Liver Tumours and Nodular Lesions

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Key Points

- Widespread use of high-resolution imaging modalities has led to increased detection of hepatic lesions.
- Hepatic lesions need to be distinguished as benign or malignant to guide therapy.
- A good understanding of radioimaging physics helps increase diagnostic yield and plan surgical and medical treatment.
- Histology is required if the lesion is suspected to be malignant.
- Liver transplant is an accepted indication with excellent long-term prognosis for unresectable hepatoblastoma, while the transplant decision for other liver tumours including hepatocellular carcinoma should be individualised.

Research Needed in the Field

- Identify the most appropriate immunosuppression protocol in a patient requiring liver transplantation for malignancy.
- Identify genotype-phenotype correlations in benign and malignant liver tumours in children and its impact on outcome and therapeutic options.
- Identify specific radioimaging features in paediatric hepatic adenoma and HCC to prognosticate outcome and guide management.
- Define indications for liver transplantation in childhood HCC.

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21.1 Introduction

21.1.1 Clinical Approach to a Newly Detected Liver Mass

A liver tumour may be detected in one of the following scenarios:

1. Routine antenatal imaging.
2. Incidental finding because of radioimaging done for unrelated conditions such as abdominal pain, cholestasis or abnormal liver function tests.
3. Medical surveillance of a recognised chronic liver disease or a cancer predisposing genetic condition.
4. Child presenting with abdominal distention and/or abdominal lump.

An early diagnosis following the detection of a mass usually incorporates a staged approach with detailed clinical history, physical examination, blood tests including tumour markers, imaging procedures and finally often liver histology. This stepwise approach is paramount to distinguish malignant lesions from benign ones and to facilitate swift appropriate treatment. Age and gender of the patient, the presenting complaint and any predisposing factors to develop liver masses, such as foreign travel and medication history, offer important clues especially if lesions have no clear diagnostic features on radioimaging.

21.1.2 Clinical History

Age and gender are important as the tumours to be considered in less than 3 years include haemangioma, mesenchymal hamartomas, simple hepatic cysts, hepatoblastoma and metastases from other malignancies most common being neuroblastoma and Wilms tumour [1] (Table 21.1). Children with metastatic malignancies are generally unwell with fever, anorexia, weight loss, irritability and

L. D'Antiga (ed.), *Pediatric Hepatology and Liver Transplantation*, https://doi.org/10.1007/978-3-319-96400-3_21

Table 21.1 Risk factors for liver tumours

Hepatoblastoma	Hepatocellular carcinoma	Adenoma	Focal nodular hyperplasia
Prematurity Low birth weight Beckwith-Weidman syndrome Simpson-Golabi-Behmel syndrome Li-Fraumeni syndrome Familial adenomatous polyposis Gardener syndrome Budd-Chiari syndrome Trisomy 18	Chronic hepatitis B infection Hepatitis C infection Tyrosinaemia 1 Familial cholestasis syndrome Fanconi anaemia Ataxia telangiectasia Biliary atresia Alpha-1 antitrypsin deficiency Alagille syndrome Glycogen storage disease Wilson's disease Congenital hepatic fibrosis Portosystemic shunt Drugs: methotrexate, oestrogens	Oestrogens Tyrosinaemia 1 GSD 1 and GSD 3	Vascular malformation Congenital portosystemic malformations

Table 21.2 Age distribution of Liver lesions

		Malignant	
Age in years	Benign	Primary	Metastatic
0–3	Haemangioma Mesenchymal hamartoma Teratoma	Hepatoblastoma Rhabdomyosarcoma Rhabdoid tumours Yolk sac tumour	Neuroblastoma Wilms tumour Leukaemia Pancreaticoblastoma
3–10	Focal nodular hyperplasia Adenoma	Rhabdomyosarcoma Undifferentiated embryonal sarcoma Hepatocellular carcinoma Angiosarcoma	
Adolescence	Adenoma Focal nodular hyperplasia	Hepatocellular carcinoma Angiosarcoma Undifferentiated embryonal sarcoma Epithelioid haemangioendothelioma Cholangiocarcinoma	Hodgkin's and non-Hodgkin's lymphoma Metastasis from extrahepatic malignancies
Any age	Hepatic cyst Hepatic abscess Nodular regenerative hyperplasia Hepatic foregut cyst Inflammatory fibroblastic tumour		

bony pains [2]. Adenomas are usually seen in adolescent females on oestrogen-based contraceptive pills or metabolic conditions such as glycogen storage disease. Hepatocellular carcinoma (HCC) is typically seen in school-aged children. It may be associated with metabolic disease (tyrosinaemia type I) but can also be sporadic. Enquiries should be made for genetic conditions like Beckwith-Wiedemann syndrome, Li-Fraumeni syndrome, Simpson-Golabi-Behmel syndrome and familial adenomatous polyposis as these conditions have a higher incidence of hepatoblastoma as compared to the general paediatric population (Table 21.2).

Liver lesions on a background of abnormal blood flow like Budd-Chiari or Abernethy malformation are usually focal nodular hyperplasia (FNH). Children treated in the past with chemotherapy or radiotherapy for solid tumours are also known to have a higher incidence of FNH.

21.1.3 Clinical Findings

Cutaneous haemangiomas or a swirl on auscultation of the fontanelle favours a diagnosis of infantile haemangioma [3]. One should look for signs of chronic liver disease, organomegaly and features suggestive of genetic syndromes in the clinical examination of the patient. "Blueberry" skin nodules seen with neuroblastoma and leukaemias metastasising to subcutaneous tissue are a diagnostic feature [4].Complications of hepatic haemangiomas like congestive cardiac failure [3] or shock in tumour bleeds may be evident at presentation [5].

21.1.4 Blood Tests

Baseline liver function tests and viral markers are done to exclude chronic viral hepatitis. Thrombocytosis may be seen

in hepatoblastomas as the tumours are known to secrete thrombopoietin [5].

21.1.5 Tumour Markers

Alpha-fetoprotein (AFP) is a glycoprotein that is produced by foetal liver cells and yolk sac tumours. In foetal life it precedes the emergence of albumin. The different glycosylation forms of AFP help to differentiate the origin of the AFP. AFP originating from the yolk sac has a different glycosylation pattern than AFP from malignant tumours and from benign hepatocytes. Standard tests usually measure all isoforms, but specific tests for the different isoforms are available. Neonates often have markedly elevated AFP levels that rapidly fall in the first 6 months of life and reach normal reference ranges by the age of 1 year. Nomograms are available to interpret AFP levels below 1 year of age. Certain cancers like teratomas and liver malignant lesions such as hepatoblastoma and hepatocellular carcinoma produce AFP which is used as an adjunct for diagnosis, prognostication, response to treatment and surveillance for recurrence. Hepatoblastomas with very high or low AFP at diagnosis and the ones that fail to respond to chemotherapy are suggestive of unfavourable histology and indicate poor prognosis. The biological half-life of AFP is approximately 5 days [6].

Levels of AFP above the reference range may be found in patients with viral hepatitis and chronic liver disease with regenerating hepatocytes. Not all hepatoblastomas and HCC have AFP above the reference range, and hence AFP alone cannot be used for diagnosis or screening. Additional biomarkers like des-γ-carboxy prothrombin, *Lens culinaris* AFP–L3 (fucosylated isoform of AFP) and Golgi protein 73 when used individually are not very useful but when combined may improve the diagnostic yield in HCC especially in the early stages [6, 7]. Vitamin B12-binding proteins such as transcobalamin 100 have been found to be elevated in fibrolamellar variant of HCC and can been used in monitoring response to treatment.

β-Human chorionic gonadotrophin (β-HCG) is produced by some hepatoblastomas causing precocious puberty. This too can be used for monitoring similar to AFP in these patients. Extremely high levels are seen in infantile choriocarcinoma of the liver [5, 7].

Urine catecholamines are helpful in suspected infiltrative neuroblastoma of the liver as they can mimic other liver tumours on radioimaging (Fig. 21.1).

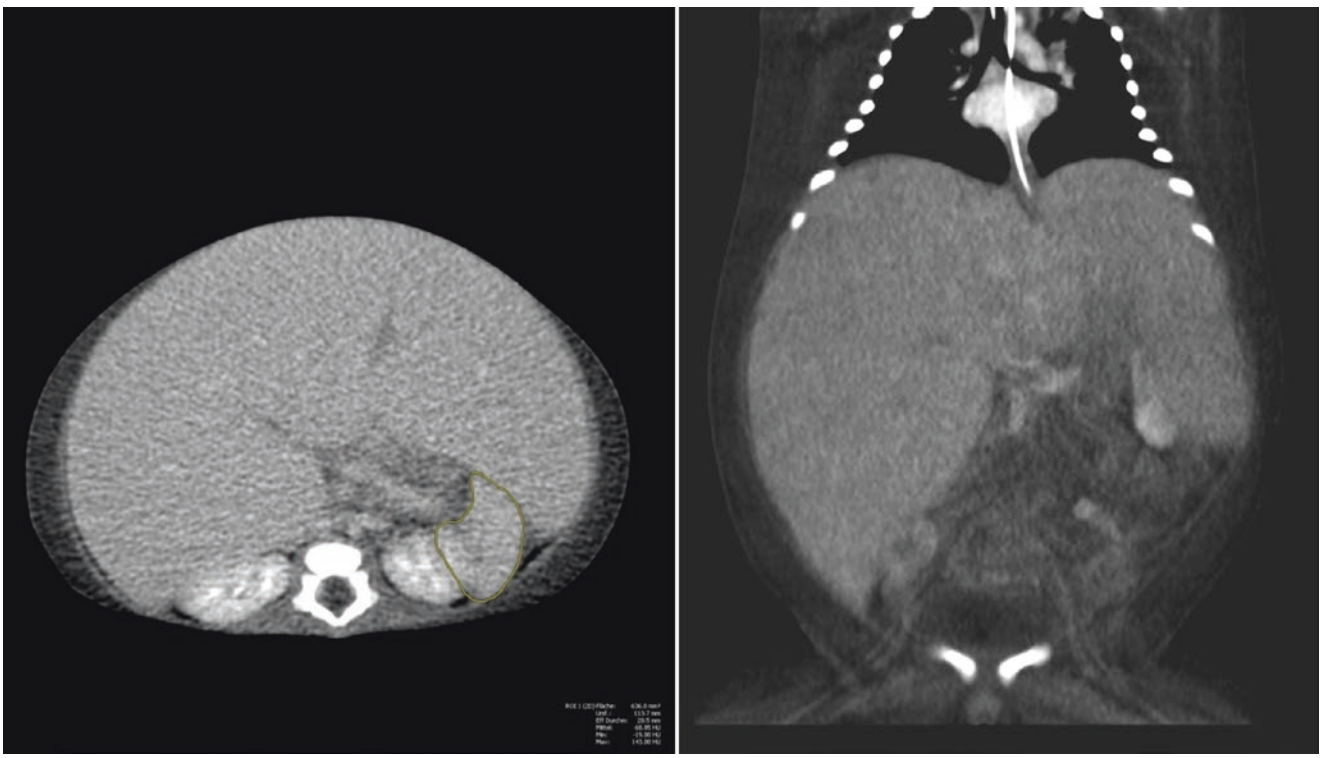

Fig. 21.1 Neuroblastoma of a 4-week neonate presenting with diffuse infiltration of the liver. At this age neuroblastoma can typically mimic metabolic liver disease with hepatomegaly and no obvious extrahepatic tumour mass. Diagnosis is may be suspected by heterogeneous enhancement of contrast media in CT, MRI or ultrasonography with calcification, haemorrhage and/or necrosis. Confirmatory tests for the diagnosis may be urinary catecholamines, histology and bone marrow aspirate

21.1.6 Choosing Appropriate Imaging Modality

Ultrasound (USS) is usually the first radioimaging modality to screen a liver lesion. It confirms the mass arising from the liver and can differentiate between cystic or solid lesions. Dopplers are helpful in determining vascularity of the lesions, and at times USS alone is sufficient in making a diagnosis. However, its sensitivity and specificity are limited in hepatic steatosis, diffuse liver disease and solid liver lesions less than 1 centimetre (cm) [8, 9]. USS if inconclusive can guide clinicians in choosing further imaging modality to characterise the lesion and stage and detect metastasis if malignant and delineate the vascular anatomy if surgical resection or liver transplantation is anticipated (Fig. 21.2).

Visibility of the liver lesion depends on the attenuation difference between the lesion and the background liver. Unenhanced CT scan is unhelpful if this attenuation difference is absent, and this is overcome by using an intravenous contrast. Due to the dual blood supply from the artery and portal vein, the liver has three distinct phases after injecting intravenous contrast. First is the arterial phase occurring 10–15 s after injecting the contrast followed by the portal venous phase, also called the hepatic phase, after 60–75 s. Finally in the equilibrium phase, also called the delayed venous phase, the contrast starts leaving the liver. Liver masses, if vascular, receive their blood supply from the hepatic artery. This vascular architecture results in different enhancement patterns during various phases of intravenous contrast circulation which is then exploited to characterise the lesion.

Hypervascular lesions such as focal nodular hyperplasia and hepatic adenoma will enhance in the late arterial phase as the liver parenchyma is comparatively hypodense and will fade out in the late portal phase as the liver brightens up

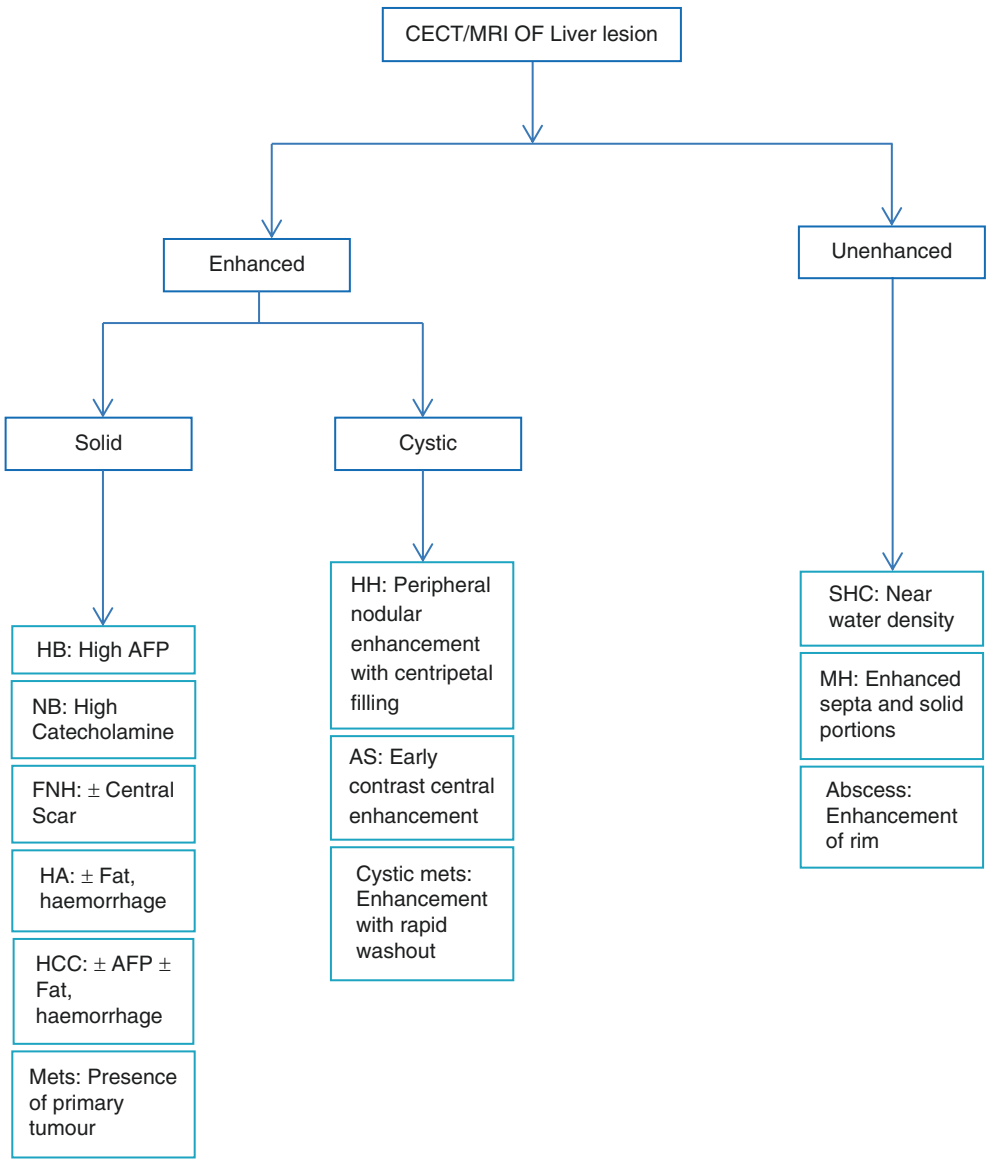

Fig. 21.2 Characterising a liver lesion on radioimaging. A flow chart approach incorporating radioimaging characteristics and biochemical tests helps in differentiating liver lesions. *HB* hepatoblastoma, *NB* neuroblastoma, *HH* hepatic haemangioma, *AS* angiosarcoma, *MH* mesenchymal hamartoma, *FNH* focal nodular hyperplasia, *HA* hepatic adenoma, *HCC* hepatocellular carcinoma, *SHC* simple hepatic cyst, *AFP* alpha fetoprotein, *Mets* metastasis

because of the portal venous supply. In contrast hypovascular lesions will be best seen in the portal venous phase. Liver lesions will be hypodense or hyperdense as compared to liver parenchyma in the equilibrium phase (scans taken 10 min after contrast) depending on the washout or retention of the contrast in the lesion [8].

Magnetic resonance imaging (MRI) with gadolinium contrast provides the best spatial resolution for liver lesions in the rapid dynamic T1-weighted images. It avoids ionising radiation making it the modality of choice. Better lesion characterisation is achieved by defining signal intensity characteristics of the lesion, vascularity, stromal component, presence of necrosis, fat and haemorrhages [8].

The characterisation and location of lesions are further enhanced by using mixed extracellular hepatobiliary gadolinium-based contrast agents such as gadoxetate disodium and gadobenate dimeglumine. Delayed hepatobiliary phase with delineation of biliary anatomy is possible as these contrast agents are partially excreted in bile after being taken up by hepatocytes, thus providing functional and morphologic information [10, 11].

This is particularly useful for differentiating adenomas and hepatocellular carcinomas from focal nodular hyperplasia. Magnetic resonance elastography and acoustic radiation force impulse imaging are currently under investigation and may potentially be useful techniques in the characterisation of liver masses [8]. In spite of these advantages, cost, long duration of procedure and need for sedation or anaesthesia limit its use in children [10, 11].

21.1.7 Histology

Liver histology often is the key to the diagnosis of a solid mass; however, liver biopsy is an invasive procedure and should be prepared following detailed radioimaging for a maximum result. Benign lesions seldom require biopsy unless the clinical picture and radioimaging have been inconclusive. Immunohistochemistry further adds to the diagnostic accuracy and is helpful in prognostication of a liver lesion. It is advisable to biopsy both the liver lesion and the back ground liver tissue in patients with sporadic adenomas or focal nodular hyperplasia to rule out underlying liver disease. Suspected malignant lesions almost always require histopathological diagnosis to guide therapy and prognosis.

21.2 Benign Lesions of Liver

21.2.1 Hepatic Haemangiomas (HH)

Paediatric hepatic haemangiomas are the most common benign liver tumours. Their nomenclature in the past has been confusing causing an irrational management approach. The Liver Haemangioma Registry from Boston in 2007 categorised hepatic haemangiomas into focal, multifocal and diffuse subtypes [3, 12]. The Boston group proposed a management algorithm of these subtypes based on their similarities in biological behaviour and natural history to the congenital and infantile cutaneous haemangiomas described in the International Society for the Study of Vascular Anomalies (ISSVA) classification [13]. HH are endothelial lined vascular mass in the liver with feeding and draining vessels and are distinct from the epithelioid haemangioendotheliomas, hepatic arteriovenous malformations and hepatic haemangiomas of adults.

Focal hepatic haemangiomas (FHH), also called congenital haemangiomas, account for one third of the HH. They are variable in size ranging from a few millimetres to more than 10 cm. Most are asymptomatic and are picked up incidentally on antenatal or postnatal scans. The large ones though can be symptomatic because of their size, location or haemodynamic effects caused by high-flow shunts. FHH begin to evolve in utero, are fully formed at birth and do not have a postnatal growth phase. They are rarely associated with cutaneous haemangiomas and have no sex predilection. These lesions begin to involute soon after birth, decreasing in size and regressing by 14–18 months of age [12]. FHH thus behave similar to the congenital cutaneous haemangiomas of rapid involuting type of the ISSVA classification.

Multifocal and diffuse hepatic haemangiomas are the true infantile hepatic haemangiomas (IHH) of the ISSVA classification [13]. They are similar to the cutaneous infantile haemangioma in their biologic behaviour and are associated with cutaneous haemangiomas at other sites. They are encountered more commonly in females and white population. Multifocal hepatic haemangiomas (MHH) appear after birth and are most commonly picked up on visceral screening for multiple cutaneous haemangiomas. About 90% are diagnosed in first 6 months of life with one third of them in the first month [2]. Some of them like the focal ones can be symptomatic with features of high-output cardiac failure, and these patients will need additional monitoring with echocardiogram and brain natriuretic peptide to guide and monitor treatment. Similar to cutaneous infantile haemangiomas, these lesions proliferate up to a year after birth, then stabilise and finally involute over several years [3, 12, 13].

The diffuse infantile haemangioma (DIH) is almost always symptomatic with abdominal distension because of hepatomegaly as majority of the liver parenchyma is replaced by the haemangioma. Hepatomegaly can be severe enough to cause abdominal compartment syndrome, inferior vena cava and renal vein compression causing poor venous return, impaired ventilation and multiorgan failure [3, 12].

Patients with IHH especially the diffuse type are likely to develop hypothyroidism. This is because the vascular endothelium of IHH produces type 3 iodothyronine deiodinase which inactivates the active form of thyroxine (T3) into an inactive form. Hypothyroidism may be severe enough to cause

heart failure and mental growth retardation. These patients need large doses of thyroxine, sometimes intravenously, to get to euthyroid state. This complication has not been described in the focal or congenital hepatic haemangioma [3, 12].

Mild anaemia and thrombocytopenia have been reported with hepatic haemangiomas unlike the severe thrombocytopenia with consumption coagulopathy of Kasabach-Merritt syndrome associated with haemangioendotheliomas. Complications associated with HH resolve once they have involuted either spontaneously or medically [3, 12].

On USS, FHH are seen as a well-demarcated hypoechoic vascular mass with heterogeneous echotexture. Feeding and draining vessels have been described but may be difficult to visualise on ultrasound. Non-contrast CT of these lesions appears as low attenuation hypodense lesions with calcifications that are more frequently seen in the involution phase. Early peripheral nodular enhancement with progressive fill-in causing centripetal enhancement is seen on contrast-enhanced CT scan (CECT). Central areas may be anechoic because of haemorrhage, necrosis or fibrosis. Multifocal and diffuse lesions have multiple well-defined lesions on USS and CT scan. The MHH are homogenous in echotexture with normal intervening liver parenchyma and enhance uniformly with contrast. In the diffuse type, liver tissue is replaced by numerous lesions with no normal intervening liver parenchyma [3].

MRI has the highest sensitivity and specificity for diagnosing haemangiomas up to 95%. On MRI they appear as hypointense on T1-weighted images and hyperintense on T2. Enhancement pattern is similar to CT scan in the gadolinium-enhanced MRI [9]. Occasionally haemangiomas are atypical and mimic other liver lesions like metastatic neuroblastoma necessitating biopsy [9]. Other indications for biopsy include late presentation beyond 1 year of life and lack of response to treatment.

Tissue diagnosis is rarely necessary but when performed in cases of uncertainty shows the tumour to be composed of vascular channels lined by endothelial cells. The cellularity is replaced by loose fibro-fatty stroma as the tumour involutes. These lesions are differentiated from other vascular lesions based on immunostaining of the endothelial cells to erythrocyte-type glucose transporter protein 1 (GLUT 1). Focal haemangiomas (congenital) are negative, while the multifocal (infantile) ones are positive for GLUT1 staining. The GLUT1 staining status is not yet established in the diffuse subtype [3, 12].

21.2.2 Management

Asymptomatic FHH are best left alone as they are known to spontaneously involute. Large focal haemangiomas with symptomatic shunts causing heart failure are considered for embolisation or selective hepatic artery ligation. The multifocal or GLUT1-positive haemangiomas are amenable to medical therapy. Recently propranolol has found favour with many clinicians as it has shown significant efficacy in multiple case reports including those with hypothyroidism and heart failure. Exact mechanism of action is not known but is thought to possibly decrease renin which in turn decreases vascular endothelial growth factor and causes vasoconstriction. Other medications such as steroids, interferon and vincristine have been used in some cases. Medically resistant symptomatic tumours may need hepatic embolisation or resection. Diffuse types are the most difficult to manage. Decompressive laparotomy may be needed for abdominal compartment syndrome, and hypothyroidism needs to be treated aggressively. Liver transplant has been reported in patients with MIH and diffuse subtypes which are not amenable to medical or surgical resection [3, 12–14].

21.2.2.1 Mesenchymal Hamartoma (MH)

Mesenchymal hamartoma is a multicystic hepatic tumour with variable amounts of solid tissue. They are seen below the age of 2 years and have a slight male preponderance. MH usually presents as a painless abdominal distension caused by enlarging liver mass but can have an acute presentation because of rapid increase in size causing mass effect. Prenatal lesions have been reported, most often in the last trimester of pregnancy, and it may be a cause of hydrops [17, 18].

Findings on radioimaging are variable and range from multiseptated cystic mass to predominantly solid mass with cysts. The cysts appear as anechoic, while the solid tissue is echogenic. On contrast-enhanced CT, the solid component, septae and peripheral rim enhance. MH commonly involves the right hepatic lobe and is not typically associated with calcification or haemorrhage [17, 18].

On MRI, the cystic content gives variable signal intensity depending on the protein content of the cyst fluid. With contrast, enhancement is limited to the septa and solid components of the tumour. Biopsy is warranted if radiology is doubtful [17].

Histologically, MH is characterised by the presence of mesenchymal stroma, cysts and bile ducts interspersed with hepatocytes. Although benign, MH shares several common histopathologic, immunohistochemical and cytogenetic features of undifferentiated embryonic sarcoma (UES). There are suggestions that UES can develop in pre-existing MH. Calcifications, haemorrhage and necrosis are not frequently seen in these tumours. MH has been considered a focal tumour, but small satellite lesions at the tumour margin have been described which could explain tumour recurrence after apparent tumour resection [17].

21.2.3 Management

MH requires surgical resection as they can grow in size and have a potential for malignant transformation. Percutaneous aspiration and drainage may initially be required for large

cystic lesions causing mass effects followed by surgical resection. Liver transplant has been considered for unresectable tumours [18].

21.2.3.1 Focal Nodular Hyperplasia (FNH)

FNH is uncommon in children and accounts for 2–4% of all paediatric liver tumours [1, 15]. A marked female preponderance has been noticed. FNH lesions are solitary in about 70–80% and less than 5 cm although larger lesions have been documented. Multiple lesions may be seen in patients with underlying vascular liver diseases like Budd-Chiari syndrome, portal vein agenesis and congenital disorders such as hereditary haemorrhagic telangiectasia [16, 17]. FNH is considered to be a proliferative or a hyperplastic cell response to increased blood flow by an aberrant vascular malformation. A higher incidence has been noted in patients with a history of previously treated malignancy as compared to general paediatric population and is possibly related to treatment-related vascular injury. The mean time to develop FNH after treatment is estimated to be between 4 and 12 years (range 2–27 years). It has also been reported in congenital portosystemic shunts and may be because of impaired portal flow with compensatory arterialisation of the liver parenchyma (Table 21.2). Compared to other liver lesions, the size of FNH remains stable over time. They are rarely symptomatic and are picked up incidentally on radioimaging although few patients may be symptomatic with abdominal pain and distension. Tumour rupture and haemorrhage are extremely rare.

The echogenicity of both FNH and its scar is variable and may not be picked up on ultrasound if they are isoechoic with the surrounding liver parenchyma. Some may be visible because of a pseudocapsule formed by compression of surrounding liver parenchyma. The diagnostic feature is the presence of a central scar which may be hyperechoic to the rest of the lesion. The central scar on Doppler examination is fed by an artery and extends to the periphery in a spoke wheel pattern. On unenhanced CT scan, FNH appears as a well-circumscribed, homogeneous hypoattenuating mass. After contrast, FNH enhances homogeneously relative to the back ground liver in the late arterial phase. In the portal and subsequent phases, the lesion becomes isoattenuated except for the central scar which is hyperintense as compared to the rest of the liver because of accumulation of the contrast. A typical scar may not be seen in as many as 20% of cases [16, 17].

MRI is comparatively more sensitive and specific to USS and CT scan in diagnosis of FNH. These lesions are seen as homogeneous, slightly hypointense on T1-weighted images and hyper- or isointense on T2 images with a bright central scar in about 80% of patients. The use of hepatobiliary MR contrast agents demonstrates features similar to contrast-enhanced CT scan.

Regenerative nodules may have similar features to FNH, and pre-contrast features may be useful to make the differentiation. Atypical features of FNH, like the presence of steatosis, strong hyperintensity on T2-weighted images, pseudocapsule mimicking true capsule and washout in the equilibrium phase, cause difficulties in characterisation of the lesion and need a biopsy for definitive diagnosis [11, 17].

Histologically, FNH is composed of hyperplastic hepatocytes arranged in nodules separated by fibrous septa that originate from the central scar. Ductular proliferation, blood vessels and inflammatory cells seen in the fibrous septa are highly suggestive of FNH. Immunohistochemical staining for glutamine synthase is specific to FNH and is used for diagnostic accuracy [17].

21.2.4 Management

A conservative approach is recommended in asymptomatic FNH given the rarity of complications [16]. However it can be difficult to distinguish from hepatocellular carcinoma (fibrolamellar) and may require surgical resection. Resection has also been considered if the FNH is pedunculated, expanding or exophytic for the theoretical risk of rupture secondary to trauma. In the past this has been a reason to consider surgical resection of this benign tumour.

21.2.4.1 Hepatic Adenoma (HA)

Hepatic adenoma is a rare benign neoplasm of the liver commonly seen in adolescent girls using oestrogen-based oral contraceptives. Conditions associated with adenomas without a sex predilection include glycogen storage disease types 1 and 3, maturity-onset diabetes mellitus, androgens (either endogenous production or exogenous therapy), congenital or portosystemic shunts, germline mutation of hepatic nuclear factor-1α (HNF-1α) gene and familial adenomatous polyposis [16–18] (Table 21.2).

HA is usually a solitary tumour, asymptomatic and discovered incidentally. Some adenomas come to medical attention because of abdominal pain, palpable mass or haemodynamic instability because of tumour rupture with bleeds. Multiple adenomas may be noticed on a background of glycogen storage disease or androgen therapy. “Adenomatosis” is a term used when there are more than ten adenomas, seen in adults without an underlying background liver disease and unrelated to oestrogen or androgen therapy. They are invariably symptomatic and need medical intervention [19].

Hepatic adenomas on USS or CT scan appear hypodense but are heterogeneous in echotexture because of necrosis, fat and haemorrhage. Doppler examination demonstrates internal vascularity. On contrast-enhanced CT scan, they show a variable pattern of enhancement in the late arterial phase and become isodense to the liver in delayed images [16, 17].

MRI is the best imaging modality for hepatic adenomas as it is sensitive in detecting fat and haemorrhage. They are

seen as heterogeneous lesions on both T1- and T2-weighted images, and the imaging features reflect the tumour subtype. Enhancement patterns with gadolinium are similar to contrast-enhanced CT, but chemical shift and fat suppression techniques facilitate identification of lesions with fat. Some HCC lesions contain fat and may make the differentiation from HA difficult warranting histopathological investigations [16].

On histological examination, HA is seen as well-demarcated tumour composed of sheets of liver cells without a fibrous capsule or portal tract elements. Very few Kupffer cells can be seen with no bile ducts, a feature that distinguishes it from FNH. Areas of necrosis and haemorrhage can be seen within the tumour [17].

Adult hepatic adenomas have been classified into four subtypes based on immunohistochemical markers: HA inactivated for HNF-1α (H-HA) characteristically associated with steatosis, inflammatory HA (I-HA) associated with mutations activating the JAK/STAT pathway, β-catenin-activated HA (β-HA) and the unclassified HA (U-HA) which do not have any specific mutation or morphology. Among these the β-HA subgroup has the highest risk for malignancy. In addition telangiectatic FNH has now been classified as I-HA based on molecular studies. This classification is helpful in prognosticating HA, thereby guiding management strategies [20, 21]. There are no reported studies on molecular subtyping exclusive to paediatric population to our knowledge.

21.2.5 Management

Good metabolic control in glycogen storage disease, androgen withdrawal, stopping oral contraceptives, weight loss and closure of congenital portosystemic shunts regress HA when associated with these conditions. Close follow-up is advised in all cases to document regression or detect any malignant change [16].

A study published by the Bordeaux group reported half of HA to be the inflammatory subtype but a significant 28% to have the β-catenin mutation explaining the higher incidence of malignant change in HA associated with glycogen storage disease [22].

Lesions more than 5 cm, growing lesions, male sex irrespective of tumour size and β-catenin-expressing adenomas are considered high risk for bleeds and malignant transformation in adults and hence surgically resected. These risk factors should be taken into consideration in paediatric HA as well. Embolisation can be performed in case of haemorrhage followed by resection for residual viable lesion. Management strategies should be discussed in a multidisciplinary team to plan the best possible surgical option [18].

21.2.5.1 Nodular Regenerative Hyperplasia (NRH)

NRH previously thought to be rare is now increasingly being reported as a cause of noncirrhotic portal hypertension. It can occur at any age and is characterised by hepatic parenchyma architecture changing into regenerative nodules surrounded by atrophic liver with no perisinusoidal or periportal fibrosis. The nodules are of variable size and small ones can coalesce to form bigger ones.

The pathogenesis of NRH is unclear but is probably a hepatocytic hyperplastic response related to altered small vessel blood flows. It has been reported in patients with Abernethy malformations and portal vein thrombosis. Other causes implicated are drugs like steroids, azathioprine, immunosuppressive drugs, autoimmune conditions, collagen vascular disease, neoplastic and myeloproliferative diseases and congenital thrombophilia.

About half of the patients with NRH will present with portal hypertension, while the others may be picked up incidentally.

It is difficult to make a definitive diagnosis of NRH on radioimaging alone as the nodules may be too small to be picked up. Nodules, even if the nodules are large, are difficult to differentiate from normal liver parenchyma. Findings related to portal hypertension may be seen. The lesions are hypoattenuated on non-contrast CT scan and do not enhance in the arterial phase of contrast-enhanced CT scan. On MR imaging, the nodules are homogeneous, slightly hyperintense to the surrounding liver parenchyma on T1-weighted images and variable on T2-weighted images. Liver biopsy is the gold standard in diagnosing NRH [17, 19].

21.2.6 Management

Managing portal hypertension is the mainstay of treatment, and the aetiological factor should be eliminated if possible. Other causes of portal hypertension should be excluded before making a diagnosis of NRH. Outcome and prognosis depend on underlying aetiological factor and severity of portal hypertension [17].

21.2.6.1 Inflammatory Myofibroblastic Tumours (IMT)

They are benign, also called as inflammatory pseudotumours. They can arise from any organ system. Histologically, they are masses of inflammatory infiltrate with collagen stroma. IMT may be difficult to differentiate from malignant lesions. Symptoms because of local effects need resection including liver transplant for unresectable hilar tumours, while asymptomatic ones are treated conservatively [23].

21.2.6.2 Hepatic Cyst

It is a benign congenital lesion resulting from abnormal exclusion of the intrahepatic biliary ducts. These lesions do not communicate with the biliary tree. They occur in approximately 2.5% of the general population, are usually asymptomatic and are discovered incidentally, but large big cysts may present with abdominal pain and distension or complications including infection and bleeding [24].

Simple hepatic cysts are thin-walled anechoic masses without septae or vascularity on USS. On CT and MRI, they appear as non-enhancing masses with attenuation and signal intensity of water.

Atypical cysts with fenestrations, septations, multiple cysts, calcifications and daughter cysts warrant further investigations to exclude cystic metastasis, hydatid or parasitic cysts. Multiple hepatic cysts (more than ten) should raise the possibility of polycystic liver disease, often referred to as ciliopathy.

Histologically simple hepatic cysts are composed of an outer layer of fibrous tissue and are lined by cuboidal, columnar epithelium that produces cystic fluid.

Asymptomatic cysts do not require treatment or follow-up. Large symptomatic cysts or cysts with complications need surgical intervention.

Ciliated hepatic foregut cyst (CHFC) is very rare in children with only a handful of cases being reported in literature. They originate from the embryological foregut. They are usually seen in segment 4 although a few have been described in the anterior segments of the liver. CHFC have similar appearances to hepatic cyst radiologically but may be iso- or hyperdense in a few because of soft tissue density. The presence of ciliated epithelium on histology differentiates them from hepatic cyst. Surgical approach is recommended given the risk for malignant transformation and biliary communication [24].

21.3 Malignant Hepatic Tumours

Malignant tumours can be classified as the most common liver tumours accounting for two thirds of all liver tumours in the paediatric population, 80% of these being hepatoblastoma (HB) [5, 25]. Hepatocellular carcinoma, mesenchymal stromal tumours, epithelioid haemangioendothelioma (which are rarely described in childhood), cholangiocarcinoma and nested tumours account for the remainder [5, 26]. The incidence of HB is rising, while the remainder have more or less remained static. This could be because of increased survival of premature babies which is a risk factor for HB. The incidence of HCC is expected to decline with universal hepatitis B vaccination, as worldwide, a large proportion of HCC in children is seen with chronic hepatitis B carriers. Surgery with or without chemo- and radiotherapy is the essence of treatment, and hence these children should be referred early to a multidisciplinary team with expertise in hepatobiliary surgery and liver transplant.

21.3.1 Hepatoblastoma

Hepatoblastomas usually present in children less than 3 years of age, and about 4% are present at the time of birth. Maternal smoking, parental occupation and genetic susceptibility have been associated with HB, and an increased risk has been reported in low-birth-weight infants with supplemental oxygen therapy, phototherapy, drugs and use of parental nutrition. Hepatoblastomas are also picked up during surveillance programmes for certain conditions like Beckwith-Weidman syndrome and familial polyposis coli (Table 21.2) [5].

Clinically, HBs are often picked up by carer or clinician as an abdominal lump. Atypical presentations include precocious puberty because of β-HCG being secreted by some tumours, osteoporotic fractures or an acute abdomen because of rupture causing intraperitoneal bleed [14]. Hepatoblastoma is often associated with underlying associated syndromes or prematurity (Table 21.1).

Blood investigations may show thrombocytosis because of thrombopoietin and interleukin 6 secreted by these tumours which stimulate the megakaryotic cell line. AFP is an important marker for diagnosis, follow-up and prognosis. It is raised in 90% of the tumours, and a falling AFP to chemotherapy indicates a good prognosis. A rise again after initial fall may mean relapse. Similarly, AFP should fall to normal ranges after surgery, and a rising AFP during postoperative follow-up should prompt the physician to look for recurrence. A tumour with low AFP or AFP that fails to fall with chemotherapy is regarded as biologically aggressive with poor prognosis [5, 14].

β-HCG can be monitored similar to AFP in tumours secreting this marker. Molecular markers like glypican 3, nuclear β-catenin and membranous EpCAM currently have limited clinical application. Research is ongoing to find molecular-genetic markers which can not only help in diagnosis but will have therapeutic and prognostic implications [27].

The first radioimaging done is usually USS. This confirms the origin of the mass to be hepatic. Further imaging with CT scan is required to characterise the lesions, stage them, investigate for pulmonary metastasis and determine if they are amenable to resection. On CT scan, HB appears as heterogeneous, low attenuation mass enhancing on arterial phase and hypoattenuates in the portal phase. Calcifications are frequently seen. MRI is becoming more popular as it avoids radiation. It shows HB as hypointense in comparison to normal liver in T1-weighted sequences and hyperintense in T2-weighted sequences, while post gadolinium, it enhances in a heterogeneous fashion with rapid washout.

Rarely angiography may be required if more clarity on vascular structures is required to aid resection [11].

Biopsy is required before start of chemotherapy in SIOPEL (Childhood Liver Tumor Strategy Group of the Societe Internationale d'Oncologie Pediatrique) protocol although the COG (Children's Oncology Group) from the United States proceeds to resection without biopsy or adjuvant chemotherapy if the presentation and evaluation are suggestive of pure foetal histology subtype. The histology is confirmed on the resected specimen [14].

HB are heterogeneous with varying combination of cell types. The international paediatric liver tumour consensus classifies HB into various subtypes that correlate well with clinical outcome [27]. The well-differentiated foetal cell type has a favourable outcome, whereas the undifferentiated small-cell subtype often has a poor outcome. Consensus has been achieved regarding a general need for pretreatment tumour histology.

21.4 Staging and Stratification of Hepatoblastoma

Children's Hepatic Tumours International Collaboration (CHIC) in an attempt to unify the approach to tumour staging and risk stratification across various tumour groups has recently proposed the new Children's Hepatic Tumours International Collaboration-Hepatoblastoma Stratification (CHIC-HS) [28]. It is based on 5-year event-free survival (EFS) and incorporates PRETreatment EXTent of disease (PRETEXT) staging, age, AFP level and the PRETEXT annotation factors, namely, metastatic disease (M), macrovascular involvement of all hepatic veins (V) or portal bifurcation (P), contiguous extrahepatic tumour (E), multifocal tumour (F) and spontaneous rupture (R) which have been identified as statistically important prognostic factors.

This risk stratification divides all hepatoblastoma cases into low risk (EFS >90%), intermediate risk (EFS 70–90%), high risk (EFS 50–70%) and very high risk (EFS <50%).

CHIC-HS will be further refined in coming years to include CHIC histology subtype review. This stratification will allow comparison of various treatment strategies and in conjunction with biological and molecular markers will pave a path for individualised approach for hepatoblastoma.

21.4.1 Management

The cornerstone of management of HB is to achieve a tumour-free resection state. Chemotherapy is able to downstage about 60% of HB that are unresectable at diagnosis. It is important to identify risk factors for unresectability at presentation so that discussions are initiated early on with a hepatobiliary centre with multidisciplinary expertise in managing these children [29–31].

Risk stratification helps guide treatment of HB, and the mainstay of treatment is cisplatin-based chemotherapy and surgery. SIOPEL treats PRETEXT 1, 2 and 3 hepatoblastomas with a combination of chemotherapy and surgery [28]. The tumours shrink because of fibrosis with chemotherapy and provide easy resectability. Usually four cycles of chemotherapy are given, and surgery is planned around this time followed by two more cycles of chemotherapy.

Multifocal as compared to focal disease, even with similar histology, is associated with poor EFS and overall survival and should have intensive chemotherapy [32]. The COG approach is to offer primary resection at diagnosis if feasible followed by chemotherapy, exception being the tumour with pure foetal cell-type histology which does not receive chemotherapy after resection. Unresectable tumours are treated with neoadjuvant chemotherapy in an attempt to shrink the tumour to facilitate resection. This is a strategy to limit the use of chemotherapy [31, 33].

Liver transplant is considered in unresectable hepatoblastomas in carefully selected patients and is discussed in the later section.

The outcomes of HB have changed significantly in the last few years, and the initiation of Paediatric Hepatic International Tumour Trial will add more to our understanding and hopefully provide solutions for tumours that are currently high risk with increased recurrence rates.

21.4.1.1 Hepatocellular Carcinoma (HCC)

HCC is uncommon in children and its incidence increases with age. They are picked up on surveillance programmes in children with a background of liver disease that predisposes them to develop HCC (Table 21.2) (Fig. 21.3). On rare occasions,

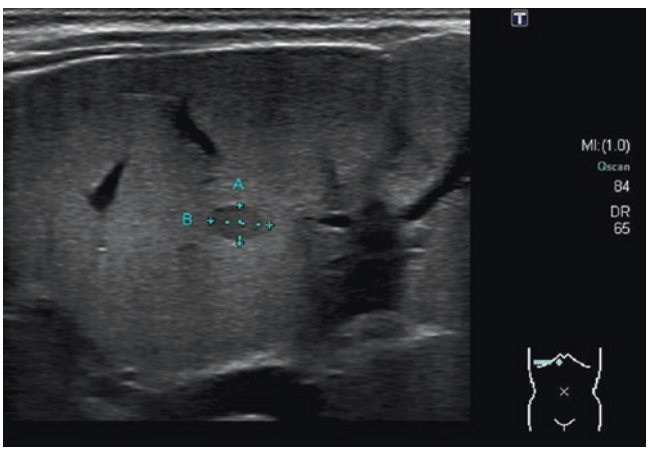

Fig. 21.3 HCC in a 1-year-old girl with TJP2 deficiency, waiting for liver transplantation for end-stage liver disease. Total AFP was 40 ng/mL, and L3 AFP was detectable at low levels of 7 ng/mL. Histology post-liver transplantation confirmed the suspicion of HCC

they are identified because of abdominal pain, a lump or jaundice because of biliary tree compression or invasion without a pre-existing liver disease where the prognosis is not so good.

AFP is used as a tumour marker for diagnosis, monitoring response to therapy and for recurrence of tumour. Some HCC may not produce AFP. Transcobalamin I 100 (vitamin B12-binding protein) is a useful monitoring marker in the fibrolamellar variant of HCC which occurs on a background of noncirrhotic liver [5, 14]. CECT and MRI are imaging modalities of choice for evaluation of HCC. The characteristic imaging appearance of HCC is early arterial enhancement followed by washout during delayed imaging. Fibrolamellar type, a variant of HCC, can have a central hypodense, hypervascular area mimicking a central scar of FNH. MRI is useful in distinguishing these two conditions [11].

Special stains (reticulin stains) can sometimes be helpful because the reticulin framework is completely lost in well-differentiated HCC. Positive immunostaining with markers such as glypican-3 and heat shock protein 70 is highly specific but not sensitive in differentiating HCC from HA [21].

21.4.2 Management

Management of paediatric HCC is challenging. Complete surgical resection is required for cure. Resectable HCC without metastasis have a 5-year EFS of 80–90%, but only 20% of HCC have been reported to be amenable to resection at the time of diagnosis. Results for unresectable HCC or HCC with metastasis are poor. Neoadjuvant chemotherapy for HCC is derived from experiences with paediatric hepatoblastoma. In contrast to adults, about 40% of tumours are chemosensitive which however does not translate to resectability. Resectability is achieved in approximately 36% even with intensification of chemotherapy. Sorafenib, gemcitabine and oxaliplatin have improved resectability in adults and need to be investigated in children. Transarterial chemoembolisation (TACE) chemotherapy has been reported in a few paediatric cases to achieve resectability. Studies are ongoing in adults with new drugs like bevacizumab, c-met inhibitors and immune checkpoint blockade agents like nivolumab [33].

Experience with liver transplantation in HCC is limited. The outcome of HCC after liver transplantation in childhood is greater than in adult patients (see below).

The radioimaging features of various liver tumours and nodular lesions is summarised in Table 21.3.

21.4.2.1 Biliary Tract Rhabdomyosarcoma (BRS)

BRS is rare and accounts for 0.8% of all rhabdomyosarcomas. It arises in the biliary system and can extend into the liver parenchyma or down into the biliary system and typically presents with symptoms and biochemical features of obstructive jaundice. It is seen in the younger age group with a median age of 3 years. After the initial radioimaging, biopsy is required to confirm the diagnosis. The pathology of the intraductal lesions is similar to that of rhabdomyosarcoma at other sites. The intraductal tumour is usually either the botryoid or embryonal subtype, unless the lesion involves predominantly the hepatic parenchyma, in which case the alveolar subtype predominates. MRCP is particularly useful in diagnosis as it delineates the biliary system. These tumours are chemosensitive and are managed with a combination of chemotherapy followed by resection [18].

21.4.2.2 Undifferentiated Embryonal Sarcoma (UES)

It is an aggressive mesenchymal tumour seen more frequently in older children. Abdominal pain, poor appetite and weight loss are typical presenting features. Malignant transformation from mesenchymal hamartomas is reported. They appear as solid on USS while cystic without solid components on CT and MRI. This discrepancy is highly suggestive of UES. Diagnosis is by histology showing spindle-shaped tumour cells in a myxoid matrix with positive immunostaining (positive expression of SMA, a-ACT, desmin, vimentin). Multimodal approach with chemotherapy, radiation and surgery has improved the outcome in recent years. Liver transplant experience in unresectable UES is limited to a few case reports [5, 18].

21.4.2.3 Angiosarcoma

This is a malignant spindle cell tumour of the liver derived from endothelial cells. Prognosis is poor with early metastasis often to the lungs. Cases treated with chemotherapy followed by hepatectomy and liver transplant have been reported [18].

21.4.2.4 Malignant Rhabdoid Tumour (MRT)

MRT shares some clinical features and may be difficult to distinguish from HB in some cases. Immunohistochemistry for INI1 is necessary for accurate diagnosis. It is treated with chemotherapy with aims of complete resection. However, outcomes are very poor [18].

21.4.2.5 Epithelioid Haemangioendothelioma

This is a very aggressive tumour with extrahepatic spread and may be difficult to resect even after chemotherapy and TACE (Fig. 21.4). Diagnosis is usually made because of symptoms related to tumour growth like pain, portal hypertension or liver failure. Newer chemotherapeutic agents have shown promising results in tumour shrinkage and may help in achieving resection. Response to chemotherapy may also help in selecting patients for liver transplant if they are unresectable [5].

Table 21.3 Radioimaging features of Liver lesions

Liver lesion	USS findings	Contrast CT scan		MRI		Other tests
		Arterial phase	Delayed portal phase	T1 weighted	T2 weighted	
HH	Heterogeneous Hypoechoic ± calcifications	Peripheral nodular enhancement	Centripetal fill-in	Hypointense	Hyperintense	Thyroid function tests, Glut1 immunohistochemistry
HB	Heterogeneous, septa Hypoechoic ± calcifications	Enhancement seen	Hypoattenuates	Hypointense	Hyperintense	High AFP ± vascular invasion
MH	Hypoechoic, echogenic septa	Unenhanced	Enhancement of septa and solid portions	Hypointense	Variable intensity Enhanced septa	
FNH	Variable echogenicity Central scar	Homogeneous enhancement, hypodense scar	Isoattenuated lesion, bright scar	Iso- to hypointense	Hyper- to isointense Scar mildly hyperintense	
HA	Variable echogenicity Heterogeneous	Enhance actively	Hypodense	Variable intensity	Hyperintense, fat, haemorrhage	MRI with chemical shift or fat suppression useful in high lipid content
HCC	Heterogeneous, Hyperechoic	Enhance actively	Hypodense, rapid washout	Variable intensity	Hyperintense ± fat ± haemorrhage	Scar may be seen in fibrolamellar variant ± vascular invasion ± high AFP
HC	Anechoic Homogeneous	No enhancement, near-water density		Hypointense, homogeneous, no enhancement	Hyperintense	
Abscess	Anechoic	Enhancement of rim		Hypointense	Hyperintense	
NB	Similar to haemangioma					Urine catecholamines, additional sites of metastasis, presence of primary tumour

HB hepatoblastoma, *HH* hepatic haemangioma, *MH* mesenchymal hamartoma, *FNH* focal nodular hyperplasia, *HA* hepatic adenoma, *HCC* hepatocellular carcinoma, *HC* hepatic cyst, *NB* neuroblastoma

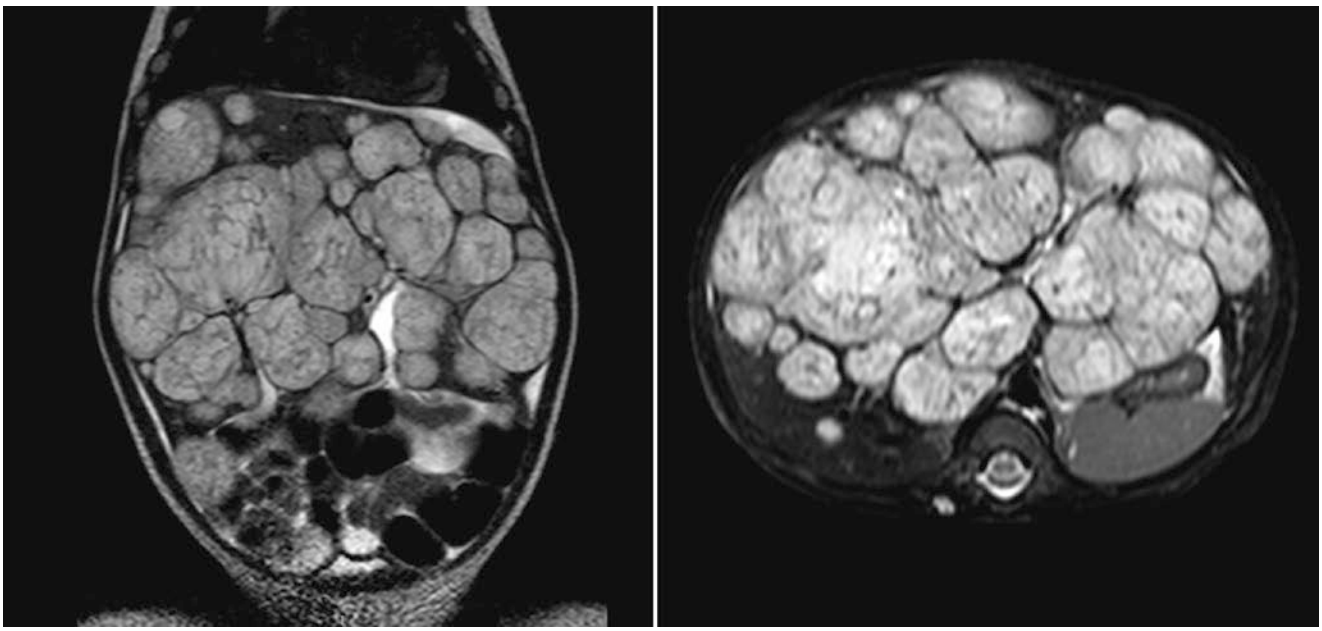

Fig. 21.4 Hepatic haemangioendothelioma in a 3-month-old child

21.5 Indications of Liver Transplant in Liver Tumours

The 5-year survival in unresectable and metastatic HB has improved following liver transplant in a select group of children, and indeed liver transplant is now an acceptable indication for this condition. Audacious attempts at resection are discouraged as outcome after primary liver transplants has proved to be far superior to ones done after recurrence following resection [25, 30, 31]. It is hence important that these tumours are staged accurately so as to plan the best surgical option.

Liver transplant is considered for unresectable HB without extrahepatic disease, exception being pulmonary metastasis provided they have been treated medically with chemotherapy or resected surgically before transplant. Recurrence of disease after resection, involvement of the hilar structures or the main portal vein and its branches and involvement of all hepatic veins which is unlikely to be amenable to resection should also be considered for liver transplant. Each patient should be individualised and discussed within the multidisciplinary team to ensure best possible outcome.

The timing to schedule liver transplant after chemotherapy is narrow, and this is overcome by prioritising them on the waiting list. Living related liver transplant options are also considered to circumvent this problem [30, 31].

The role of post-transplant chemotherapy is not very clear, and the recommendations vary from centre to centre. Some have reported it to be beneficial and some not [34].

In contrast to HB, experience with liver transplantation that is offered to unresectable HCC without extrahepatic spread or macroscopic vascular invasion is limited. Results are improving due to appropriate patient selection and advances made in surgical techniques and chemotherapy. It is currently under debate if the adult Milan criteria should be applied in children as biology of tumours is different and each patient needs to be individualised [35]. Successful liver transplants have been reported in children even when transplanted beyond the more liberal University of California, San Francisco, criteria (single tumour ≤6.5 cm or maximum of three tumours ≤4.5 cm and cumulative tumour size ≤8 cm) or the up-to-seven criteria (absence of angioinvasion, number of nodules plus the maximum size of the largest nodule ≤7 cm) and the United Kingdom criteria (single tumour ≤5 cm or maximum of three tumours ≤3 cm or tumour >5 cm and ≤ 7 cm without tumour progression, extrahepatic spread and no new lesions over a 6-month period) [36–38]. Outcome for liver transplantation for primary HCC is generally better in children than in adult patients. It is not clear if this statistic is solely due to less cirrhotic liver disease in the background of tumourigenesis, superior grafts in younger patients or different tumour biology. Favourable outcomes of liver transplants have been reported if HCC is found incidentally on explant livers as compared to children transplanted for HCC [39]. A recent analysis of the European Liver Transplant Registry data for patient and graft survival in children and adults transplanted for HCC found superior long-term survival in paediatric HCC on a background of inherited liver disease when compared to paediatric HCC without

underlying inherited liver disease and adult HCC patients with or without inherited liver disease. They suggest factoring in this advantage when considering liver transplantation in this subgroup of children [40].

Other rare tumours that may be amenable to liver transplant are epithelial haemangioendothelioma, embryonal cell sarcomas and metastatic neuroendocrine liver tumours after removal of the primary tumour. Although good outcomes have been reported with the exception of angiosarcomas [30, 34, 39], the role of liver transplant is uncertain as very few patients are transplanted because of these tumours and the long-term data is awaited.

Among the benign tumours, liver transplants in symptomatic mesenchymal hamartomas, hepatic haemangiomas and inflammatory myofibroblastic tumours have been reported to have failed medical therapy and are not amenable to resection [41].

Paediatric liver unresectable tumour observatory (PLUTO) is a multicentre, multi-institutional registry that provides database of children transplanted for an unresectable malignant liver tumour. As malignant liver tumours are so rare, results from this registry may provide some answers in the future [42].

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