Multi modality imaging of diffuse liver diseases in pediatric candidates for liver transplantation.

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Learning objectives

The aim of this review is to present the wide spectrum of common and uncommon focal liver diseases affecting neonatal and pediatric liver transplant candidates, analyzed using ultrasonography (US), 16 or 64 multi-detector row helical CT (MDCT) and 1.5 T MRI fast imaging. Correlation of imaging findings and explanted liver or histology is illustrated in representative cases. Associated uncommon congenital anomalies are shown.
Background

**Ultrasonography**: According to the size of the patient, studies may be performed using a microconvex, convex or linear transducer, with anterior and lateral approach, without sedation. This permits detection of morphologic changes in the liver, hepatic focal lesions (cystic or solid) or abdominal masses, and signs of portal hypertension, such as hypersplenism, perihepatic or perisplenic varices, and ascites.

**MDCT**: Studies are usually performed with and without isosmolar or lower osmolar (Iodixanol 320 mgI/ml, Optiray 320, respectively) intravenous contrast material (IVCM), with a dose of 1.5 ml/kg body weight at a rate that depends on the age of the patient (0.5-4 mL/sec). When needed, the procedure is performed under monitored anesthesia care. Our institutional protocol requires that images of the liver be acquired in a cranium-caudal direction, with slice thickness of 1.25 mm if 16MDCT is used, or 0.625 mm if 64MDCT is used, collimation of 2.5 mm and table speed of 7.5 mm per gantry rotation. Tube voltage (80-120 kV) and tube current with automatic dose modulation (160-260 mA) are modified according to body weight.

Three phases are usually acquired: an unenhanced phase, an arterial phase and a portal venous phase. Unenhanced, low dose acquisition is performed primarily in order to evaluate the unenhanced density of hepatic nodules (possible hyperdense regenerative nodules) and to evaluate calcifications. The arterial phase, with 3D reconstruction, is performed to evaluate hepatic artery anatomy, to detect possible replaced or accessory hepatic arteries, and to identify hypervascular lesions. The portal venous phase is performed to evaluate the presence of signs of portal hypertension (varices, spontaneous spleno-renal shunts), the patency of the portal system, and anatomical variants (Abernethy malformation, etc), which can require changes to the surgical plan. Moreover, the portal venous phase gives information about the vascularity of the lesions, if present.

Post-processing of the dataset allows a variety of advanced three-dimensional models of the hepatic artery and vein using multi-planar reconstruction (MPR), maximum intensity projection (MIP), and volume rendering (VR) reconstructions. The volume of the liver in pediatric recipients is usually calculated with dedicated software as a guide for donor-to-dimensional matching.

**MR**: MR examinations are usually performed using a head coil for small infants and body coils for bigger children. All images are acquired in the axial plane in breath-hold or with suspended respiration if general anesthesia is employed. If necessary, contrast media (Mangafodipir trisodico 0.01 mmol/ml, GE, 0.5 ml per Kilos, or Gadobenato dimeglumina 0.1 ml per Kilos, Bracco) is injected. MR Cholangio-Pancreatography (MRCP) with Single
Shot Fast Spin Echo (SSFSE) single and multisection, parallel and radial images are acquired.
Hepatoblastoma

Hepatoblastoma (HB), the most common pediatric hepatic malignancy, accounts for 1% of all pediatric malignancies and for 79% of all liver cancers in children under the age of 15, and is more common in boys (M:F ratio of 3.6:1) (1-3). HBs are classified as either epithelial (56%) or mixed epithelial/mesenchymal (44%). The epithelial group is further subdivided into fetal (31%), embryonal (19%), macrotrabecular (3%) and small-cell undifferentiated subtypes (3%). Pure fetal histology is associated with a better prognosis, while undifferentiated histology is associated with a poor prognosis. In the mixed epithelial/mesenchymal type, the presence of mesenchymal elements is associated with a better prognosis. The most common mesenchymal elements found are cartilage and osteoid. Risk factors for HB are congenital: adenomatous polyposis syndrome and Beckwith-Wiedemann syndrome.

HB is usually asymptomatic, large and solitary, but can also be multifocal. Weight loss, anorexia, emesis and abdominal pain indicate advanced disease. Approximately 90% of patients have elevated serum #fetoprotein levels (4-6). Extrahepatic metastases are present in about 20% of patients at the time of diagnosis. The lung is the most common site of metastasis; other common sites are the brain and bone.

The US findings of HB depend on the histologic types. Usually, HBs are well delineated, multilobulated, and septated: the epithelial type is homogenous and hypoechoic, whereas the mixed mesenchymal-epithelial type is heterogeneous due to calcifications and necrosis.

Both CT and MRI play a key role in diagnosing, staging, and treatment of HB. These modalities are used to define the borders of the tumor and its segmental involvement, and the relation of the tumor to the portal and/or hepatic veins.

On unenhanced CT, an epithelial-type tumor appears as a homogeneous hypodense mass, while a mixed mesenchymal-epithelial tumor has a more heterogeneous appearance. Calcifications may be found in either type: small and thin in the epithelial type, and coarse and extensive in the mixed type. After IVCM, the tumor shows inhomogeneous enhancement, usually lower than that of the surrounding normal liver (Fig.1, 2). A peripheral rim of enhancement can be observed if imaging is performed during the early arterial phase.

The MRI characteristics of HB vary with the histological nature. The epithelial type is homogeneous, hypointense on T1W images, and hyperintense on T2W images. The mixed type is heterogeneous, depending on the presence of necrosis, hemorrhage, fibrosis, calcification, cartilage or septa (7).
Treatment strategies currently combine surgery, chemotherapy (adjuvant and neo-adjuvant) and transplantation. Complete resection of HB is the mainstay of treatment and is the only chance of a cure. Liver transplantation is indicated in unresectable cases (bilateral involvement).

**Hepatocellular carcinoma**

Hepatocellular carcinoma (HCC) is the second most common malignant hepatic neoplasm in children after HB, with an incidence of 0.5-1.0 cases per million. HCC is usually associated with chronic liver diseases, such as Wilson's disease, biliary atresia, tyrosinemia, glycogen storage disease type IA, cystinosis, and Byler disease. However, most pediatric cases of HCC involve de novo tumors and are not necessarily related to chronic liver disease (8, 9).

Long-term survival after complete excision ranges from 18% to 36% (10) depending on the stage of disease. Non-surgical and adjuvant treatments of HCC include chemoembolization, percutaneous ethanol injection and radiofrequency ablation. The role of liver transplantation in pediatric HCC is controversial (11).

On US, HCC is predominantly hypoechoic, though it sometimes appears isoechoic with a thin hypoechoic halo corresponding to the tumor capsule. In diffuse HCC there is subtle disruption of the normal echo pattern with anechoic areas due to necrosis.

Unenhanced CT scans of HCC are hypovascular, or less frequently isovascular, to liver parenchyma. After IVCM, HCC lesions appear as hypervascular in the arterial phase due to the increased tumor vascularity, iso-hypovascular in the portal-phase, and hypovascular in delayed-phase. A fibrous capsule, when present, is characteristically hyperattenuating in delayed-phase. Areas of necrosis, hemorrhage, fat and calcifications may be present (Fig. 3). Less frequent is the hypovascular variant of HCC (Fig. 4).

On MRI, HCC may be hypo-, iso- or hyperintense relative to hepatic parenchyma on T1W images. Typically, most HCCs are hyperintense on T2W images, with the remainder of the liver appearing isointense. Dynamic contrast-enhanced MRI is similar to that of multiphasic enhanced CT (7,11-13).

**Infantile hepatic Hemangioendothelioma**

Infantile hepatic Hemangioendothelioma (IHE) is the third most common hepatic neoplasm under 5 yrs of age; More than 85% of lesions are diagnosed in the first 6 months of life (14). There is a female predominance, with a F:M ratio of 2:1.

Histologically, IHE is a mesenchymal tumor composed of narrowed anastomosing vascular channels lined by a single or multiple layers of plump endothelial cells. Two types of IHE are known. Type I is more common and has lesions that will typically involute
and regress spontaneously after the first year of life. Type II is more aggressive and often multicentric.

In the majority of patients, IHE is clinically silent, even if accompanied by hepatomegaly. When present, the symptoms are non-specific: abdominal pain, vomiting and nausea, jaundice, fever, anemia, respiratory compromise, failure to thrive, weight loss, and intestinal obstruction, though rarely the disease presents as hemoperitoneum with shock secondary to tumor rupture. A consumptive coagulopathy (Kasabach-Merrit Syndrome) is common and the bleeding complications can be life threatening (14-16). Cutaneous hemangiomas are present in 10%-50% of children with IHE.

In certain cases, it can be impossible to distinguish hemangioendothelioma from the cavernous hemangioma on imaging studies.

US may show a complex, mostly solid hepatic lesion with variable hypo- and hyperechoic echotexture. In cases of significant arteriovenous shunting, dilated hepatic vasculature with prominent blood flow at Doppler US is typical.

On CT, hepatic IHE appears as a well-defined, hypoattenuating mass; after IVCM, the mass shows early peripheral enhancement followed by variable delayed and progressive centripetal filling. Large solitary lesions are often associated with central hemorrhage, fibrosis or necrosis, and do not show enhancement. Conversely, small lesions, which tend to be multifocal, frequently enhance completely and typically do not demonstrate hemorrhage or necrosis (2, 3, 7, 13-15).

On MRI, the lesion is predominantly hypointense on T1W images, but areas of hyperintensity are present in the largest lesions, corresponding to presumed areas of hemorrhage. On T2W images, the lesions are usually heterogeneously hyperintense. The gadolinium intake is similar to that of iodinated contrast material during enhanced CT. In cases of extensive liver involvement, lesions with homogeneous enhancement in the arterial phase, lesions with homogenous enhancement in the delayed phase, or both can be seen (Fig. 5) (13, 14). Liver transplantation is considered if all the other possible treatments (steroids, interferon, embolization and resection) fail (15).

Hemangiomatosis

Hemangiomatosis is a rare condition characterized by multiple cutaneous and visceral (liver, gastrointestinal tract, lungs, brain, oral cavity and eyes) hemangiomas in the neonatal period, without malignancy. These benign vascular lesions typically undergo a rapid postnatal growth phase for 8 to 12 months, followed by a prolonged involuting phase lasting 1 to 5 years. Children with hemangiomas involving the liver most frequently have increasing abdominal girth, hepatomegaly, or jaundice (16). Most patients require no treatment because of spontaneous regression. However, a small percentage of cases may become life-threatening and require treatment (Fig. 6). In the case of large hepatic lesions, hemangiomatosis can be associated with congestive
heart failure secondary to arterio-venous shunting, with a mortality rate of between 50% and 90%. Consumptive coagulopathy (Kasabach-Merrit syndrome) and rupture with hemoperitoneum are possible (17).

US can show multiple hyperechoic lesions involving almost the whole liver.

CT findings consist of multiple hypoattenuating lesions on unenhanced images. After IVCM, arterial-phase CT shows early, peripheral enhancement of the lesions, with centripetal filling in portal and delayed phase.

On MR imaging, hemangiomas are characterized by well-defined margins, low signal intensity on T1WI, and high signal intensity on T2WI, which is similar to the appearance of cerebrospinal fluid. The gadolinium intake is similar to that of iodinated contrast media (2, 3, 7).

Hepatic Epitheloid hemangioendothelioma

Hepatic epitheloid hemangioendothelioma (HEHE) is a rare tumor resulting from a malignant transformation of vascular endothelium. Clinically silent in most cases, it appears as a multiple bilobar large lesion and is often unresectable (18).

With imaging, it is possible to identify two different patterns of HEHE: a) a nodular pattern characterized by multiple rounded and peripheral lesions, with a target pattern due to a central sclerotic zone and a peripheral region of cellular proliferation that is separated from the surrounding liver parenchyma by a connective edematous tissue, and b) a diffuse pattern characterized by a large, mainly peripheral mass that usually causes infiltration of the hepatic vessels and nodular transformation of uninvolved liver. In both types, compensatory hypertrophy of the unaffected liver or signs of portal hypertension, as well as capsular retraction and calcification can be seen. (20%) (19).

On US, the nodules usually appear hypoechoic but iso-hyperechoic patterns are also described. The diffuse pattern appears as heterogeneous echogenicity.

On CT scan, before IVCM, the nodular type appears as low-density multiple lesions. The target pattern is best depicted after IVCM, with an enhancement of the cellular proliferation zones, and low density of the central sclerotic zone and the edematous rim. The diffuse type appears as a heterogeneous and large mass with inhomogeneous enhancement (Fig. 7).

On MRI, the HEHE nodules appear hypointense on T1WI and hyperintense on T2WI, with a relative hyperintensity of the sclerotic zone. The dynamic enhancement is similar to a previously reported CT study (19).

Liver transplantation, in most cases, is the only therapeutic option; post-transplantation results for HEHE are comparable to those after OLT for viral-induced cirrhosis (20).
Hepatic Adenomas

Hepatic Adenomas (HA) are uncommon, benign tumors of the liver; these occur primarily in young women with a history of oral contraceptive use and are usually solitary, though multiple adenomas are described in some patients. Adenomatosis (10 or more HA in an otherwise normal liver) is considered a different clinical picture, not correlated with steroid assumption. Because of the high risk of rupture and bleeding in the peritoneum, and of HCC development, there is controversy over treatment options, which range from conservative monitoring to resection or liver transplantation (21, 22).

On US, HA may appear as a well-demarcated hyper-echoic mass, but necrosis or hemorrhage gives rise to heterogeneous echogenicity (hypoechoic or cystic areas).

On CT, HA fat or hemorrhage can easily be identified on unenhanced images. After IVCM, HA enhance rapidly if small. If large, peripheral enhancement can be seen and reflects the presence of large subcapsular feeding vessels; a centripetal pattern of enhancement can also be seen. On delayed phase, washout predominates because of arterio-venous shunting.

On MR without IVCM, HA can be heterogeneous, depending on grading of fat, or on necrosis or hemorrhagic degeneration. HA can appear hypointense on T1WI and hyperintense on T2WI. The fat, when present, is well depicted in the T1 out-phases imaging, resulting in marked hypointensity.

Dynamic gadolinium-enhanced MR imaging is similar to a previously reported CT study (Fig. 8).

Adenomas usually do not show uptake of superparamagnetic iron oxide particles, resulting in decreased signal intensity on T2-weighted images. After injection of a hepatocellular-specific contrast agent, such as Gd-BOPTA, there is usually no substantial uptake (23).
Fig. 1 Hepatoblastoma in a 5 months-old male.

a) CT scan MIP reconstruction shows a hypoattenuating, heterogenous 6-cm lesion, associated to infiltration of right hepatic and portal veins.

b) b). The gross examination shows a spoke-wheel pattern.
Fig. 2. Hepatoblastoma in a 14-years-old boy. a-b) Contrast-enhanced CT scan shows a low-dense, heterogeneous mass with multiple satellite nodules. Portal vein and hepatic veins were compressed and displaced but patent (not shown). c) The gross examination shows a spoke-wheel pattern and areas of necrosis. d) Microscopy shows hepatoblastoma with foci of extramedullary hematopoiesis.
Fig. 3. Type I tyrosinemia. 11 years-old girl with HCC on cirrhosis. a) After i.v. c.m., MR arterial phase acquisition shows a 26-mm lesion, with remarkable enhancement. b) In delayed phase wash out and capsule are present. c) The explanted liver shows cirrhosis and a capsulated HCC.

Fig. 0

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Fig. 4. 12 years-old girl with liver cirrhosis for Wolman disease (absence of acid lipase enzyme). a) portal venous phase contrast MDCT acquisition show a nodular hypodense lesion (circled) into the seventh segment. B) The image shows section from the explanted liver which revealed a orange-yellow in colour and diffusely micronodular parenchyma. The nodules vary in size ranging from 0.2 to 1.4 cm in diameter. The right lobe of the liver showed a 1.4 cm diameter, sharply circumscribed, yellow-orange, soft nodule that bulged above the cut; final diagnosis was hypovascular HCC.
Fig. 5. Diffuse hemangioendotheliomatosis type II in a 2-month-old male.

a) Multiple lesions hyperintense on T2w images. b-c) Dynamic gadolinium enhanced MR shows lesions hyperintense in arterial phase and lesions with delayed filling. d) The explanted liver and the gross examination show multiple nodules ranging from 1 to 2.5 cm in diameter.

Fig. 0

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Fig. 6. Diffuse hemangiomatosis in a 11 months old male. a) MRI shows multiple lesions hyperintense on T2w images. b-c) Dynamic contrast shows early, centripetal and progressive enhancement of the lesions. d) intra-operative picture.

Fig. 0

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Fig. 7. Multiple hepatic epithelioid hemangioendotheliomas with simultaneous localization in the right pleura in a 14 y/o female. a) Unenhanced MDCT show a hypodense lesions with central necrosis. b) After c.m.i.v. the image shows a peripheral enhancement, hypodense centre, and hypodense rim of the lesions (target pattern). The biopsy of the liver (c) and of the pleura (d) show almost entirely of relatively dense fibrous tissue. The neoplastic cells (CD34 positive) are arranged in cords within the mixed hyalinized and myxoid stroma. The cells are rounding to slightly spindled with increased nuclear to cytoplasmic ratio and contain prominent nucleoli. Many of the cells form intracellular lumina. The neoplastic cells stained positive with Factor VIII, CD34 and CD31. e) The scout of MDCT shows a marked scoliosis due to an infiltration of the pleura that in axial image (f) appears like strongly thickened.

Fig. 0

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Fig. 8 Male 17 y/o with six bilobar hepatic adenomas. a) T1 out-phase shows in segment five a lesion (2 cm) with low signal intensity demonstrating the intracellular fat. b) on arterial phase the lesion show a marked enhanced. c) on portal phase non typical finding of adenoma, representing by wash-out, was found. d) On delayed hepato-biliary phase the lesion shows a homogenous hypointensity. e) A biopsy was performed showing lesional tissue comprised of mature, benign-appearing hepatocytes that are fed by multiple aberrant arteries (arrow). These arteries are not contained within connective tissue septa and no bile ducts or metaplastic cholangioles are appreciated. Compared to the surrounding non-lesional hepatic parenchyma, the hepatocytes within the lesion showed slightly increased cellularity and steatosis. However, no obvious cytologic or architectural atypia was appreciated. Final diagnosis was adenoma.

Fig. 0

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Conclusion

Pediatric liver transplantation is the standard of care for patients with end-stage liver diseases. US is usually the first imaging modality utilized for evaluating a patient because it is easy to perform, widely available, and relatively inexpensive. MDCT and fast MRI imaging play a key role in pre-transplantation workup, allowing for the staging of liver disease and the evaluation of associated congenital anomalies.
Personal Information

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