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Bile Duct Paucity in Infancy

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1. Introduction

Approach to an infant with jaundice and persistent conjugated hyperbilirubinemia includes several pediatric investigations with a different spectrum of invasiveness ranging from clinical biochemistry to liver biopsy. The broad and intense level of investigation needs to be set up soon to exclude surgical conditions that would prompt the child to a beneficial - at least temporary - solution. Paucity of the interlobular bile ducts (PIBD) is defined as a low ratio of interlobular bile ducts to portal tract ratios. However, obtaining adequate tissue for a definitive diagnosis can be a problem in young children. The interlobular bile duct to portal tract ratio is a value that has been considered differently from several authors, but major consensus and discussion platforms among pathologists and hepatologists seem indicate a cut-off value of 0.6 as highly likely for PIBD. PIBD may occur in a non-syndromic setting with various conditions or in genetic syndromes with a peculiar association with simple or complex congenital heart disease. Two well-established syndromes have been identified as genetic syndromes with a PIBD, although the list of the syndromes may be growing in the future. The first syndrome described in the literature is Alagille syndrome (AGS) or arteriohepatic dysplasia with pulmonary stenosis as the most common cardiac single finding and tetralogy of Fallot as the most common complex cardiac defect. Alagille syndrome can be caused by either mutation in the Jagged-1 gene (JAG1) mutation or in the NOTCH2 gene (Bauer et al. 2010). The second syndrome is Williams-Beuren syndrome (WBS), which is a neurodevelopmental disorder with supravalvular aortic or pulmonary stenosis. The WBS is associated with a microdeletion within the 7q11.23 chromosomal band, which encompasses 28 genes and specific low copy repeats serve as substrate for non-allelic homologous recombination leading to the deletion. The most common deletion, which occurs in about 95% of cases, involves a 1.5 megabase DNA segment (Henrichsen et al. 2011). Interestingly, in both genetic syndromes an abnormality of the outlet tract of the ventricular pump of the heart represents one of the most salient feature.

2. Development of intrahepatic biliary system

Understanding the development of the intrahepatic biliary system is crucial to interpret categories of neonatal and infantile cholangiopathies, particularly if infants are preterm or small for gestational age. At the 3rd postovulation week, endodermal cells sprout from

the cranial portion of the primitive foregut and grow towards a loosely arranged mesoderm in the direction of the plexus vitellinus of the embryo. Caudally, a bud arises from the foregut and precisely form the anlage of the extrahepatic biliary system (Hammar,1926; Van Eyken et al, 1988; Nakanuma et al, 1997; Desmet,1985; Sergi et al, 2000b). The ductular reaction observed after sub-massive through massive liver necrosis in individuals with fulminant hepatitis supports the theory proposing the presence of common progenitor cells that may differentiate in bile duct cells along the portal vein branches (Desmet,1985; Sergi et al, 2000b; Dorn et al, 2009). At the hilum hepatis between the 6th and the 9th postovulation week, progenitor cells in contact with the mesenchyme surrounding the portal vein form first mono- and later double-layered cell cords with a slit-like lumen. This structure represents indeed the primitive intrahepatic biliary structure, which is also called "ductal plate". From 12 weeks of intrauterine gestation on, a continuous and progressive remodeling of the ductal plate occurs. A few parts of the primitive intrahepatic biliary structures dilate and slightly migrate toward the center of the portal tract, which are called "peripheral tubular or ductular structures" and represent the immature form of the interlobular bile ducts. Subsequently, one or two immature, mostly peripherally located ductular structures transform into mature interlobular bile ducts, while most of them gradually disappear (Sergi et al, 2008a). The transformation of the ductal plate into mature interlobular bile ducts is accompanied by the expression of specific intermediate filaments of the cytoskeleton, the cytokeratins (CK) (Van Eyken et al, 1988; Sergi et al, 2008b; Sergi et al, 2000a). Epithelial cells forming bile ducts express CK-7 and CK-19 in addition to CK-8 and CK-18, the latter two being also positive in normal adult hepatocytes. Quantification of biliary structures and their maturity may be useful in the evaluation of the maturation of the intrahepatic biliary tree in neonatal and infantile cholangiopathies. The ratio between the number of bile ducts and portal tracts during human fetal development has been extensively studied and morphometric and quantitative studies elaborating the dynamics of the remodeling of the primitive fetal biliary structures have been reported using a computer-based image-analysis system as well (Sergi et al, 2000b).

3. Liver biopsy

The liver biopsy is still the gold standard for the diagnosis of neonatal surgical conditions with cholestasis, e.g. biliary atresia (BA), which is the most important surgically correctable form of persistent conjugated hyperbilirubinemia. Liver biopsy is accurate in more than nine cases out of ten, provided that the hepatic tissue contains more than five portal tracts. However, in the routine practice of many pathology services liver biopsy interpretation at neonatal and infantile age is also a true challenge and difficulties can arise not only from atypical presentations, but also from abnormal maturation of the intrahepatic bile duct system (IBDS). In fact, sometimes the initial injury is more severe in the intrahepatic biliary tree rather than the extrahepatic one, and this can result in ductopenia as a first manifestation. Thus, the concept of a neonatal obstructive cholangiopathy as a pathology continuum with a single underlying cause has been proposed, despite it is still being a matter of controversy (Sergi et al, 2008a). According to our previously published data, patterns of ductular reactions may confound the pathologist and ductal plate remnants may indeed recapitulate the embryonic anlage, which can be a true challenge for the pathologist

interpreting the liver biopsy (Sergi et al, 2008a). In fact, there are biliary structures that may represent a form of ductular proliferation, which seems to be peculiar to the neonate. It is highly likely that there are probably only limited ways of response to different disorders in the neonatal liver and all of them may record the development of the primitive intrahepatic biliary system or ductal plate.

4. Ductal plate malformation

In the liver, the ductal plate is the protostructure of the intrahepatic biliary system and consists of a double-layered cylinder of biliary-type cells with a slit-like lumen forming around the portal vein and its surrounding mesenchyme (stage of ductal plate). The remodeling of the ductal plate is characterized by the incorporation of a few ductal plate cells into the mesenchyme surrounding the portal vein to form bile ducts as well as by the disappearance of nonmigrating ductal plate cells (stage of remodeling ductal plate and stage of remodeled bile ducts). The development of intrahepatic bile ducts proceeds from the hilar to peripheral portions. Two or more of these developmental stages may be present in the same liver specimen and this should be taken into account in evaluating the maturation of the IBDS. The complete or partial persistence of the primitive double-layered cylinder of biliary-type cells in the developing liver gives rise to portal tracts with an increased number of bile duct structures. The term "ductal plate malformation of the liver" was coined to label this complex biliary plexus with an excess of primitive bile duct structures (Sergi et al. 2000a; Sergi et al. 2000b; Sergi et al. 2000c). Previously, we examined the patterns of cytokeratin 7 (CK7) expressing biliary structures of liver biopsies of infants aged less than one year and found specific patterns in biliary atresia, neonatal hepatitis (a category of inflammation of the liver probably including several conditions showing lobular disarray of the hepatocytes and giant cell transformation as well as presence of extramedullary hematopoiesis) and paucity of the intrahepatic bile duct system or paucity of the interlobular bile ducts (PIBD). Cytokeratins are intermediate filaments of the cytoskeleton and ductal plate remnants have been demonstrated to be present, recapitulating the primitive stages of the IBDS. We also found that the lack of intrahepatic bile ducts in infants aged less than one year is an adverse prognostic factor, which was independent from the etiology of neonatal liver disease (Sergi et al, 2008a) and this is supported by the expression of polyductin or fibrocystin, the gene product of the autosomal recessive polycystic kidney disease (Dorn et al, 2009). Ductal plate malformation may be quite variable, but represents altogether a common way to show a disorder of the correct development of the intrahepatic biliary system in which the apoptosis may play a major role (Sergi et al, 2000a). Studying the models of response to liver injury we found a unimodal distribution of the developmental stages, with many remodeling bile ducts seen in surgically correctable cholangiopathies. The major power of our studies was the blind evaluation of the physiological developmental stages of the intrahepatic bile duct formation through a schematic representation of the stages. This emphasizes how consecutive liver biopsies of patients with biliary atresia (BA) may show characteristic changes in singular cases. In our study, we found an increase of the immunoreactivity of the ductal plate cells in BA and PIBD, but this was a factor that was also observed in other infantile cholangiopathies (neonatal hepatitis, NH; other liver

disease, OLD). In the routine practice, it is important to apply a strict definition of interlobular bile duct. The interlobular bile duct should not be confused with neoductules. Indeed, although immunostaining for CK7 is an advance to identify even minute or hypoplastic bile duct radicles that might well be missed in routinely stained sections, an interlobular bile duct is a defined structure with more or less round, well-developed lumen, and is accompanied by an arteriole usually within three arteriolar diameters of distance. In all biopsies an arteriolar to portal tract was calculated to justify the absence of the interlobular bile ducts. Thus, PIBD may be only one aspect or manifestation of a disease primarily characterized by other features and prognosis may be highly variable. Our study aimed to identify a prognostic factor independent from etiology of neonatal liver disease. We chose CK7 instead of CK19 to better highlight the reactive patterns. The ductular proliferation in infants with BA is frequently encompassed in the enlarged and inflamed portal tracts where on-going bile duct destruction takes place. BA affects the development of the intrahepatic and extrahepatic biliary system and results in the progressive fibrotic obstruction of the pre-formed bile ducts. The rapid advances in the understanding of the cellular and molecular physiology of bile secretion have led to a better knowledge of the pathophysiology of cholangiopathy and structural cell damage caused by various hereditary and acquired cholestatic disorders.

5. Developmental Immaturity of the biliary tract

Hepatic haematopoiesis extends from 5 to 6 weeks of embryogenesis to shortly before the time of birth, although at the mid-term the bone marrow begins to take over. Erythropoiesis decreases from a diffuse to an insular pattern (mid-gestation) in the hepatocellular plates, whereas periportal granulopoiesis increases at mid-gestation and correlates with the slow-down of the intrahepatic biliary system development. Besides haematological disorders, fetal haematopoiesis may return to a lesser degree in the form of extra-medullary hematopoiesis (EMH) with insular pattern, during various insults to the intrahepatic biliary system in the young child. In fact, in previous studies, we frequently found EMH in a more or less similar distribution of the four disease classes, which was studied in the CK7-based study. The granulopoietic periportal phase does not seem to be reactivated, because the neutrophils seen in typical or atypical ductular reaction are not accompanied by the presence of periportal myeloblasts. The results of this investigation further defined the important role of liver biopsy in identifying abnormality of the development of the intrahepatic biliary system and correlate it to the development of the hepatic hematopoiesis. This is extremely determining for the outcome in infants presenting with liver disease and to identify "immaturity" in the development of the biliary tract, which can be mis-interpreted as true PIBD (Sergi et al. 2000b). The results of our investigations indicate that early recognition of BD/PT = 0 is clinically significant and is highly likely a harbinger of later worse outcome. The more close and efficient the liaison between histopathologist and clinician, the higher the possibility to rank possible disorders as more or less likely among the set that other observations suggest. We were not able to identify other independent prognostic factors, such as the portal fibrosis and gamma-glutamyl transpeptidase (GGT) levels, in our sample of 87 subjects younger than 1 year of age and undergoing a liver biopsy. Most probably, this was due to the

heterogeneity of our cases. The heterogeneity of our cases and the presence of different diagnoses under the heading of NH may also be a limitation in the interpretation of the 'abnormal reactive patterns' and biliary patterns. To date, the sensitivity of liver biopsy in diagnosing BA is greater than 90% and the specificity probably approaches 80% in several centers of excellence for health care. However, the variety of clinical presentation and the associations with congenital defects in other organs have suggested that BA is a heterogeneous disorder. It is plausible that various injuries may damage the normal pathway of development of the intrahepatic biliary system by infections, toxic iatrogenic, immunorelated or ischemic, depending on the presence of specific genetic or other factors. GGT is a molecule located on canalicular and luminal surfaces of liver cells. Bile is a detergent and elutes GGT into the biliary-tract lumen as it travels along the biliary tree and in our double-blind investigation represents the only clinical-biochemistry analyte differing in a statistically significant manner between groups. Thus, biliary epithelial cell patterns do recapitulate the primitive stages of IBDS, which seems to represent a form of ductular proliferation that is peculiar to the neonate. Abnormal reaction patterns occur mainly in NH, and most remarkably with reference to the clinical impact, the lack of intrahepatic bile ducts in infants aged less than 1 year is an adverse prognostic factor independent from etiology of neonatal liver disease.

6. Causes of paucity of interlobular bile ducts in infants

Bile duct paucity or ductopenia may arise in a syndromic or non syndromic setting. For long time ''syndromic'' bile duct paucity was considered synonymous with arteriohepatic dysplasia, or Alagille syndrome (AGS), which includes congenital heart disease, ocular posterior embryotoxon, and vertebral anomalies (the so-called "butterfly vertebrae"). Alagille syndrome (AS) is an autosomal dominant disorder associated with abnormalities of the liver, heart, skeleton, eye, and kidneys and a characteristic facial appearance (hypertelorism, prominent forehead, flattened nose, and small mandible with pointed chin) and paucity of the interlobular bile ducts or ductopenia (Kamath et al, 2010). Alagille syndrome is characterized by a variable expression and this should be taken into account from both the clinician and the pathologist. The intimate relationship of Notch signaling with the intrahepatic biliary system seems to be fascinating and novel aspects will probably create a platform for future studies (Zanotti et al, 2010). Some patients are diagnosed with AS after prolonged jaundice at neonatal or perinatal age or when liver biopsy findings reveal ductopenia when the children are a little older (Figure 1). Others may be diagnosed during evaluation for right-sided heart disease and congenital heart disease with disturbances of development of the outflow tract of the right heart. Some patients with Alagille syndrome (AS) start to lose interlobular bile ducts in the first months of life, although it seems that in other patients with AS the ductopenia does not appear until 3 years of age. Thus, the morphologic diagnosis of AS cannot be ruled out on the basis of a normal number of ducts in a single liver biopsy early in life. A mild lymphocytic infiltrate with or without an increase of the periductular fibrous tissue accompany the damaged interlobular bile ducts. Moreover, there may be some degree of bile ductular proliferation, canalicular cholestasis, a mild degree of giant cell transformation of hepatocytes, and some degree of hepatocellular necrosis with or
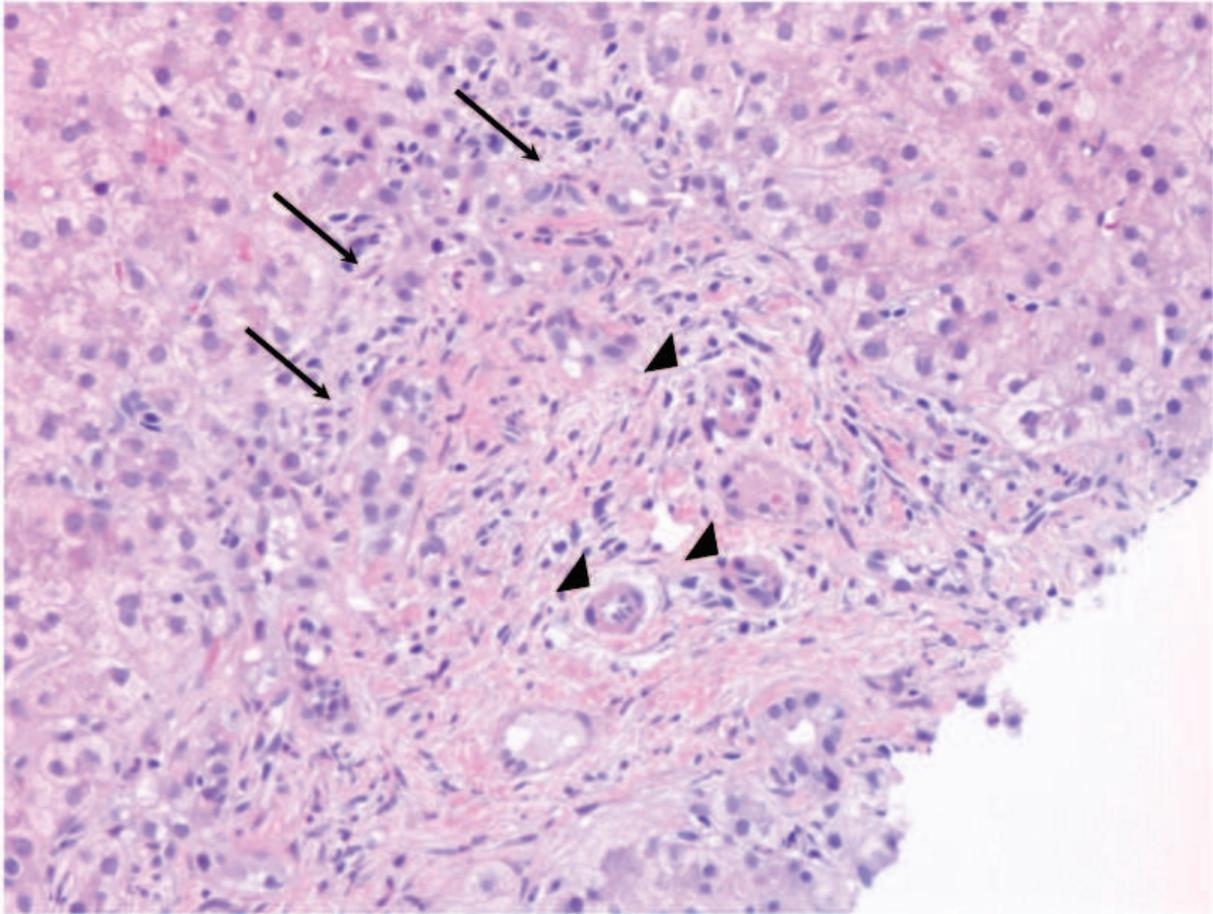
Fig. 1. Paucity of intrahepatic bile ducts in a portal tract of the liver biopsy of a 6-month old male child with Alagille syndrome with tetralogy of Fallot as congenital heart disease. Note the presence of arterioles (arrowheads) and venules (close to the center of the microphotograph) but no accompanying interlobular bile duct. Some biliary ductular proliferation with mononuclear cell inflammation is present at the periphery of the portal tract (arrows) (hematoxylin and eosin staining, x200 original magnification).

without bridging fibrosis and/or cirrhosis. To date, syndromic PIBD is not any more synonymous with AS, but PIBD may be found in at least an additional genetic syndrome, which is the Williams-Beuren or Williams syndrome (WBS). WBS is a rare neuro-developmental disorder caused by a large deletion encompassing about 26 genes localized in the long arm of chromosome 7 (Pober, 2010). Typically, WBS features include a distinctive, "elfin" facial appearance with a low nasal bridge, a cheerful character with strangers as well as delay in the language development, feeding difficulties, and cardiovascular defects, including supravalvular aortic stenosis and more or less transient endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). Other cardiovascular defects found most often in association with WBS are ventricular septal defect, patent ductus arteriosus, stenosis of supracardiac arteries (cerebral, carotid, coronary, brachiocephalic, and subclavian) but also stenosis of renal and mesenteric aretries, coarctation of the aorta, mitral valve incompetence, tetralogy of Fallot (TOF), and vascular ring. An additional syndrome is Ivemark syndrome or heterotaxy (Cohen et al,

2007). Ivemark syndrome (IS) is a rare disorder that affects multiple organ systems of the body. In most patients the phenotype includes absence (asplenia) or underdevelopment (hypoplasia) of the spleen, congenital heart malformation, and an abnormal arrangement of the internal organs of the chest and abdomen, which is also called "situs viscerum inversus". It is known, however, that the symptoms of IS can vary greatly depending upon the specific abnormalities present. The complex arrangement of the visceral organs indicates how life-threatening complications may occur during infancy. The exact cause of Ivemark syndrome is under investigation. The nonsyndromic category of bile duct paucity includes metabolic disorders, perinatal infections, chromosomal anomalies, abnormalities in bile metabolism and transport, and a large miscellaneous group (Table 1). The histology of early biopsies in nonsyndromic paucity mimics AS in many ways, typically showing cholestasis and giant cell transformation. However, though specific histologic features reflect the etiologic heterogeneity, it has been reported that early portal and perisinusoidal fibrosis seem to be more frequently observed in nonsyndromic PIBD than in AS. Identification of nonsyndromic disorders relies on detailed and collaborative clinical and pathology evaluation, which may include cytogenetics, serologic and biochemical blood tests, molecular studies, special histochemical stains, immunohistochemistry, and transmission electron microscopy. The ultrastructural examination of the bile canaliculus and its lumen is central and is performed for all cases with neonatal, infantile and pediatric cholangiopathy in our centre. There is a significant amount of overlap between the clinical manifestations of WBS and AS. Both syndromes have distinct facies, congenital heart disease of the outflow tract of one or both ventricles, musculo-skeletal anomalies, growth and developmental delay, and occasional renal involvement, but both have different genetic implications. In AS, mutations in the JAG1 gene on chromosome 20p12 are identified in 70% of the cases, whereas 96% of patients affected with Williams syndrome show elastin gene deletion. At the end of the chapter table 1 summarizes the etiology of PIBD.

7. Conclusion

In summary, bile duct paucity or ductopenia can be classified as syndromic or nonsyndromic. Syndromic paucity was originally described as being specific for AS, but it is not true anymore. In addition to bile duct paucity of patients with AS present with characteristic facial appearance and developmental abnormalities affecting the heart, eyes, and vertebrae, a couple of other syndromes have been discovered to have ductopenia and the list will probably grow in the future. A caveat to histologic diagnosis in the young child is that ductopenia may not be present on initial biopsy in as many as 20% to 40% of infants with AS. To further complicate matters, ductular biliary proliferation is identified in a small number of infants with AS, leading to potential diagnostic confusion with biliary atresia, which is a surgical condition. In fact, it is important to remember that the porto-enterostomy or Kasai procedure is not a marker for an underlying severe liver disease and may have a detrimental effect on outcome (Kaye et al. 2010). The normal liver in a term infant and older individual demonstrates an interlobular bile duct to portal tract ratio of 0.9 to 1.8, but it should be emphasized that in a preterm infant or in a small-for-gestational age infant the intrahepatic biliary system may still be developing and this ratio may not be applicable with certainty.

Furthermore, obtaining adequate tissue for diagnosis can be a problem in infants. Repeated liver biopsies should be considered as a guideline in cases where the diagnosis is clinically suspected but not confirmed on histology of the first biopsy. A strict liaison between pediatric hepatologist, pediatric cardiologist and pediatric pathologist is crucial. "Primum non nocere", i.e. the Latin words for the medical professional sentence "First do no harm," are still up to date and remain a fundamental medical precept of Hippocrates (ca. 460-ca. 377 B.C.).

Syndromic	Alagille syndrome Williams syndrome Ivemark syndrome or Heterotaxy syndrome

Nonsyndromic	- Congenital infections
	    Rubella Virus
	    Cytomegalovirus
	    Hepatitis Virus
	    Treponema pallidum
	- Metabolic
	    Alpha-1-Antitrypsin deficiency
	    Cystic fibrosis (Mucoviscidosis)
	    Niemann-Pick type C
	    Cerebro-hepato-renal syndrome or Zellweger syndrome
	- Endocrine Disorders
	    Hypopituitarism
	- Chromosomal Defects
	    Trisomy 21
	    Monosomy X0 or Turner syndrome
	- Progressive intrahepatic familial cholestasis (PFIC)
	- Immunologic disorders
	    - Graft-versus-host disease
	    - Chronic hepatic allograft rejection
	    - Neonatal sclerosing cholangitis
	- Miscellaneous
	    Maternal use of progesterone during α pregnancy, Norwegian cholestasis, cholestasis with some non-specific familiarity, familial α hemophagocytic lymphohistiocytosis, congenital pancreatic hypoplasia, and renal microcystic disease
	- Idiopathic

Table 1. Causes of Paucity of Interlobular Bile Ducts in Infants

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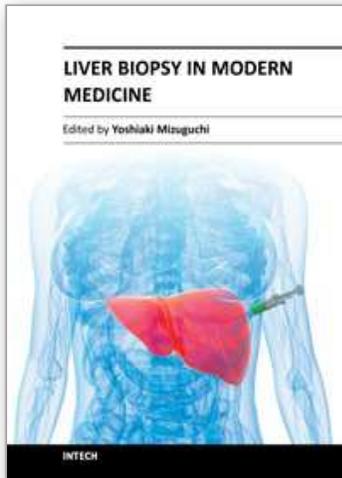
Liver Biopsy in Modern Medicine

Edited by Dr. Yoshiaki Mizuguchi

Liver biopsy, first performed by Paul Ehrlich in 1883, remains an important diagnostic procedure for the management of hepatobiliary disorders and the candidate/donated organ for transplantation. The book "Liver biopsy in Modern Medicine" comprises 21 chapters covering the various aspects of the biopsy procedure in detail and provides an up-to-date insightful coverage to the recent advances in the management of the various disorders with liver biospy. This book will keep up with cutting edge understanding of liver biopsy to many clinicians, physicians, scientists, pharmaceutics, engineers and other experts in a wide variety of different disciplines.

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