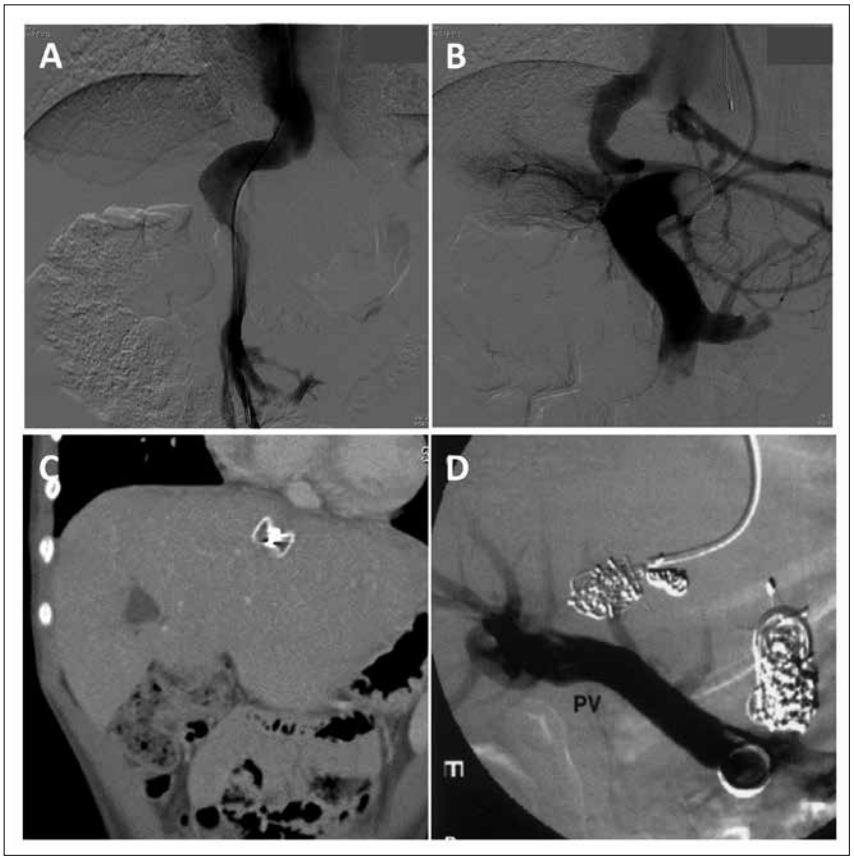

Fig. 4. Endovascular closure of congenital portosystemic shunts. Patient 1: (A) Venogram demonstrated a large fistula between the portal vein and right atrium. (B) Intrahepatic branches of the portal vein were visualised following balloon occlusion of the shunt. (C) Postoperative computed tomography scan showing an Amplatzer plug which successfully occluded the shunt. Patient 2: (D) Coil embolisation is an alternative endovascular modality for shunt closure. (Reproduced here with permission from Lautz TB, Superina RA. Congenital anomalies of liver vasculature. In: Davenport M, Superina RA, Heaton ND, eds. Surgery of the Liver, Bile Ducts and Pancreas in Children. 3rd ed. Boca Raton: CRC Press, 2017:267-278.

Arteriovenous malformation (AVMs)

True isolated arteriovenous malformations (AVMs) are exceedingly rare and the literature is limited to few case reports.[8] Often, the literature has mistakenly categorised infantile hepatic haemangiomas (IHH) as AVMs, as they often have an element of arteriovenous shunting. However ,the former are tumours of markedly different aetiology and have a distinct clinical evolution. True AVMs have been associated with hereditary haemorrhagic telangiectasia (Osler-Weber Rendu syndrome) and children with trisomy 21.[12] They are present at birth, at which point they are often clinically silent, and grow proportionally with the child. The most frequent complication is high-output cardiac failure and anaemia, but bleeding, embolism, and pain may occur. On imaging, they are seen as dysplastic arteries and veins with high flow and, importantly, do not have an associated soft-tissue mass. Treatment is aimed at closing the shunting vessels and is most commonly attempted by an endovascular approach, but surgical options may still be required. Due to the limited number of reported cases in the literature, it

is not possible to accurately state the prognosis; however, one group found that 2 of 4 of their patients died (1 immediately after birth and 1 intraoperatively) and that all of them had presented with symptoms of cardiac failure.[13]

Infantile hepatic haemangiomas

Infantile hepatic haemangiomas (IHHs) are benign endothelial tumours, predominantly affecting the skin. IHHs affect up to 5% of white infants. While they are most commonly found in the cutaneous form, visceral involvement is not infrequent; the latter affects mainly the liver, with some reports of tumours in the brain, lungs and eyes. IHHs were initially described as 'haemangioendotheliomas' by Kunstadter[14] in a series of 15 cases in 1933 and are now recognised as the most common benign vascular tumour of infancy.[16] Despite this, IHHs have remained somewhat of an enigma because of significant variation in clinical course and a wide variation in nomenclature over time. These lesions are, however, distinct from both epitheloid haemangioendotheliomas, which is a multifocal, proliferative low-grade malignant tumour with metastatic potential, and adult liver haemangiomas, which are vascular malformations – neither of these lesions involute. As such, the term 'infantile hepatic haemangioma' has been adopted owing to the clinical and biological similarity with infantile haemangiomas affecting the skin with similar rapid postnatal proliferation followed by spontaneous involution.

Over the past 10 years, our understanding of IHH has improved significantly, mainly owing to work from the Vascular Anomalies Centre in Boston, USA. Christison-Lagay *et al.*[15] published a seminal paper in 2007 in which they proposed a classification stratifying IHH into focal, multifocal and diffuse lesions (Fig. 5). The simultaneous development of a prospective liver haemangioma registry with a recommended management algorithm has helped to quantify the differences in presentation and prognosis, and has significantly advanced the understanding of the natural history of these lesions.[16]

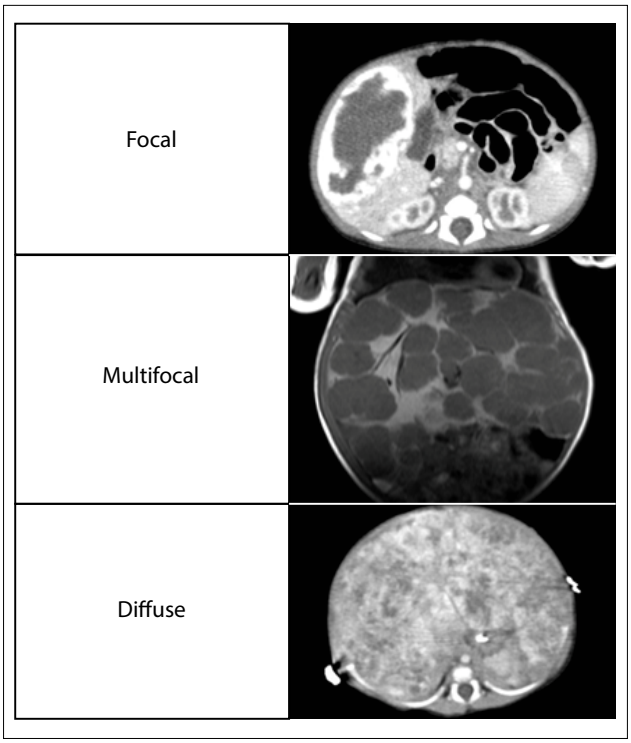

Fig. 5. Clinical classification of infantile hepatic haemangiomas.

Clinical features

Most IHHs present within the first 6 months of life, with an increasing proportion of up to 30% detected antenatally. Most studies suggest a female preponderance of 3:1 but this appears to apply only to multifocal and diffuse lesions rather than focal lesions. White infants are also most frequently affected.

Although histologically benign, there is a proportion of IHHs that produce life-threatening clinical symptoms owing to the size of the lesion, an abdominal compartment syndrome, and the futile haemodynamic shunting of blood rapidly through the liver, which leads to high-output cardiac failure. Less major symptoms include abdominal distension, hepatomegaly, or simply other cutaneous haemangiomas. Kasabach-Merritt syndrome describes a consumptive coagulopathy and platelet trapping in the interstices of the tumour that can be seen in ~10% of cases and is particularly ominous. Historically, cardiac failure has been reported in 50 - 70%, with a mortality rate of up to 90% in some series.[17]

Increased antenatal detection and incidental discovery hasve highlighted the phenomenon of the 'focal IHH.' They appear to be clinically and biological distinct from their 'multifocal' and 'diffuse' siblings representing the pure hepatic form of their rapidly involuting congenital cutaneous counterpart. The natural course of these lesions is one of rapid postnatal proliferation (months), involution (years) and finally an involuted phase during which endothelial cells are eventually replaced by fibro-fatty tissue. Focal lesions commonly regress fully postnatally and rarely require any form of intervention. Symptoms may rarely occur depending on location, size and arteriovenous shunting. Interestingly, a number of studies have shown cutaneous lesions are found in only 5% of infants with focal lesions (similar to that of the baseline population) while they may be present in up to 70% of infants with the multifocal or diffuse types.[16] Increased ultrasound screening for hepatic lesions where ≥5 cutaneous lesions are present has almost certainly contributed to the increase in the incidence of IHH seen in recent years.

No studies have reported antenatal detection of multifocal and diffuse lesions and therefore they are typically thought to develop postnatally, undergo proliferation for up to 1 year and gradually regress thereafter. In one study of 121 patients,[16] biological differences included immunoexpression of glucose transporter-1 (GLUT-1) in all resected specimens of multifocal and diffuse subtypes compared with no expression of GLUT-1 in those with focal disease. There is a relationship between IHH and thyroid dysfunction, typically in hypothyroidism[18] but also hyperthyroidism;[19] however, this relationship has only been described in multifocal and diffuse subtypes (Table 2) .

Investigation and management

Diagnosis is based on a combination of clinical findings and radiological appearance. Ultrasonography is the primary imaging modality and the characteristic finding is a well-defined, hypoechoic lesion. Cross-sectional imaging in the form of a CT or MRI scan is then reasonable Characteristically lesions are universally spherical and homogenous, and commonly hypodense. Intravenous contrast will show centripetal enhancement, i.e. the periphery enhances initially before the centre. Calcification is not infrequent. Aortic tapering is a common feature, as is the recruitment of other feeding vessels, and the inflow hepatic artery can become very hypertrophic. If hepatic artery ligation or embolisation is considered as a treatment choice, angiography (typically magnetic resonance arteriography nowadays) can provide an essential road map.

In the presence of atypical imaging findings or unexpected clinical behaviour, further investigation should be undertaken. The main differential diagnoses for focal IHHs are hepatoblastoma and mesenchymal hamartoma, and as such α-fetoprotein should be measured despite the fact that raised levels are also seen in IHH. Other differential diagnoses include AVMs and metastatic neuroblastoma although normal urinary catecholamines exclude the latter as a possibility. In a study by Kassarjian *et al.*,[20] 5% of cases who were initially diagnosed with IHH on characteristic imaging findings, were subsequently found to have a malignant appearance on histology. Furthermore, angiosarcoma has been described in resection specimens and it has been suggested that later age at diagnosis of multifocal IHH may increase the likelihood of angiosarcoma.

Due to the natural history of spontaneous regression in IHH, observation is the mainstay of treatment in asymptomatic patients. If symptomatic, supportive medical therapy in the form of diuretics, digoxin and assisted ventilation may be needed. Thyroid function should be closely monitored as hypothyroidism can have significant and permanent effects on neurocognitive development. Thyroxine supplementation may be indicated, although hypothyroidism is frequently reported to resolve with regression of the tumour. Coagulation status should be monitored and corrected appropriately.

Where necessary, medical treatment can induce regression of IHH beyond that expected from the natural involution of the lesion. Steroid therapy originated in the 1970s and for many years this was the first-line therapy, with reported response rates of up to 45%;[20] however, it is not without associated risks, including growth delay, hypertension and cardiomyopathy. The mechanism of action is unclear but thought to cause vasoconstriction in the rapidly proliferating immature tumours. Other medical treatments have since been used as second-line therapies including cyclophosphamide, vincristine, interferon–alpha and radiotherapy with varying efficacy and frequently serious complications. The serendipitous discovery of propranolol promoting regression of a cutaneous haemangioma in a heart failure patient in 2008 has led to its extensive use as a medical treatment for IHH.[22] While its superiority in treating cutaneous haemangiomas has been proven, there is little beyond anecdotal evidence to suggest the same effect in IHH. Nevertheless, our experience with 29 infants since 2008 has been very favourable, with a decreased need for surgical intervention and an overall decrease in the mortality rate in this, the propranolol era. Combination therapy with propranolol and prednisolone seems to have become the mainstay of medical treatment in most centres.

Regardless of the subtype of IHH, there is a cohort of patients who will not respond to medical therapy and for them surgery is advocated. The approach chosen is based on tumour size, localisation, anatomy of feeding and draining vessels, and cardiorespiratory condition. Where possible, focal lesions are most commonly treated with surgical resection – this offers complete resolution.

Hepatic artery ligation[19] or more recently embolisation if expertise is available, has been shown to be a safe and effective treatment for predominantly multifocal and diffuse bilobar disease as these are artery-dependent. Ligation is well tolerated if perfusion and oxygenation can be maintained and dramatically reduces arteriovenous shunting and initiates tumour regression. In the event of extensive involvement and no response to alternative therapy, liver transplantation may still be indicated although the rate of transplantation was <2% in our experience.

Conclusion

Congenital hepatic vascular malformations are a rare and diverse group of anomalies. CPSs have a wide range of possible clinical manifestations and can be a cause of major morbidity, while IHH can be life-threatening. Recent advances in medical and surgical therapy now means that most cases can be treated effectively with preservation of the native liver.

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