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EDITORIAL

Hepatic Embryonic Development and Anomalies of the Liver

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ABSTRACT

Hepatic embryonic development occurs in three phases. Competence phase (or pre-pattern phase): where the hepatic diverticulum is seen on the 18th day of gestation as a thickening of the ventral floor of the distal foregut endoderm. Specification phase: specification of the liver gene program within the entoderm by signals from cardiac mesoderm that will, later, later to liver formation. Morphogenesis phase: refers to growth of the hepatic bud in the septum transversum mesenchyme and formation of the liver by integration of the parenchymal cells within the developing vascular system. The origin of the anomalies of hepatic morphology occurring in the course of organogenesis remains to be elucidated. Actually, congenital abnormalities of hepatic morphology, as opposed to anatomical variations, are rare. Nevertheless, knowledge of such anomalies is important since they do not always remain clinically latent. Awareness of these anomalies will decrease morbidity and keep away from a number of medical and surgical pitfalls.

Key words: Liver embryology; Hepatic anomalies

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INTRODUCTION

The origin of the anomalies of hepatic morphology occurring in the course of organogenesis (secondary to known and unknown causes) remains to be elucidated. The basic knowledge of embryologic development and normal anatomy of biliary tree will help in understanding and identifying this group of anomalies. In point of fact, congenital abnormalities of hepatic morphology, as opposed to anatomical variations, are rare. Nevertheless, knowledge of such anomalies is important since they do not always remain clinically latent. A possibility of the presence of the abnormal liver has to be kept in mind when an unexplained abdominal mass is encountered. It is very essential to know the variable morphological segmentation of the liver for surgeons. Familiarity of these variants is imperative prior to laparoscopic cholecystectomy, however, preoperative diagnosis by routine investigations is difficult and is only seen in exceptional cases and they often turn out to be unexpected findings during laparoscopic surgery. Congenital anomalies and anatomical variations of extra- hepatic biliary tree and blood vessels though are not common but can be of clinical importance and surprise if present. Every surgeon should assess for these anomalies during laparoscopic cholecystectomy or other invasive diagnostic or therapeutic techniques in order to prevent inadvertent ductal clipping, ductal injuries, strictures and bleeding problems. Awareness of these anomalies will decrease morbidity, conversion and re-exploration in these patients. The current article was intended to provide an overview of the up to date status of different hepatic congenital anomalies based on understanding the nature of embryonic development of the liver.

EMBRYONIC DEVELOPMENT OF THE LIVER AND BILIARY DUCT

The hepatic diverticulum is seen at the 18th day of gestation (2.5 mm stage) as a thickening (pre-pattern or competence stage) of the ventral floor of the distal foregut endoderm[1]. This small hepatic diverticulum is the analog for the development of the liver, extrahepatic biliary ducts, gallbladder, and ventral pancreas[2]. Dynamic signaling plays a role for the specification (second stage) of embryonic liver progenitors. Bone morphogenetic protein from septum transversum, transforming growth factor-beta (TGF beta), and fibroblast growth factor signaling pathways from hepato-cardiac

mesoderm converge on the earliest genes that elicit pancreas and liver induction in mouse embryos[3]. The above signaling factors specify the ventral foregut entoderm to become a precursor of hepatic epithelium by expressing several liver- specific genes[4].

By the 5-mm stage, hepatic diverticulum divides into a solid cranial portion and a hollow caudal one, the cystic part. The cranial part forms the hepatic parenchyma, and differentiates into proliferating cords of hepatocytes and intrahepatic bile ducts, while the smaller cystic portion is the primordium of the gallbladder, common bile duct and cystic duct. The parenchymal cords anastomose around pre-existing endothelial-lined spaces. They increase in mass and become more organized (Morphogenesis stage) at the expense of the septum transversum that eventually forms the liver capsule[5]. Primitive hepatocytes in contact with the mesenchyme surrounding developing hepatic portal veins form a single-layered structure known as the ductal plate. The ductal plate becomes bi-layered with a parenchymal and a mesenchymal facing sheet, respectively. The ductal plate consists of cuboidal cells with increased immunoreactivity for epithelial intermediate filaments such as cyto-keratins relative to the surrounding parenchymal cells[6]. The ductal plate gives rise to cholangiocytes lining the intrahepatic bile ducts, including its most proximal segments. It also generates periportal hepatocytes and adult hepatic progenitor cells[7].

The budding liver invades the vitelline veins and then the umbilical veins. Vitelline veins run from the gut-yolk sac to the heart. The cranial ends of the veins persist as the portal vein and the caudal ends as the hepatic veins. The hepatocytes grow as thick epithelial plates intermingling branches of vitelline veins within the septum transversum to form a system of connecting liver cells plates. On the other hand, the angioblast forms the liver sinusoids. These sinusoids present by 5th week gestation act as templates for the three dimensional growth of hepatic cords. Initially, liver cell plates are 3 to 5 cells thick. Then gradually they become one cell thick plates. Intrahepatic bile ducts begin to form at 6th week gestation at the hilum of the liver and gradually reach the periphery at 3 months. It seems that VEGF-Flk-1 signaling may play an important role in the growth and morphogenesis of primitive sinusoids during fetal liver development[8].

By the 5th week, all elements of the biliary tree are recognizable. Marked elongation of the common duct occurs with plugging of the lumen by epithelial cells. Recanalization of the lumen of the common duct starts at the end of the 5th week and moves slowly distally. By the 6th week, the common duct and ventral pancreatic bud rotate 180 degrees clockwise around the duodenum. Early in the 7th week, the bile and pancreatic ducts end in closed cavities of the duodenum[2]. Notch signaling[4] is required for normal duct formation. That means it stimulates the cells adjacent to the hepatocyte to differentiate into another cell type (duct cells). Notch signals are required for bile duct morphogenesis, and activation of Notch signaling in the hepatic lobule promotes ectopic biliary differentiation and tubule formation in a dose-dependent manner[9]. The originally hollow cystic portion becomes obliterated owing to the rapid proliferation of its epithelium. At first the gall bladder and common bile duct are solid cords under the developing liver in the 6 to 7-mm embryo. Recanalization of the hepatic, common bile duct, cystic duct, and proximal gall bladder then occur by the 16-mm embryo. At the third month, the gall bladder is fully open, and connected with the intrahepatic biliary system.

ANATOMIC HEPATIC ANOMALIES

Morphological anomalies

Morphological developmental anomalies include: *agenesis* (absence of a lobe that is replaced by fibrous tissue); *aplasia* (small lobe with abnormal structure, few hepatic trabeculae, numerous bile ducts, and abnormal blood vessels); or *hypoplasia* (small lobe but with normal structure).

Agenesis of a lobe of the liver: Agenesis of the right lobe of the liver is a rare finding with preservation of the middle hepatic vein. It is usually an incident finding reveled by imaging exams or during abdominal surgery[10].

Hypoplastic right lobe: Hypoplasia of right hepatic lobe is a rare congenital anomaly that is sometimes associated with ectopy of gall bladder[11].

Positional anomalies

Accessory lobes: Accessory lobes of the liver may be attached to the liver tissue by a mesentery and to be viable, the lobe should contain hepatic artery, hepatic vein, portal vein and a bile duct. Gradual worsening of the circulation to the lobe is the cause of late onset of the symptoms and signs as a result of torsion of the lobe or traction and compression of neighboring structures[12,13].

Ectopic hepatic tissue: This rare ectopic tissue is seen frequently in the abdominal cavity attached to abdominal structures as the spleen, pancreas, and adrenal glands by mesenteries or stalks. Heterotopic liver tissue may be present above the diaphragm, but mostly connected to the liver by a small pedicle piercing the diaphragm or passing through a small hiatus[14].

Heterotopias of the liver: Multiple foci of heterotopic liver in the jejunum were discovered in an infant. Jejunal heterotopic liver showed progressive histological changes indicative of biliary duct obstruction. No connections to the main body of the liver or biliary tree were found[15].

Focal nodular hyperplasia (FNH): FNH has various labels: solitary hyperplastic nodule, hepatic hamartoma, focal cirrhosis, hamartomatous cholangiohepatoma, and hepatic pseudotumor. Focal nodular hyperplasia (FNH) is the second most common tumor of the liver, surpassed in prevalence only by hepatic hemangioma. FNH is believed to occur as a result of a localized hepatocyte response to an underlying congenital arteriovenous malformation. FNH is a hyperplastic process in which all the normal constituents of the liver are present but in an abnormally organized pattern. The CT appearance is generally that of a small (<5 cm), smooth, or lobular mass with a hypodense central scar[16] (Table 1).

VASCULAR ANOMALIES

Variant hepatic arterial anatomy

Variation in hepatic arterial anatomy is seen in 40-45% of people[17]. Classic branching of the common hepatic artery from the celiac artery, and the proper hepatic artery into right and left hepatic arteries to supply the entire liver, is seen in 55-60%. In general, the common hepatic artery may arise from the abdominal aorta or superior mesenteric artery (SMA), and all or part of the right and left hepatic arteries may arise from (be replaced to) other vessels. The two commonest variants are right hepatic artery replaced to the SMA and left hepatic artery replaced to the left gastric artery.

Most common variants are given here[17]:

Common hepatic artery: from aorta: 2%; from SMA: 2%; trifurcation into RHA, LHA and GDA: 4 - 8%.

Right hepatic artery (RHA): from coeliac artery: 1-4%; from SMA: 9-15%; accessory RHA from SMA : 1-7%.

Left hepatic artery (LHA): from left gastric artery (LGA): 4-11%; accessory LHA from LGA: 4 -11%.

Right and left hepatic arteries: RHA from SMA and LHA from

LGA: 0.5-2%; accessory RHA and LHA: 1%.

It is prudent during hepatic angiography to perform selective runs of both the coeliac artery and SMA to look for variant anatomy[17].

Portal vein anomalies

Defects of the portal venous system include those in which the portal vein is completely absent, has an abnormal communication or course, or is duplicated[18]. In their study Zafer *et al*[19] reported the prevalence of portal vein (PV) variations was as high as 27.4%. The rate of main PV branching variation was 21.5%, right PV variation was 3.9%, and segmental PV origin reversing the interlobar boundary was 4%. The most common main PV variations were trifurcation (11.1%) and the right posterior PV branch being the first branch of the main PV (9.7%).

Hepatic veins anomalies

Hepatic vein variants are more frequent in women than in men, and they may be accompanied with portal vein variation[20]. Most affected patients have a single accessory inferior hepatic vein, although occasionally there can be two such veins. An accessory RHV occurs in 52.5% of patients, two accessory hepatic veins in 12%, and an accessory vein draining the caudate lobe in 12%[21].

HEREDITARY ANOMALIES

Hereditary hemorrhagic telangiectasia(Osler- Rendu-Weber disease)

Hereditary hemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome), is an autosomal dominant vascular disorder with a variety of clinical manifestations (epistaxis, gastrointestinal bleeding, characteristic mucocutaneous telangiectasia). In addition, arteriovenous malformations (AVMs) commonly occur in the pulmonary, hepatic, and cerebral circulations. Large AVMs between the hepatic artery and hepatic vein can cause a significant left-to-right shunt with increased cardiac output[22,23]. Portal hypertension and hepatic encephalopathy, particularly after episodes of gastrointestinal bleeding, may result both from shunts between the hepatic artery and portal vein, and from increased sinusoidal blood flow, leading to enhanced deposition of fibrous tissue and cirrhosis of the liver[22].

Ataxia telangiectasia

Ataxia-telangiectasia is an autosomal recessive, multisystem disorder characterized by progressive neurologic impairment, variable immunodeficiency with susceptibility to sinusitis and pulmonary infections, impaired organ maturation, x-ray hypersensitivity, ocular and cutaneous telangiectasia, and a predisposition to malignancy. Veno-occlusive disease of the liver may accompany ataxia telangiectasia[24].

Von Hippel-Lindu disease

Von Hippel-Lindau disease is a rare autosomal dominant familial tumor syndrome associated with brain, retinal, and spinal cord hemangioblastoma; renal cysts and renal cell carcinoma; pheochromocytoma; and pancreatic cysts, pancreatic serous cystadenomas, and pancreatic neuroendocrine tumors. Liver cysts have been associated with von Hippel-Lindau disease[25].

BILIARY SYSTEM ANOMALIES

Congenital anomalies of the bile ducts are relatively common with a reported prevalence of 15% based on surgical studies[26].

Table 1 Anomalies of the liver.

Anomalies of the liver	
Morphological anomalies	Lobe of liver agenesis Lobe of liver aplasia Lobe of liver hypoplasia
Positional anomalies	Accessory lobe Ectopic hepatic tissue Heterotopias of the liver Focal nodular hyperplasia
Vascular anomalies	Variant hepatic arteries anomalies Variant hepatic veins anomalies Variant portal vein anomalies
Biliary system anomalies	Bile duct agensia Gall bladder interposition Right hepatic duct abnormal insertion Accessory bile duct
Hereditary anomalies	Hereditary anomalies: Hemorrhagic telangiectasia Ataxia telangiectasia Von Hippel-Lindu disease (cystic liver)

Agenesis of common bile duct

Congenital absence of the common bile duct, the common hepatic duct emptied directly into the gallbladder; the latter drained by a long cystic duct into the second part of the duodenum. Only eight prior cases with this or very similar anomalies have been reported in the literature[27].

Agenesis of common hepatic duct with interposition of the gall bladder

Interposition of the gall bladder is a rare, surgically correctable anomaly in which the cystic duct is absent and one or both hepatic ducts empty into the gall bladder, which in turn empties into the common bile duct[28].

Anomalous insertion of the right hepatic duct

The right hepatic duct entering the cystic duct is an anomaly that can be detected by intra-operative cholangiography. This can help to avoid any injury to the bile duct during cholecystectomy[29].

Anomalous ('accessory') bile ducts

Accessory bile ducts, often draining a segment of the right lobe of the liver into the common bile duct or the gallbladder, have been found at as many as 4% of necropsies[30].

Duplication of the bile ducts

Congenital anomalies of the bile ducts are relatively common. Congenital doubling of the extrahepatic biliary tract, is extremely rare with discussion primarily limited to sporadic case reports. The anomaly has also been associated with a high incidence of concomitant malformation of the pancreaticobiliary union, especially in cases where the accessory bile duct opens into the second portion of the duodenum or the pancreatic duct[31]. Most cases of duplicated extrahepatic bile ducts that have been reported up to now were diagnosed based on the abnormalities that were found by endoscopic retrograde cholangiography (ERC), MR cholangiopancreatography (MRCP) or operative cholangiography[32].

Congenital broncho-biliary and tracheo-biliary fistulas

Congenital broncho-biliary fistula is an uncommon malformation of the digestive tract. The patient age distribution ranges widely from infants to adults, despite the congenital nature of the anomaly[33].

Ciliated hepatic foregut cyst

Ciliated hepatic foregut cyst (CHFC) is a very rare, benign and

solitary cyst. The radiologic features mimicked cystic-solid mass of the liver[34].

Agenesis (absence) of the common bile duct

Agenesis of the gallbladder is a rare congenital anomaly occurring in 13 to 65 people of a population of 100 000. The rarity of the condition, combined with clinical and radiologic features that are indistinguishable from those of more common biliary conditions, means that it is rarely diagnosed preoperatively, and patients undergo unnecessary operative intervention[35]. In congenital absence of the common bile duct, the common hepatic duct empties directly into the gallbladder; the latter drained by a long cystic duct into the second part of the duodenum. This rare arrangement is common in certain lower animals and is explainable by embryologic studies. Cholecystectomy in these cases inevitably produces a complete defect in the biliary tract, which should be recognized and repaired primarily[36].

Biliary atresia

Biliary atresia is characterized by obliteration or discontinuity of the extrahepatic biliary system, resulting in obstruction to bile flow. Progressive damage of extrahepatic and intrahepatic bile ducts secondary to inflammation may occur, leading to fibrosis, biliary cirrhosis, and eventual liver failure. Patients with biliary atresia can be subdivided into two distinct groups: those with isolated biliary atresia (postnatal form), which accounts for 65-90% of cases, and patients with associated situs inversus or polysplenia/asplenia with or without other congenital anomalies (fetal/embryonic form), comprising 10-35% of cases[37].

Biliary atresia can be classified according to their location and degree of pathology (Kasai classification system) into three main types:

Type I is obliteration of the common bile duct, while the proximal bile ducts are patent.

Type IIa is atresia of the hepatic duct, with cystic bile ducts found at the porta hepatis. Both cystic and common bile ducts are patent.

Type IIb is atresia (obliteration) of the cystic duct, common bile duct, and hepatic ducts.

Type III (>90% of patients) is involvement of the extrahepatic biliary tree and intrahepatic ducts of the porta hepatis. There is discontinuity of the right and the left hepatic ducts to the level of the porta hepatis. This form of biliary atresia is common, accounting for more than 90% of cases. These variants should not be confused with intrahepatic biliary hypoplasia, which comprises a group of distinct and surgically non-correctable disorders[38-40].

CONCLUSION

Congenital abnormalities of hepatic morphology, as opposed to anatomical variations, are rare. Most of them vascular origin. Biliary are more than hepatic lobules anomalies. Nevertheless, knowledge of such anomalies is important since they do not always remain clinically latent. Awareness of these anomalies will decrease morbidity and keep away from a number of medical and surgical pitfalls

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