Phenotypes of Liver Diseases in Infants, Children, and Adolescents

6

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Introduction

Liver disease in childhood is rare and is frequently the cause of dismay as the medical care provider attempts to recall the myriad of diagnoses that they read about during their training but may never have encountered. In the minds of most, jaundice or elevated liver function tests equals liver disease, but many questions tend to surface: What is the etiology? Can referral wait until more diagnostic information is available? What are the appropriate tests to do and how urgently? What is the likely progression and are there potentially life-threatening consequences of delayed diagnosis and treatment? None of these questions can be answered without formulating a reliable differential diagnosis.

The aim of this chapter is to describe hepatic disease phenotypes based simply on age and primary manifestation of liver disease such as cholestasis, hepatomegaly, or acute liver failure (see Table 6.1) and to provide a reasonably comprehensive list of hepatic diseases that may present with these clinical phenotypes. The hope is to help primary medical providers determine the differential diagnosis and thus guide early studies and appropriate referral and pediatric gastroenterologists and trainees to determine a comprehensive differential diagnosis for their patients on which to base a rational work-up and management plan. This chapter is not intended to be a plan for the detailed investigation of a child with liver disease or a commentary on the probability of any given diagnosis when encountering a patient that fulfils a particular clinical phenotype, but to list the diagnoses that have been recognized, even if only very rarely. Any schema describing the investigations to work through a differential diagnosis is dependent on local conditions dictated by resource availability, priorities, and the probability of a specific diagnosis. For example, in the northwest of the USA, dengue fever would not be included in most differential diagnoses of a local patient, but in Southeast Asia, this would be a major priority.

Hepatology patients range from day-old premature infants to 18-year-old young adults and from seemingly healthy children in the outpatient clinic to profoundly sick infants in the intensive care unit (ICU) on life support. The best way to determine a diagnosis safely and efficiently is to develop a deep understanding of the pathophysiology of liver disease, but even for the most experienced, a checklist of diagnostic possibilities may be helpful to ensure no oversights.

Physicians have always suspected a patient of having disease of the liver from a relatively limited number of clinical signs or symptoms, namely, jaundice, a palpable liver mass or generalized hepatomegaly, splenomegaly, or ascites [1]. Within the last century, blood test abnormalities [2] or aberrant anatomical findings on imaging, commonly

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Table 6.1 List of clinical phenotypes in pediatric patients with liver involvement

The sick infant in NICU with other known disease (frequently a premature infant with respiratory distress syndrome or chronic lung disease of prematurity and often on parenteral feeding support)
(a) Congenital ascites with hepatomegaly or hepatosplenomegaly
(b) Hemorrhage (e.g., gastrointestinal or intracranial) with coagulopathy or low platelets
(c) Necrotizing enterocolitis or surgical resection for congenital bowel malformation
(d) Hepatomegaly or liver dysfunction associated with congenital heart disease or heart failure
(e) An abdominal mass
(f) Cholestatic jaundice or abnormal transaminases
The sick infant in the emergency room or transferred from another hospital
(a) Hepatitis – acute hepatitis or fulminant hepatic failure
(b) Metabolic decompensation – acidosis, hyperammonemia, or hypoglycemia
(c) Abdominal mass with heart failure or Kasabach-Merritt syndrome
(d) Hepatomegaly and abnormal liver function with systemic infection
The stable infant referred to clinic with liver disease
(a) Cholestasis
(b) Elevated liver function tests
(c) Hepatomegaly
(d) Abnormalities found on ultrasound
(e) Asymptomatic infant of mother with chronic viral hepatitis
(f) Asymptomatic sibling of child with known liver disease
Younger child with liver involvement (cholestasis, transaminitis, and/or hepatomegaly)
(a) Acute hepatitis
(b) Presentation of a chronic liver disease
(i) Jaundice
(ii) Ascites
(iii) Gastrointestinal bleeding
(c) Hepatomegaly or hepatosplenomegaly on routine exam
(d) Abdominal mass
(e) Elevated liver function tests on routine screening or tests drawn for other reasons
(f) Abnormal liver or spleen finding on abdominal ultrasound done for other reasons
Older child/adolescent with liver involvement (cholestasis, transaminitis, and/or hepatomegaly)
(a) Acute hepatitis
(b) Presentation of a chronic liver disease
(i) Jaundice
(ii) Ascites
(iii) Gastrointestinal bleeding
(c) Hepatomegaly or hepatosplenomegaly on routine exam
(d) Abdominal mass
(e) Elevated liver function tests on routine screening or tests drawn for other reasons
(f) Abnormal liver or spleen finding on abdominal ultrasound done for other reasons
Acute liver failure
(a) Acute hepatitis with coagulopathy and encephalopathy
Consult from other specialties with liver dysfunction in association with known disease
(a) Gastroenterology
(i) Abnormal liver function or hepatomegaly associated with known gastrointestinal disease, e.g., inflammatory bowel disease or celiac disease
(ii) Transaminitis or cholestasis in children on long-term parenteral nutrition for intestinal failure
(b) Cardiology
(i) Ascites (often chylous) with Fontan circulation
(ii) Hepatosplenomegaly, abnormal LFTs, or ascites-associated heart failure
(iii) Ischemic hepatitis (shock liver) and acute liver failure post-cardiac surgery
(iv) Alagille syndrome

Table 6.1 (continued)

(c) Hematology/oncology
(i) Liver dysfunction associated with liver tumor
(ii) Cholestasis, elevated transaminases, and hepatomegaly in child with hematologic disease, e.g., sickle-cell anemia
(iii) Hepatitis and/or cholestasis associated with chemotherapeutic agents
(iv) Hepatitis and/or cholestasis following bone marrow/stem cell transplantation
(d) Pulmonology
(i) Liver diseases in patients with cystic fibrosis
(ii) Hepatitis in patients with other pulmonary diseases, e.g., sarcoidosis, histoplasmosis, or tuberculosis
(e) Nephrology
(i) Hepatomegaly and splenomegaly associated with polycystic kidney disease
(ii) Cholestasis or abnormal liver function and tubulointerstitial nephritis/nephronophthisis
(iii) Portal hypertension associated with IgA nephropathy or membranoproliferative glomerulonephritis
(f) Endocrine
(i) Hyperlipidemic and obese patients with abnormal transaminases
(ii) Hepatomegaly and transaminitis in poorly controlled diabetics
(iii) Cirrhosis in patients with generalized lipodystrophy
(g) Immunology
(i) Hepatitis or cholestasis in children with defined immunodeficiency syndromes
(ii) Granulomatous hepatitis in chronic granulomatous disease
(h) Rheumatology
(i) Hepatitis associated with lupus, other generalized autoimmune conditions, juvenile idiopathic arthritis, and macrophage activation syndrome
(i) Genetics
(i) Liver abnormalities as part of a dysmorphic or multisystem syndrome
Others: Isolated splenomegaly, unconjugated jaundice, isolated ascites, itching, hemorrhage, or hypocalcemia and rickets

sonography, have suggested liver problems prior to the appearance of clinical signs. Patients commonly have other features of disease such as hypoglycemia, metabolic bone disease, or anemia, and these additional features do indeed constitute the patient's disease phenotype and aid with the refining of a differential diagnosis. However, one should be wary of attempting to define precise and detailed liver disease phenotypes because they may fail to take into account the great variability in how individual disease states may be manifest and consequently lead to a diagnosis being overlooked if not "classical" in its presentation.

Disclaimer

The goal of this chapter is to form the basis of an organized list of diseases of the pediatric liver. It is likely that the most significant gaps will relate to extremely rare hepatological diagnoses and multisystem genetic syndromes with occasional incidental hepatic associations.

Many diagnoses are the subject of detailed discussion in other chapters (and cross-reference will be included where appropriate); however, the more esoteric and unusual may require other resources for in-depth review.

Clinical Assessment: The Importance of a Careful History and an Expert Physical Examination

The value of careful history taking cannot be overemphasized. It is important to understand the timing and the evolution of the features of liver disease, as well as any symptoms originating outside of the liver and gastrointestinal tract. A full inquiry about birth and pregnancy history, previous medical history, family history, and social history is crucial and should include any exposure to drugs and dietary supplements; household, garden, or garage products; and complementary medicinal products. Similarly, a careful history of contact with infectious disease, foreign travel,

and occupational exposure should be obtained. It is important to examine the urine and stool color if possible or, at a very minimum, have the parents describe these colors; stool color charts have been designed for this purpose (see chapter 13). It is not adequate to ask them whether the urine and stools are normal.

Similarly a skilled physical examination will not only assist with making a prompt diagnosis but can save considerable cost to the care of the patient. Eliciting clinical signs on physical examination of a patient may not be easy, particularly with a squirming infant, a frightened toddler, a giggling child, or an overtly belligerent adolescent, but the skills must be well learned and then practiced patiently and conscientiously throughout one's career. It is not enough to expect the correct diagnosis to eventually reveal itself if a multitude of laboratory tests and imaging studies are ordered. In the absence of an expert physical examination, a child with ascites of cardiac origin may undergo multiple studies of the liver over many weeks before the correct etiology is recognized. Similarly the patient with pancytopenia, but in whom the modest splenomegaly is not recognized, may be investigated extensively (and expensively) in the hematology department before portal hypertension with hypersplenism is diagnosed.

In the clinical assessment of a patient with suspected liver disease, there are a number of general considerations to be taken into account when trying to formulate a differential diagnosis. The first of these is age at presentation, primarily because many diseases have a typical age (range) of onset. This may allow us to eliminate some diseases completely, for example, primary biliary cirrhosis has never been described in a young child, and to relegate the possibility of yet others, for example, hepatomegaly first encountered in an adolescent is unlikely to be due to glycogen storage disease. Evidence of liver disease present at birth may imply an intrauterine process such as defects of embryonic developmental genes, congenital infections, or isoimmune phenomena, whereas early postnatal disease may indicate an inborn error of metabolism or infection acquired perinatally.

The next general consideration is whether there is a predisposition to developing certain forms of liver disease, i.e., other medical conditions that may predispose to specific liver diseases such as primary sclerosing cholangitis in patients with preexisting ulcerative colitis or hepatoblastoma in a child with Beckwith-Wiedemann syndrome. Similarly the onset of liver disease during pregnancy such as HELLP (hypertension, elevated liver tests, and low platelets) syndrome or acute fatty liver of pregnancy may indicate metabolic disease in the fetus and usually carrier status in the woman. A detailed family history will help reveal potential familial predisposition such as parental consanguinity or a previous sibling with a single-gene defect. Occasionally there is manifestation of a heterozygous status in relatives such as cholelithiasis in the family of the child with MDR3 deficiency. In a patient suspected of having autoimmune hepatitis, a history in the extended family of other autoimmune conditions such as lupus or hypothyroidism is likely to be relevant.

Environmental exposure to infectious or toxic agents is another general consideration that may alter probabilities within a list of differential diagnoses. Infectious etiologies may gain priority due to an endemic risk at place of abode or recent travel to an at-risk area. A history of drinking or bathing in water from a local supply while traveling raises the possibility of a whole range of infectious agents capable of inducing liver injury. International travel is not, however, a prerequisite for unusual infections that may manifest as liver disease; for example, Histoplasma capsulatum, a cause of granulomatous hepatitis especially in the immunocompromised, is endemic in some central and southern US states [3], and baylisascariasis, a rare cause of hepatomegaly and meningoencephalitis, has been described in young children who have ingested soil contaminated with raccoon feces [4]. Knowledge that a mother has a chronic transmissible infection, particularly hepatitis B but also including hepatitis C, HIV, malaria, and Chagas disease [5], may simplify the diagnosis of an infant with liver disease. Exposure to industrial toxins, particularly from pollutant

spills, is usually reported, but particularly in the developing world, there may not be a full disclosure; therefore, direct questioning is essential. Also all drug exposures should be assessed including herbal and homeopathic remedies and dietary supplements. Ingestion of wild mushrooms is a particular risk. Amanita species are found in many parts of the world, while other foods collected straight from nature may be either directly toxic or chemically contaminated. Not all effects of environmental exposure occur immediately upon exposure; minocycline-induced autoimmune hepatitis takes a period of 12–20 months from initiation of treatment for teenage acne, for instance, before liver dysfunction appears [6].

Triggering factors are specific environmental exposures that do not cause disease but reveal its presence. Glycogen storage disease type 1 may become manifest only at weaning from breastfeeding or during an episode of poor intake due to intercurrent illness. Hereditary fructose intolerance may be revealed by the inadvertent administration of intravenous fructose or medicine containing sucrose or sorbitol [7] and the administration of valproate to an infant with seizures due to an unrecognized mitochondrial cytopathy may trigger acute liver failure [8].

Why Diagnosing Liver Disease May Be Difficult

Pediatric liver disease is not common in the general practitioners' experience, and therefore, the diagnoses and its diagnostic work-up may be relatively unfamiliar. Additionally, although established liver disease is rare, it is not uncommon to see mild abnormalities of liver function tests. In infants jaundice is frequently seen in the form of physiologic neonatal jaundice and breast milk jaundice. Although these causes manifest as unconjugated hyperbilirubinemia, it does mean that the mere presence of jaundice in a newborn infant does not necessarily raise the suspicion of liver disease. The difficulties of diagnosis are doubly increased when dealing with acute liver failure; not only are there severe constraints on the time available for a full diagnostic work-up but hepatic metabolic function is severely deranged, sometimes making the differentiation between primary and secondary metabolic abnormalities virtually impossible by biochemical means. Fortunately there are now much greater nucleic acid-based options for primary diagnosis of specific inborn errors of metabolism, but results can take time to become available. Another concern in the early detection of pediatric liver disease relates to the difficulty of maintaining basic clinical examination skills in an age of advanced imaging techniques. The ability of the physician to use hands and eyes to detect clinical signs such as hepatomegaly, ascites, and cutaneous features of liver disease needs to be carefully nurtured among medical students and junior medical staff. Finally, there are a number of terms that are commonly used in regard to liver disease that mean the diagnosis has not been identified such as "idiopathic" fulminant hepatic failure, "cryptogenic" cirrhosis, and "neonatal hepatitis." It is important to remember that these are not diagnoses but an admission that the diagnostic work-up has failed to identify the primary cause of liver disease. The acceptance of these terms as seemingly discreet diseases may be in some way responsible for incomplete diagnostic work-up. Narkewicz et al. describe how frequently a suboptimal diagnostic work-up is seen in children presenting with acute liver failure when given a diagnosis of idiopathic liver failure even in the context of a multicenter study [9].

Phenotypes

The Sick Newborn

Most consultations done for suspected liver disease in the newborn nursery or neonatal intensive care are on infants with other reasons to be there and have not yet been home. Less frequently their primary reason is because of liver dysfunction at or within days of birth. Liver dysfunction may be inherent from congenital infection or inborn error of metabolism or secondary to other peri- or postnatal events such as isch-

emia, necrotizing enterocolitis, congenital heart disease, abdominal surgery, or the need for parenteral feeding.

Clinical features which may indicate liver disease include ascites, hyperammonemia, hypoglycemia and coagulopathy, hepatomegaly with or without splenomegaly, cholestasis, and abnormal liver function tests. Congenital liver disease may result in early fetal loss, but the classical presentation is the hydropic infant with hepatomegaly, congenital ascites, hypoalbuminemia, coagulopathy, and very-early-onset cholestasis. These findings are not specific for primary congenital liver disease as congenital ascites is commonly due to severe fetal anemia, both isoimmune and nonimmune causes such as alpha thalassemia, or fetal heart failure, and is mostly seen in the setting of generalized hydrops fetalis (see Table 6.2 for a more complete list of causes). When primary liver disease is suspected, an important diagnosis to consider is "neonatal hemochromatosis." Studies by Whitington and colleagues have demonstrated that the majority of these cases are due to a maternal factor (presumably an IgG alloantibody) crossing the placenta and inducing complement-mediated hepatocellular injury, one result of which is excessive iron deposition [10]. This immune-mediated "neonatal hemochromatosis" condition has been renamed *gestational alloimmune liver disease* (GALD) (see chapter 10).

There are also infants who were seemingly healthy at birth but within a few hours to a few days develop features of acute liver failure (see Table 6.3) with coagulopathy and hyperammonemia. There is considerable overlap with

Table 6.2 Causes of congenital ascites

Immune	Isoimmune hemolytic disease of newborn
	Gestational alloimmune liver disease (neonatal hemochromatosis)
	Congenital lupus erythematosus
Nonimmune anemias	Other hemolytic disorders affecting fetus
	Disorders of red cell production, e.g., α-thalassemia
	Congenital leukemia
	Fetal hemorrhage
	Twin-to-twin transfusion
Infectious	Parvovirus B19
	Cytomegalovirus (CMV)
	Syphilis
	Herpes simplex
	Toxoplasmosis
	Hepatitis B
	Adenovirus
	Ureaplasma urealyticum
	Listeria monocytogenes
	Enterovirus
	Lymphocytic choriomeningitis virus (LCMV)
Chromosomal	Cri-du-chat syndrome (chromosomes 4 and 5)
	Trisomy 13
	Trisomy 18
	Trisomy 21 (Down syndrome)
	Turner syndrome
Genetic syndromes	Smith-Lemli-Opitz syndrome
	Beckwith-Wiedemann syndrome
	Klippel-Trenaunay-Weber syndrome
	Yellow nail syndrome
Metabolic	Glycogen storage disease, type IV
	Gaucher disease, type II
	Morquio disease (MPS IV)
	Hurler syndrome (MPS 1H)
	Sly syndrome (MPS VII)
	Farber disease
	G_{M1} gangliosidosis
	Sialidosis II
	I-cell disease
	Niemann-Pick type C
	Wolman
	Infantile sialic acid storage disorder
	Primary carnitine deficiency
	Congenital defects of glycosylation
Cardiovascular	Congenital heart disease
	Congenital arrhythmias
	Congenital myocarditis
Liver tumors	Hepatoblastoma
	Mesenchymal hamartoma
	Hemangioendothelioma
Miscellaneous	Intussusception
	Meconium peritonitis
	Lymphangiectasia
	Urinary tract malformations
	Placental abnormalities
	Teratoma
	Extra-abdominal tumors
	Hypothyroidism and hyperthyroidism

Table 6.3 Causes of acute liver failure in infancy

Infectious	
Viral	Herpes simplex
	Varicella zoster
	Cytomegalovirus
	Human herpes virus 6
	Adenovirus
	Enterovirus
	Hepatitis B
	Parvovirus B19
	Influenza
Bacterial	Septicemia
Protozoal	Malaria
Genetic	Tyrosinemia type 1
	Galactosemia
	Hereditary fructose intolerance
	Fructose 1,6-bisphosphatase deficiency
	Organic acidemias
	Urea cycle disorders
	Fatty acid oxidation defects
	Mitochondrial/respiratory chain defects
	Carnitine defects
	Niemann-Pick type C
	Glycogen storage disease type 1
Immune	Neonatal hemochromatosis
	Hemophagocytic lymphohistiocytosis
	Autoimmune hemolytic anemia with giant cell hepatitis
Vascular	Heart failure
	Cardiac surgery
	Ischemic hepatitis
	Budd-Chiari
	Congenital portal vein anomalies
Neoplastic	Infantile leukemia
	Hemangioendothelioma
Nutritional/toxic	Drugs/toxins
Other	Reye syndrome

the causes of congenital ascites although viral infection acquired at or around the time of birth is more likely, disseminated neonatal herpes simplex being a frequently encountered cause. Generalize septicemia and, in at-risk populations, congenital malaria may also present in this manner. Inborn errors of metabolism with infantile acute presentation may include lysosomal storage defects but are more likely to be defects of intermediate metabolism such as galactosemia, organic acidemias, and glycogen storage disease type I (see chapter 8). GALD may also present similarly although there is usually evidence of chronic liver disease. An important diagnosis to exclude, because liver transplantation is contraindicated, is hemophagocytic lymphohistiocytosis (HLH), but HLH characteristically has a more delayed onset with patients tending to present later in infancy (see chapters 12 and 29). Severe liver dysfunction may be seen with vascular compromise as well, such as thrombosis of the inferior vena cava or hepatic veins, and with congenital portal vein anomalies. Heart failure secondary to congenital heart disease may result in an ischemic hepatitis, and rarely congenital leukemia or myelodysplasia can present with acute liver failure.

Commonly, despite intensive work-up, no specific cause is found; however, as has been cautioned in the introduction, the diagnosis of "idiopathic" neonatal hepatitis should not be assumed until all recognized causes have been excluded (see chapter 12). Certainly the proportion of patients with this label of idiopathic neonatal hepatitis has fallen over the years with the discovery of novel conditions and disease mechanisms, and it is to be hoped that eventually the term will become unnecessary. Until then idiopathic neonatal hepatitis should be seen as a challenge to further diagnostic adventure rather than an end in itself.

Although not all infants in the neonatal unit with evidence of liver disease are as sick as patients with hydrops or acute liver failure, the differential diagnosis for hepatitis with or without cholestasis remains large (see Table 6.4). Certainly the diagnoses that were entertained for the sicker group of infants may be found manifest with less severe disease; thus, congenital infection, storage disorders, and GALD still appear in the differential diagnosis for infants with simple cholestasis and elevated transaminases, but a larger spectrum of etiologies also needs to be considered including genetic and chromosomal

Table 6.4 Causes of hepatitis and/or cholestasis in infancy

Infectious	
Viral	Herpes simplex
	Varicella zoster
	Cytomegalovirus
	Human herpes virus 6
	Adenovirus
	Enterovirus
	Hepatitis B
	Rubella
	Parvovirus B19
	Human immunodeficiency virus (HIV)
Bacterial	Syphilis
	Listeria
	Septicemia
	Urinary tract infection
	Acute cholecystitis
	Acute cholangitis
	Pyogenic liver abscess
Fungal	Hepatosplenic candidiasis
	Other systemic fungemias
Protozoal	Malaria
	Toxoplasmosis
	Congenital Chagas disease
Immune	Neonatal hemochromatosis
	Hemophagocytic lymphohistiocytosis
	Neonatal lupus
	Autoimmune hemolytic anemia with giant cell hepatitis
	Erythroblastosis fetalis
	Graft versus host syndrome
	Autoimmune hepatitis
	Kawasaki disease
	Myeloproliferative disorder
Nutritional/toxic	TPN/intestinal failure
	Drugs/toxins/herbals
	Breast milk jaundice
	Indian childhood cirrhosis
	Other copper toxicoses
Metabolic	Crigler-Najjar
	Dubin-Johnson syndrome
	Rotor syndrome
	Tyrosinemia type 1
	Galactosemia
	Glycogen storage diseases
	Organic acidemias
	Urea cycle disorders
	Citrin deficiency
	Fatty acid oxidation defects
	Cholesterol synthesis defects
	Mitochondrial/respiratory chain defects
	Congenital defects of glycosylation
	Bile acid synthesis defects
	Peroxisomal defects
	Niemann-Pick type C
	Lysosomal storage diseases
	Mucopolysaccharidoses
	Alpha 1-antitrypsin deficiency
	Cystic fibrosis
	Defects of biliary transport (PFIC)
	Familial cholanemias
	Erythropoietic protoporphyria
Syndromic	Trisomy 21
	Trisomy 18
	Trisomy 13
	Cat-eye syndrome
	Alagille syndrome
	ARC syndrome
	Aagenaes syndrome
	Donohue syndrome
	MODY 5
	Jeune syndrome
	COACH syndrome
	Joubert syndrome
	Bardet-Biedl syndrome
	Ivemark syndrome
	Beckwith-Wiedemann syndrome
	NISCH syndrome
	North American Indian childhood cirrhosis
	Cri-du-chat syndrome
	GRACILE syndrome
	McCune-Albright syndrome
	Septo-optic dysplasia
	Smith-Lemli-Opitz syndrome
Endocrine	Panhypopituitarism
	Hypothyroidism
	Hypoadrenalism
	Hyperinsulinism
Cardiovascular	Portal vein thrombosis
	Congenital anomalies of portal vein
	Ischemic hepatitis
	Heart failure
	Hepatic artery-portal vein fistula
	Sinusoidal obstruction syndrome
	Budd-Chiari
Neoplastic	Langerhans cell histiocytosis
	Hepatoblastoma
	Leukemia
	Other primary or metastatic liver tumors

Table 6.4 (continued)

Others	Choledochal cyst
	Choledocholithiasis
	Biliary atresia
	Inspissated bile
	Spontaneous perforation of bile duct
	UVC trauma and extravasation
	Neonatal sclerosing cholangitis
	Caroli disease

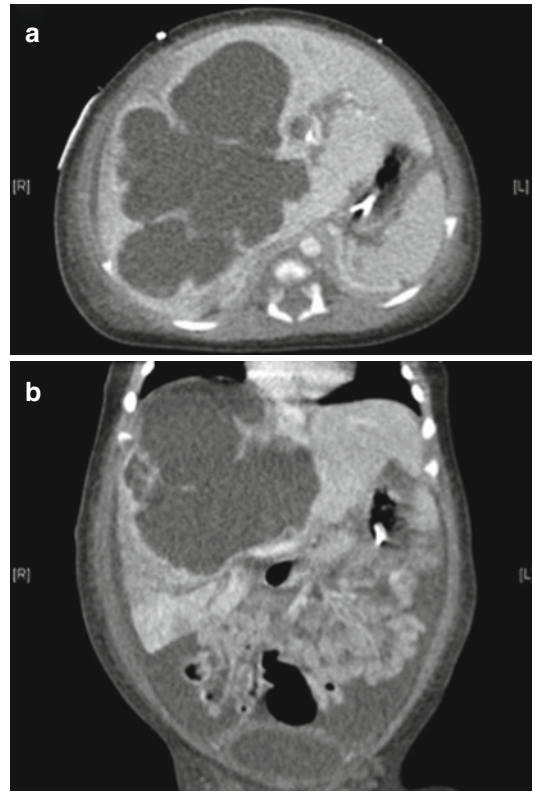

Fig. 6.1 Massive extravasation of PN solution from an umbilical venous catheter which migrated into the liver – (**a**) axial and (**b**) coronal CT views

syndromes that may be apparent from abnormal physical features, as well as vascular, endocrine, and neoplastic causes. Additionally, in those infants who have intestinal failure (usually related to surgical resection for necrotizing enterocolitis or congenital intestinal anomalies), cholestasis is related to enteral starvation and the need for intravenous feeding (see chapter 17). Less commonly iatrogenic causes of neonatal liver disease may be seen, such as portal vein thrombosis or extravasation of parenteral fluids into the liver substance (see Fig. 6.1) complicating umbilical venous catheterization [11].

Although hepatomegaly, abnormal transaminase, and even cholestasis may be present in multisystem diseases, these may not be the key features on which the diagnosis is based. For example, in many lysosomal storage conditions, abnormal facies, neurological findings, skeletal malformations, or other tissue involvement may point to the diagnosis (a list of metabolic defects that have been associated with liver disease is shown in Table 6.5). Certain syndromes such as ARC (arthrogryposis, renal anomalies, and cholestasis), Aagenaes, Donahue, or Beckwith-Wiedemann syndrome also have characteristic physical manifestations, and the presence of hepatomegaly or liver function abnormalities simply supports the diagnosis. Liver involvement in multisystem diseases may manifest in some infants with hepatomegaly alone and will be reliant upon a careful physical examination to identify the relevant finding. The request for a hepatological opinion in such circumstances is to determine if the findings are consistent with the primary diagnosis, if there is a second diagnosis responsible for the liver abnormalities observed, to estimate prognosis, and to advise on appropriate management of the liver dysfunction.

The Sick Infant

Infants discharged from the nursery presenting within days of birth with acute liver failure (see Table 6.3) (see chapter 23) have a large diagnostic overlap with those who have been seen as a consultation presenting in the newborn period. Inborn errors of metabolism, perinatally acquired infection, GALD, and other conditions may have an apparent period of health prior to postnatal decompensation.

The history collected from family must include preceding signs and symptoms, details of the pregnancy and delivery, a dietary history with

Table 6.5 Inborn errors for metabolism associated with hepatic manifestations

Enzyme defects	Specific disease	Manifestations
Defects of bilirubin conjugation	Gilbert	UH
	Crigler-Najjar	UH
Defects of carbohydrate metabolism	Galactosemia	NC, ALF, CLD
	Hereditary fructose intolerance	NC, ALF, CLD
	Fructose 1,6-bisphosphatase def.	NC, ALF
	PEPCKD	S, R
	GSD 1a	HM, T, adenoma
	GSD3	HM, T, CLD
	GSD4	NC, T, CLD
	GSD6	HM, T
	GSD9	HM, T
	Glycerol-3-phosphate dehydrogenase deficiency 1	HM, T
Defects of amino acid metabolism	Tyrosinemia type1	NC, ALF, CLD, HCC
	s-Adenosylhomocysteine hydrolase	NC, CLD
	Maple syrup urine disease	NC
	Methylmalonic acidemia	R, HM
	Propionic acidemia	R
	Isovaleric acidemia	R
	3-Methylcrotonylglycinuria	R
	3-OH-3-methylglutaryl-CoA lyase def.	R
	Holocarboxylase synthase def.	R
(Urea cycle disorders)	N-Acetylglutamate synthase def.	R
	Carbamoylphosphate synthase def.	R
	Ornithine transcarbamylase def.	R
	Citrullinemia	R
	Argininosuccinic aciduria	R, T
Defects of fatty acid oxidation	VLCAD def.	HM, R
	LCHAD def.	T, R, ALF
	MCAD def.	R
	3-Hydroxyacyl-CoA dehydrogenase def.	R, ALF
Defects of ketogenesis	3-HMG-CoA lyase	HM
Defects of carnitine metabolism	Primary carnitine deficiency	HM, R
Defects of mitochondrial metabolism	Mitochondrial DNA mutations	NC, T, ALF, R, CLD
	Mitochondrial DNA deletions	NC, T, ALF, R, CLD
	Mitochondrial DNA depletion	NC, T, ALF, R, CLD
	Respiratory chain defects	T, R, ALF, CLD
	Multiple Acyl-CoA dehydrogenase def.	HM, R
Peroxisomal defects	Zellweger syndrome	NC, T, HM, CLD
	Neonatal adrenoleukodystrophy	NC, T, HM, CLD
	Infantile Refsum	NC, T, HM, CLD
	Pipecolic acidemia	NC, T, HM, CLD
	Bifunctional protein def.	NC, T, HM, CLD
Defects of lipoprotein metabolism	Tangier disease	HM, SM
	Abetalipoproteinemia	HM, S
Defect of cholesterol synthesis	Cerebrotendinous xanthomatosis	NC
	Smith-Lemli-Opitz syndrome	NC
	Mevalonate kinase def.	NC

Table 6.5 (continued)

Enzyme defects	Specific disease	Manifestations
Lysosomal storage diseases	GM1 gangliosidosis	HM, SM
	GM2 (Sandhoff) gangliosidosis	HM, SM
	Niemann-Pick A and B	HM, SM
	Niemann-Pick C	NC, SM, CLD, HCC
	Gaucher	HM, SM
	Farber	HM, SM
	Lysosomal acid lipase def. (Wolman and CESD)	NC, T, S, HM, SM, CLD
	Mucopolysaccharidoses (I, II, III, IV, VII)	HM, SM
	Multiple sulfatase def.	HM, SM
	I-cell disease	HM, SM
	Pseudo-Hurler polydystrophy	HM, SM
	Aspartylglucosaminuria	HM, SM
	Fucosidosis	HM, SM
	α-Mannosidosis	HM, SM
	Sialidosis	HM, SM
	Galactosialidosis	HM, SM
	Infantile sialic acid storage disease	HM, SM
Congenital defects of glycosylation	Type I subtypes a, b, h	NC, T, HM, SM, CLD
	Type II subtypes b, e, h	NC, T, HM, SM, HSM
Porphyrias	Erythropoietic protoporphyria	T, CLD
Defects of bile acid metabolism	Cerebrotendinous xanthomatosis	NC
	3β-Hydroxy-Δ_5-C^{27}-steroid oxidoreductase def.	NC, T, CLD
	Oxysterol 7α-hydroxylase def.	NC, T, CLD
	2-Methylacyl-CoA racemase def.	NC, T, FSVM
	BAAT def. (bile acid CoA:amino acid N-acyltransferase)	NC, T, FSVM, P
	TJP2 def. (tight junction protein)	FSVM, P
	Epoxide hydrolase def.	FSVM, P
Endoplasmic reticulum storage diseases	α_1-Antitrypsin def.	NC, T, CLD
	Fibrinogen storage disease	T, CLD
	Hereditary amyloidosis	T, HM, CLD
Defects of metal metabolism	Wilson disease	T, HM, ALF, CLD
	Hemochromatosis	T, CLD, HCC
Transporter defects		
Defects of bilirubin transport	Dubin-Johnson syndrome	NC
	Rotor syndrome	NC
Defects of biliary transport	FIC1 def. (PFIC 1)	NC, T, CLD
	BSEP def. (PFIC 2)	NC, T, CLD, HCC
	MDR3 def. (PFIC 3)	NC, T, CLD
Defects of carbohydrate transport	GSD1b	HM, T, adenoma
	Fanconi-Bickel	HM,
Defects of amino acid transport	HHH syndrome	R
	Citrin def.	NC, T, S, R
	Lysinuric protein intolerance	R
Defects of ion transport	Cystic fibrosis	NC, T, CLD

(continued)

Table 6.5 (continued)

Enzyme defects	Specific disease	Manifestations
Defects of carnitine transport	Carnitine-acylcarnitine translocase deficiency	HM, S, CLD
	Carnitine palmitoyltransferase II deficiency	HM, S, R, CLD
	Carnitine palmitoyltransferase I deficiency	HM, S, R

Splenomegaly, fat-soluble vitamin malabsorption, and pruritus are only designated if the feature is present in the absences of fibrotic liver disease

NC neonatal cholestasis, *UH* unconjugated hyperbilirubinemia, *T* elevated hepatic transaminases, *S* steatosis, *HM* hepatomegaly, *SM* splenomegaly, *ALF* acute liver failure, *CLD* chronic fibrotic liver disease, *HCC* hepatocellular carcinoma, *FSVM* fat-soluble vitamin malabsorption, *P* pruritus

attention to weaning, fasting and recent feed changes, and consideration of possible precipitating exposures along with a family history, noting any consanguinity of the parents.

Infants have limited responses to severe illness, and the complaints from family may be nonspecific and include poor feeding, vomiting, lethargy, and seizures. There is little in the physical examination that will differentiate cause in such cases, but it is important to remember that many of the diagnoses may result in multisystem involvement and not just liver failure. Therefore, investigation should also be directed at detecting encephalitis, myocarditis, renal failure, adrenal and thyroid insufficiency, and almost any other tissue involvement. Significant encephalopathy in infants is more likely to be due to primary metabolic encephalopathy or infectious encephalitis, as hepatic encephalopathy tends to occur in infants only very late in the course of their liver disease, if at all.

While investigating the specific diagnosis is important, the most urgent need is to respond to the immediate threats to life. Empiric antibacterial and antiviral medications should be considered once appropriate cultures (blood, urine) and viral studies (herpes simplex) have been collected. Manage hypoglycemia, fluid and electrolyte imbalance, and acidosis if present. Intravenous fluids must supply adequate glucose to prevent catabolism, while defects of protein or lipid metabolism (or both as in glutaric aciduria type II) are being investigated – hepatic glucose release for healthy infants may be in the range of 12–14 mg/kg/min, and therefore, this should be the delivery rate to prevent hypoglycemia and endogenous protein catabolism. Coagulopathy may be very severe without outward signs, so it is imperative to check coagulation profile with initial suspicion of liver dysfunction. Occasionally biliary atresia or other cholestatic infantile conditions present acutely with hemorrhage or ecchymoses secondary to vitamin K deficiency.

For details on diagnostic workup and management, see chapter 23.

The Stable Infant with Liver Disease

The infant referred to clinic with jaundice in the first few weeks of life is another common scenario for the general pediatrician and pediatric gastroenterologist. The general pediatrician sees more children with unconjugated hyperbilirubinemia secondary to prolonged physiologic jaundice or breast milk jaundice than they do children with cholestatic jaundice. Infants with unconjugated hyperbilirubinemia have colorless urine and pigmented stools (yellow-green or brown) [12]. It is important to recognize that infants without conjugated hyperbilirubinemia do not pass yellow or amber urine because they drink at least 100 mL/kg/day and therefore pass dilute urine, unlike adults who frequently pass more concentrated yellow urine. Unconjugated jaundice still needs to be investigated if it is either very early in onset, prolonged beyond 10–14 days, very high levels, or of late onset. If breast milk jaundice is suspected and there is no evidence of hemolysis or infection, thyroid function is normal, and bilirubin levels are not progressively increasing,

breast-feeding does not need to be discontinued. However, if the bilirubin level continues to rise, defects of bilirubin conjugation (Crigler-Najjar syndrome) should be considered. The high frequency of unconjugated jaundice in the infant population is one factor that has been suggested for late referrals of infants with biliary atresia; the rare case of conjugated hyperbilirubinemia is like a proverbial needle in the haystack of infants with unconjugated jaundice! It is important for the general pediatrician to remain alert to the possibility that an infant's jaundice is cholestatic and request split bilirubin levels – total and direct or better still conjugated and unconjugated bilirubin levels (see chapter 3).

Referrals to the pediatric gastroenterologist or hepatologist are most commonly for conjugated hyperbilirubinemia, although the type of jaundice is not always characterized before referral. Due to the importance of a timely hepatoportoenterostomy to the prognosis of the affected infant, the diagnosis of biliary atresia needs to be ruled out promptly. There has been much discussion on the best combination of sonography, scintigraphy, liver biopsy, and cholangiography (see chapter 13), but efficiency of work-up demands a certain degree of experience in the team and institution caring for the infant. If it is not possible to make this diagnosis in a few days, the infant should be transferred to a center that has the required experience and where the appropriate surgical expertise exists to proceed to portoenterostomy. There is no justification for delaying transfer until the diagnosis is certain.

The investigations for other causes of infantile liver disease should be carried out concomitantly with the evaluation for biliary atresia. The priorities depend on the most likely causes relevant to the population served. Citrin deficiency, for example, is a relatively common cause of neonatal cholestasis in Japan and China but rare in Northern Europe, while for α_1-antitrypsin deficiency and cystic fibrosis, the relative regional prevalence is reversed. It is wise to have an established protocol for first-line investigations according to your particular population, followed by a second line of investigations for less frequently encountered conditions and finally the very rare causes investigated sequentially to make best use of both patient's and hospital's resources.

Quite frequently a healthy, asymptomatic infant with proven or suspected perinatally acquired hepatitis B or hepatitis C will be referred to clinic for confirmation of diagnosis, management, and parental counselling. The child may be accompanied by natural parents, but often the patient may be brought to clinic by a foster family and the child's social worker or by the adoptive parents in the case of an adoptee from a region of the world where HBV is endemic. See chapter 15 for an approach to these infants. Another group of asymptomatic infants seen in clinic with liver-related questions include those with siblings affected by an inheritable liver disease whose parents either wish this child to be tested or who is already known to carry the mutation(s) and are seeking advice (e.g., α_1-antitrypsin deficiency).

Rarely a family seeks medical attention because they have either identified a lump in the abdomen or notice abdominal distention. More commonly nonspecific features such as poor feeding or growth, vomiting, sweatiness, or tachycardia may first bring the infant to medical attention. Occasionally hepatomegaly with or without splenomegaly may be identified as one feature of multisystem genetic disorders such as a cilial dysfunction syndrome (see chapter 14) or a lysosomal storage disorder. In yet others, a completely asymptomatic mass may be identified on routine examination during a well-baby check. It is not always easy, especially in infants, to determine if an enlarge liver is due to diffuse enlargement of the liver or due to a circumscribed lesion or lesions.

The investigation of these infants depends largely on whether there is homogenous hepatic enlargement or the finding of a mass or masses arising from the liver (see Table 6.6). Ultrasound findings are the best guide to further diagnostic approach. Bland hepatomegaly would point to the possibilities of hepatitis, metabolic storage, outflow obstruction as in heart failure, or syndromic

Table 6.6 Infant with a liver mass

Benign tumor	Hemangioma	Infectious	Amebic abscess
	Infantile hemangioendothelioma		Pyogenic liver abscess
	Mesenchymal hamartoma		
	Adenoma	Traumatic	Hepatic hematoma
			Fluid extravasation from UVC
Malignant tumor	Hepatoblastoma	Other	Choledochal cyst
	Rhabdoid tumor		Mucocele of gall bladder
	Rhabdomyosarcoma		Simple hepatic cyst
	Neuroblastoma		Riedel's lobe
	Other hepatic malignancy		

organomegaly (e.g., Beckwith-Wiedemann syndrome). Discrete lesions on imaging imply tumor, cyst, or abscess. Undoubtedly, further imaging can help refine the diagnosis in these cases (see chapter 5), and some lesions may have highly characteristic findings on well-conducted studies. Delaying referral to an experience center is not usually beneficial and can result in multiple nonuseful investigations being carried out. Early referral to an experience center who can direct an appropriate diagnostic workup (chapter 22) is recommended. For those without diagnostic findings on imaging, the lesions may need histological evaluation, and therefore, biopsy is necessary.

Young Child with Liver Disease (1–4 Years)

Most patients with newly recognized liver disease (see Table 6.7) in this age range will present with hepatitis (inflammation of the liver) recognized by the primary provider because of elevated liver function tests. The blood tests are usually provoked by some combination of new onset of jaundice, fever, anorexia, vomiting, or malaise, although in a significant number of cases may be found on testing for nonspecific complaints of headache or abdominal pain or even on routine well-patient screening.

Causes of hepatitis include infectious, commonly viral, autoimmune, and some metabolic diseases which had escaped detection in ear-

Table 6.7 Causes of cholestasis in the younger child (1–4 years)

Infectious	
Viral	Hepatitis A
	Hepatitis B
	Hepatitis C
	Cytomegalovirus
	Epstein-Barr
	Adenovirus
	Parvovirus B19
Bacterial	Urinary tract infection
	Septicemia
	Acute cholangitis
	Pyogenic abscess
	Leptospirosis
Parasitic	Malaria
	Trematodes (liver fluke)
	Ascariasis
	Hydatid (Echinococcus)
	Amebic abscess
Immune	Autoimmune hepatitis
	Sclerosing cholangitis
	Kawasaki disease
	Graft versus host disease
	Immunodeficiencies
Metabolic	α_1-Antitrypsin deficiency
	Tyrosinemia
	FIC1 def. (PFIC1)
	BSEP def. (PFIC2)
	MDR3 def. (PFIC3)
	Peroxisomal defects
	Mitochondrial defects
	Cholesteryl ester storage disease
	Dubin-Johnson syndrome
	Rotor syndrome
	Erythropoietic protoporphyria

Table 6.7 (continued)

Syndromic	Alagille syndrome
	Ciliopathies (e.g., COACH, Bardet-Biedl)
	NISCH syndrome
	North American Indian childhood cirrhosis
	Mulibrey nanism
	Tubulointerstitial nephropathy with cholestasis
Toxic	Drugs/toxins/herbals
	Copper toxicosis
Vascular	Budd-Chiari
	Sinusoidal obstruction syndrome
	Constrictive pericarditis
	Heart failure
	Congenital heart disease
	Liver trauma
Neoplastic	Langerhans cell histiocytosis
	Tumors of liver or bile ducts
	Leukemia
Other	Choledochal cyst
	Caroli disease
	Choledocholithiasis
	Sickle-cell disease

lier life. Children with chronic viral hepatitis (hepatitis B and hepatitis C) contracted from the mother at birth may remain completely asymptomatic and be detected during investigation of other complaints, especially if the mother has not been previously diagnosed and had suboptimal antenatal care. This is particularly applicable to young children from high endemic risk areas of the world (recent immigrants and adoptees) and mother's with a history of at-risk behaviors such as intravenous substance abuse. Autoimmune hepatitis can occur at any age, but in this age group, liver-kidney-microsomal (LKM) antibody-positive disease constitutes a larger proportion of cases than is seen in older children (see chapter 16). Kawasaki disease, although rarely seen in GI clinic, very commonly has abnormal transaminases and bilirubin levels at presentation. Similarly, children with celiac disease may have abnormal transaminases, but these tend to resolve upon diagnosis and initiation of a gluten-free diet.

Chronic liver diseases with a gradual progression may be first revealed in the young child, as in some cases of α-1-antitrypsin deficiency (see chapter 9) and Alagille syndrome (see chapter 11). Despite there being no history of neonatal cholestasis, these diseases may progress silently to fibrotic liver disease, detected either by the astute primary doctor finding splenomegaly on routine examination or with the first onset of complications of cirrhosis or portal hypertension.

In the developed world, the infectious causes of liver disease are relatively limited especially in the essentially healthy child, but in the tropics, there are many more pathogens that may induce deranged liver function (see Table 6.8). On the other hand, obesity is now endemic (and some have said epidemic) in the developed world driven by excessive nutritional intake and an increasingly sedentary lifestyle. Nonalcoholic fatty liver disease is now regularly being diagnosed as early as second year of life (see chapter 18). Lastly, drug-induced or toxic hepatitis may result from inadvertent ingestion by the adventurous toddler or due to an idiosyncratic reaction to prescribed medication (see chapter 19) (see Table 6.9).

Non-hepatic causes of laboratory abnormalities and clinical signs and symptoms typically attributed to liver disease must also be considered. Although abnormal "liver" function tests equate in most practitioners' mind to liver disease, there are important exceptions. "Transaminitis" without jaundice is commonly seen in diseases of skeletal and cardiac muscle. The inclusion of γ-glutamyl transferase and creatine kinase (or other muscle-derived enzyme such as aldolase) can help differentiate the tissue source of elevated levels of AST and ALT. Duchenne muscular dystrophy is a particularly important diagnosis to consider. Another cause of elevated transaminase levels in the absence of liver disease is due to macroenzymes (especially macro-AST) [13]. Serum enzymes may complex with immunoglobulins resulting in a high molecular weight complex that has a prolonged half-life because of reduced plasma clearance. Although macroenzymes have been associated with acute, chronic,

Table 6.8 Infectious agents associated with hepatic involvement

Viral	*Bacterial*	*Fungal*
Hepatitis A	Urinary tract infection	Histoplasmosis
Hepatitis B	Septicemia	Hepatosplenic candidiasis
Hepatitis C	Acute cholangitis	Disseminated aspergillosis
Hepatitis D	Acute cholecystitis	Trichosporon cutaneum
Hepatitis E	Pyogenic abscess	Penicillium marneffei
Herpes simplex	Perihepatitis (gonorrhea, chlamydia)	Coccidioidomycosis
Varicella zoster	Toxic shock syndrome (staphylococcus)	Cryptococcosis
Cytomegalovirus	Scarlet fever	
Epstein-Barr virus	Salmonella typhi/paratyphi	*Protozoal*
Human herpes virus 6	Shigella	Toxoplasmosis
Human herpes virus 7	Yersinia	Malaria
Human herpes virus 8	Clostridium perfringens	Amebic abscess
Rubella	Brucellosis	Toxocariasis
Adenovirus	Listeriosis	Cryptosporidium
Enterovirus	Borrelia (Lyme borreliosis)	Chagas disease
Parvovirus B19	Leptospirosis	Leishmaniasis
Paramyxovirus	Syphilis	Babesiosis
Reoviruses (Colorado tick fever)	Bartonella (cat scratch, Carrion disease)	
Influenza/parainfluenza	Actinomycosis	*Parasitic*
Coronavirus (SARS)	Legionella	Clonorchiasis
Human immunodeficiency virus (HIV)	Tularemia	Fascioliasis
Yellow fever	Melioidosis	Opisthorchiasis
Dengue fever	Tuberculosis	Dicrocoelium dendriticum
Other flavivirus hemorrhagic fever	Leprosy	Paragonimiasis
Lassa fever	Rocky Mountain spotted fever	Schistosomiasis
Lymphocytic choriomeningitis virus	Scrub typhus	Echinococcus (hydatid disease)
Other arenavirus hemorrhagic fevers	Ehrlichiosis	Ascariasis
Filovirus fevers (Ebola, Marburg)	Q fever	Strongyloides
Hantavirus hemorrhagic fever		Trichinella
Other bunyavirus hemorrhagic fevers		Capillariasis
		Baylisascariasis

and malignant liver disease, most cases appear benign and self-limiting although the triggers for formation are not fully understood. Benign (or transient) hyperphosphatasia is frequently seen in young children possibly provoked by a mild intercurrent illness [14]. The alkaline phosphatase level can peak in the thousands and remains elevated for a few weeks to a few months before settling to the normal range. If the isoenzymes of alkaline phosphatase are assayed, the largest increase is seen in bone-derived isoenzyme although liver isoenzyme can be increased as well. In the absence of bone disease (e.g., rickets or fracture) and otherwise normal liver laboratory values, no further investigation is required.

Jaundice may be secondary to acute hemolysis; for example, a child with the glucose-6-phosphate dehydrogenase "favism" variant may be first exposed to broad (fava) beans as a young child and present with new-onset jaundice. Even massive ascites may not be what it seems; Fig. 6.2 shows the CT appearance of a young child with a giant omental cyst.

Hepatomegaly or a liver mass may turn out to be the anatomical variant, Riedel's lobe, an elongated right lobe. Incidental hepatomegaly is the likely presenting feature for the benign glycogen storage diseases due to phosphorylase and phosphorylase kinase deficiency (GSD VI and IX, respectively). Sizable liver masses, however, at

Table 6.9 Pharmaceuticals and toxins that have been reported to cause liver disease

Antibiotics	Anticonvulsants and CNS-acting drugs	Chemotherapeutics	Miscellaneous drugs	Wild plants/herbals	Dietary supplements and recreational drugs	Non-medicinal chemicals
Amoxicillin/clavulanate	Carbamazepine	Methotrexate	Acetaminophen	Amanita	Vitamin A	Carbon tetrachloride
Flucloxacillin	Lamotrigine	Azathioprine	Alcohol	Comfrey	Hydroxy Cut	Chlorobenzene
Sulfonamides	Phenobarbital	6-Mercaptopurine	Allopurinol	Pyrrolizidine alkaloids	Ecstasy	Vinyl chloride
Erythromycin	Phenytoin	Cyclophosphamide	Amiodarone	Senna glycosides	Cocaine	Other organic solvents
Azithromycin	Valproate	Propylthiouracil	Estrogens	Germander		Pyrrolizidine alkaloids
Cephalosporins	Felbamate	Nitrosoureas	Anabolic steroids	Chaparral		Yellow phosphorus
Minocycline	Atomoxetine	cis-Platinum	Aspirin	Kava-kava		2-Nitropropane
Nitrofurantoin	Chlorpromazine	Many others	Diclofenac	Jin bu huan		Copper
Isoniazid	Methyldopa	Rarely used singly	Ketoprofen	Ephedra (ma huang)		Iron
Rifampin	Fluoxetine		Ibuprofen			
Quinine/quinolones			Naproxen			
Azole antifungals			Halothane			
Antiretrovirals			Troglitazone			
			Cyclosporin			
			Pemoline			
			Cimetidine			

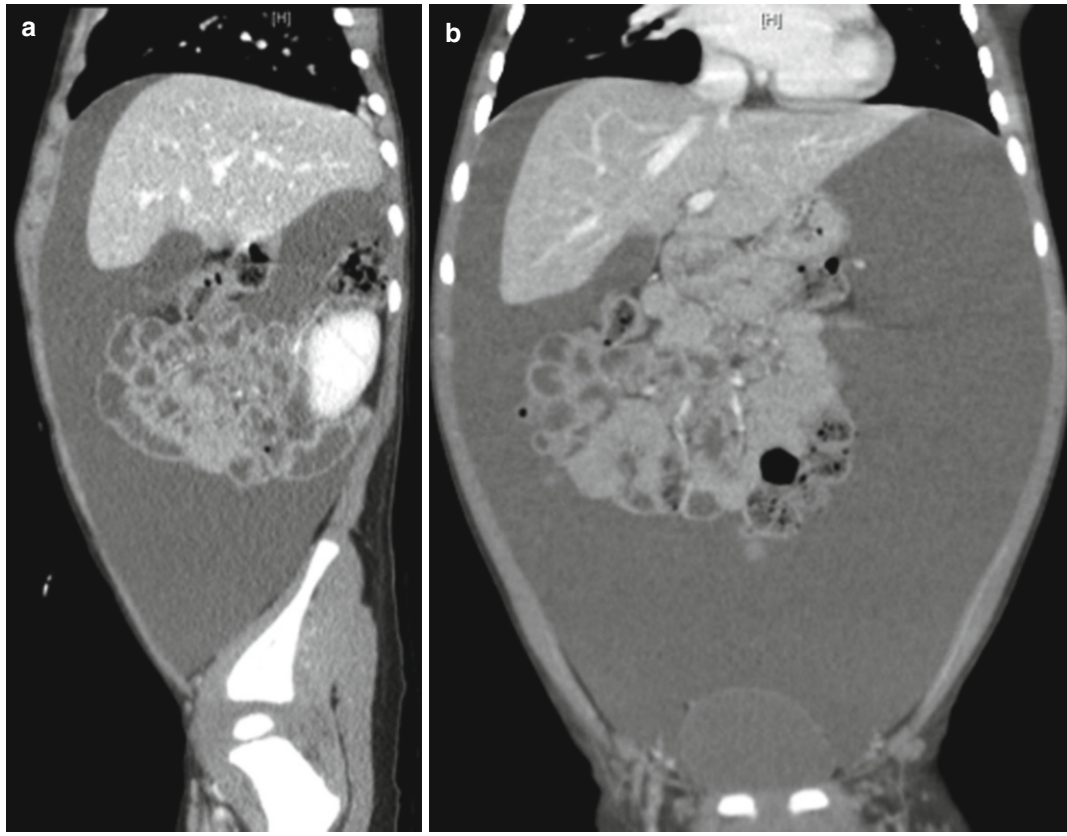

Fig. 6.2 Pseudo-ascites due to giant omental cyst – (**a**) sagittal and (**b**) coronal CT views

this age are likely to be primary hepatoblastoma, neuroblastoma, or other abdominal malignancy (see chapter 22). Hepatocellular carcinoma (HCC) occurs in association with advanced chronic liver disease and in conditions with a specific predisposition such as tyrosinemia and PFIC type 2 but is vanishingly rare as a de novo tumor in an otherwise healthy young child. Benign lesions are most commonly detected on abdominal imaging that was done for other indications and, as discussed for infants, early referral to an experienced center will expedite appropriate management.

Older Child/Adolescent with Liver Disease (>5 Years)

Just like in the younger children, suspicion of liver disease arises from the appearance of specific symptoms such as jaundice, chance pickup on routine physical examination, or investigation of nonspecific and possibly unrelated medical concerns (see Table 6.10). Acute hepatitis due to hepatitis A and Epstein-Barr virus (EBV) is relatively common and new infection with hepatitis B and hepatitis C becomes more common in adolescent populations. Hepatitis E in endemic areas rarely causes significant clinical disease in young children but is more likely to cause acute hepatitis as subjects' age and is particularly dangerous for the pregnant teenage girl (see chapter 15). Autoimmune hepatitis often presents with acute hepatitis and although more frequent in adolescent girls can occur in both sexes and at any age (see chapter 16). Most cases of Wilson disease diagnosed in childhood and adolescence manifest as acute, often fulminant, hepatitis, and although rare, an expedient diagnosis may prevent death or liver transplantation (see chapter 9).

Everyone involved in the care of children recognizes the obesity crisis that is so highly prevalent in the USA and is also sweeping the rest of the developed world. This single factor accounts for the majority of new referrals of children with elevated transaminases in the USA as a result of nonalcoholic fatty liver disease (NAFLD) (see chapter 18). This was an uncommon diagnosis 25 years ago, and despite multicenter collaborative efforts to design treatments for this condition, it is likely that the solution, if one is to be forthcoming, will be in the realm of public policy development to curtail obesity rather than single-patient medical management.

Gall stones and gall bladder disease can cause jaundice and elevated transaminases and increase as adulthood approaches (see chapter 20). Gilbert syndrome is an essentially benign condition manifest as an unconjugated jaundice with normal transaminases. The jaundice is frequently first noted around the time of puberty and these patients are often referred to liver clinics. As for younger children, elevated transaminases with no jaundice may be seen in many liver diseases, but muscle injury, myositis, muscular dystrophy, or cardiomyopathy should not be dismissed without a careful history, physical examination, and a creatine kinase level.

Chronic liver disease may present at any age (see chapters 25 and 26). As disease progresses jaundice may eventually appear. Abdominal distention from hepatomegaly or ascites may rarely lead to the request for medical attention. More commonly isolated splenomegaly is identified, and if portal hypertension is not considered, the child or teenager may go through detailed hematological investigations unnecessarily. Extrahepatic portal hypertension, due to portal vein thrombosis having occurred usually years

Table 6.10 Causes of cholestasis in older children and adolescents

Infectious	
Viral	Hepatitis A
	Hepatitis B
	Hepatitis C
	Hepatitis E
	Cytomegalovirus
	Epstein-Barr virus
	Adenovirus
Bacterial	Septicemia
	Acute cholangitis
	Pyogenic abscess
	Leptospirosis
	Rocky Mountain spotted fever
	Borrelia (Lyme's)
	Salmonella typhi/paratyphi
	Tuberculosis
Parasitic	Malaria
	Trematodes (fluke)
	Ascariasis
	Leishmaniasis
	Echinococcus (hydatid)
	Amebic abscess
	Cryptosporidium
Metabolic	Wilson disease
	Cholesteryl ester storage disease
	Benign recurrent intrahepatic cholestasis
	Juvenile hemochromatosis
	HELLP syndrome (pregnant teenage women)
Immune	Autoimmune hepatitis
	Sclerosing cholangitis
	Primary biliary cirrhosis
	Kawasaki disease
	Graft versus host disease
	Immunodeficiencies
	Systemic lupus erythematosus
	Sarcoidosis
Toxic	Drugs/toxins/herbals
Vascular	Budd-Chiari
	Sinusoidal obstruction syndrome
	Congenital heart disease
	Constrictive pericarditis
	Heart failure
	Liver trauma
	Hereditary hemorrhagic telangiectasia
Neoplastic	Langerhans cell histiocytosis
	Leukemia
	Lymphoma
	Hepatocellular carcinoma
	Cholangiocarcinoma
	Other tumors of liver or bile ducts
Other	Choledochal cyst
	Caroli disease
	Choledocholithiasis
	Sickle-cell disease
	Postnecrotic cirrhosis

Table 6.11 Causes of portal hypertension

Post-hepatic	Heart failure
	Cardiomyopathy
	Congenital heart disease
	Constrictive pericarditis
	Inferior vena caval thrombosis
	Congenital web in inferior vena cava
	Budd-Chiari syndrome
	Tumor
Intrahepatic	
Post-sinusoidal	Veno-occlusive disease
Sinusoidal	Cirrhosis
	Nodular regenerative hyperplasia
	Hypervitaminosis A
Pre-sinusoidal	Schistosomiasis
	Congenital hepatic fibrosis
	Sarcoidosis
	Portosclerosis
	Hepatic artery-portal vein fistula
Pre-hepatic	Portal vein thrombosis
	Portal vein stenosis
	Cavernous transformation of portal vein
	Congenital anomalies of portal vein
	Tumor
Sinistral (left sided)	Splenic vein thrombosis
	Pancreatitis
	Pancreatic pseudocyst
	Tumor
	Retroperitoneal fibrosis
	Retroperitoneal abscess

Table 6.12 Causes of hepatic masses beyond infancy - found either on physical examination or imaging

Neoplastic	
Malignant	Hepatoblastoma
	Hepatocellular carcinoma
	Neuroblastoma
	Neuroendocrine tumors
	Rhabdoid tumor
	Rhabdomyosarcoma
	Embryonal sarcoma
	Epithelioid hemangioendothelioma
	Cholangiocarcinoma
	Hepatic teratoma
	Other primary hepatic malignancy
	Metastatic malignancy in liver
Benign	Adenoma
	Mesenchymal hamartoma
	Fibronodular hyperplasia
	Hemangioma
Infectious	Amebic abscess
	Hydatid (Echinococcus)
	Pyogenic liver abscess
Other	Nodular regenerative hyperplasia
	Simple cyst
	Hematoma
	Mucocele of gallbladder
	Choledochal cyst
	Focal fatty infiltration
	Riedel's lobe

before frequently in infancy related to umbilical sepsis or catheterization, can present with splenomegaly. Alternatively, the detection of portal hypertension may be the first sign of chronic liver injury, for example, in autoimmune hepatitis or chronic viral hepatitis, resulting in cirrhosis, but with no history of previous ill health in the child (see Table 6.11). In these circumstances the liver is usually shrunken, and therefore not palpable, but on imaging is heterogenous and nodular and the biopsy specimen severely fibrotic.

With increasing age the incidence of embryonal tumors diminishes and the risk of HCC and metastatic liver tumors increases (see Table 6.12). Greatest risk for HCC is in association with chronic fibrotic liver disease, but the fibrolamellar variant can be encountered in the adolescent without preexisting liver disease. Benign lesions can get big enough to present as a mass or with abdominal discomfort and include nodular regenerative hyperplasia, focal nodular hyperplasia, and adenoma. Leukemias and lymphomas are the most common cancers in children and adolescents and may present with evidence of liver infiltration causing deranged liver function.

Although identification of asymptomatic chronic viral hepatitis via at-risk screening (immigration or infected family) is less common in this age group, they do occur. Adoptees and recent immigrants from HBV endemic regions may present with chronic HBV carriage for management advice. Additionally, family screening

because of hereditary hemochromatosis may identify an older child with biochemical evidence of iron overload but normal or mildly altered transaminases (see chapter 9). Similarly, a diagnosis of Wilson disease mandates the screening of all first-degree relatives, including other children, before signs of liver injury exist.

Acute Liver Disease and Failure

Acute liver disease is the recent onset of liver dysfunction in a patient with no history or investigational evidence of preexisting liver disease (see Table 6.13). This gets a little convoluted when one considers the acute onset of, say, Wilson disease, acute decompensation of chronic hepatitis B, or autoimmune liver disease, where the clinical picture is of a disease of no longer than a few weeks duration but in whom the liver biopsy shows established fibrosis. As is the convention for this chapter in general, we will limit the discussion to the clinical phenotype, i.e., those who have an apparent acute onset of disease with no history of preexisting liver disease.

Acute liver failure results from massive or submassive hepatocellular necrosis, but the syndrome is defined in terms of the duration of the illness (less than 8 weeks) and the presence of coagulopathy and hepatic encephalopathy (see chapter 23 for more details). One important consideration is to differentiate between the acute failure of liver functions manifest by coagulopathy, cholestasis, hyperammonemia, loss of glycemic control, encephalopathy, etc., and the criteria for entry into the PALF (Pediatric Acute Liver Failure) study. In an attempt to be inclusive and to observe the progression from early disease to liver failure, the criteria for entry into PALF were set relatively low, namely, coagulopathy secondary to acute liver disease with an INR of ≥1.5 with hepatic encephalopathy or ≥2.0 in the absence of encephalopathy. There was never an intention to liberalize the definition of acute liver failure, and yet more and more frequently, these study entry criteria are being quoted as the "definition" of acute liver failure which they patently are not.

Table 6.13 Causes of acute liver failure outside of infancy

Viral	Hepatitis A
	Hepatitis B
	Hepatitis D
	Hepatitis E
	Herpes simplex
	Epstein-Barr virus
	Varicella zoster
	Paramyxovirus
	Adenovirus
	Parvovirus B19
	SARS
	Hemorrhagic fever viruses
Bacterial	Septicemia
	Leptospirosis
	Salmonella typhi/paratyphi
	Bartonella
	Rocky Mountain spotted fever
Metabolic	Hereditary fructose intolerance
	Urea cycle disorders
	Organic acidemias
	Fatty acid oxidation defects
	Mitochondrial disorders
	Carnitine defects
	Wilson disease
	Tyrosinemia type 1
	Acute fatty liver of pregnancy
Immune	Autoimmune hepatitis
	Hemophagocytic lymphohistiocytosis
Toxic	Drugs/toxins/herbals
	Amanita phalloides
Vascular	Budd-Chiari
	Sinusoidal obstruction syndrome
	Ischemic hepatitis/shock liver
	Post-cardiac surgery
	Liver trauma
Neoplastic	Leukemia
	Lymphoma
	Hepatocellular carcinoma
Other	Reye syndrome
	Hypothermia
	Heat stroke
	Massive liver resection
	Sickle-cell anemia

Differentiating between the causes of acute liver failure can be challenging. Nonspecific

metabolic derangement adds another level of complication to identifying a liver based-metabolic disease. Similar challenges to acute diagnosis exist with many other causes, and great care is required to not miss a potentially treatable cause of liver disease such as autoimmune hepatitis or Wilson disease. Although the single largest group of acute liver failure patients in childhood is those in whom a specific etiology is not identified, it does not negate the need for a full and detailed workup. Sadly, even in the context of a multicenter study with recommendations made for appropriate investigation, inadequate investigation of cause is frequently encountered [9].

There may be clues such as a history of medication or herbal ingestion (see chapter 19), encephalopathy that is fluctuating or out of proportion to the liver dysfunction may point towards a mitochondrial or other metabolic disease, hemolysis can suggest Wilson disease, or foreign travel increasing the likelihood of an infectious cause. Unfortunately these features are neither specific nor sensitive, and as much as we may like to narrow our differential diagnosis to address the most likely or most serious diagnoses first, in the situation of acute hepatic failure, all causes are life-threateningly serious, and therefore, an inclusive panel of investigation is the safest and most efficient approach. Clearly, investigations, especially for infectious causes, will be tempered by knowledge of local occurrence; we in Seattle do not, for example, routinely check for the flavivirus that causes yellow fever. For more details on the approach to acute liver failure, see chapter 23.

Consult from Other Services with Liver Dysfunction in Association with Known Disease

When a consult comes in from another specialist service, there is always the possibility that the liver disease has nothing to do with the condition that the specialist has been managing. This is essentially a caution because the referral from cardiology of the child with Eisenmenger syndrome, abnormal transaminases, and mild splenomegaly may automatically become hepatic congestion and portal hypertension secondary to right heart failure, while their autoimmune hepatitis goes unrecognized and untreated! Therefore, no matter who the originator of the referral is, the approach to differential diagnosis should be based on the child themselves as outlined in the sections above. Having said this, there is probably a different weighting of the diagnostic possibilities in patients with non-liver diseases with known hepatic pathological associations. Table 6.14 lists some of the particular diagnostic considerations based on the specialty team requesting a hepatological consultation on one of their patients.

Other Phenotypes

Although singly or in combination jaundice, hepatitis, hepatomegaly, or liver mass account for the majority of new presentations of liver disease in childhood, occasionally none of these features are immediately obvious and in some cases absent completely (see Table 6.15). Pruritus in the absence of jaundice can rarely be due to cholestasis, although dermatological causes are far more prevalent. Gastrointestinal bleeding from esophageal varices or ascites usually occurs in the presence of recognized chronic liver disease but in some cases are the first overt signs of its presence. Variceal bleeding as a first presenting feature is seen not uncommonly in cavernous transformation of the portal vein secondary to temporally distant portal vein thrombosis. The child or teenager with isolate splenomegaly may be found to have developed cirrhosis with no past history of jaundice or other features of liver disease. Finally, a few infants and toddlers may manifest with hypocalcemic tetany or rickets and be found to have profound fat-soluble vitamin deficiency. If due to liver disease, other features almost always are

Table 6.14 Conditions in other organ systems associated with recognized patterns of liver involvement

(A) Gastroenterology
(i) Inflammatory bowel disease associated with sclerosing cholangitis or autoimmune hepatitis
(ii) Celiac disease associated with autoimmune hepatitis
(iii) Parenteral nutrition-associated liver disease in patients with intestinal failure
(iv) Shwachman-Diamond syndrome – pancreatic insufficiency and neutropenia often associated with hepatomegaly and transaminitis
(B) Cardiology
(i) Fontan circulation with ascites
(ii) Heart failure associated with hepatosplenomegaly, hepatic fibrosis, and sinusoidal dilation
(iii) Cardiac surgery leading to shock liver (ischemic hepatitis) and acute liver failure
(iv) Alagille syndrome
(v) Constrictive pericarditis
(vi) Cardiomyopathy
(C) Hematology/oncology
(i) Sinusoidal obstruction syndrome
(ii) Drug effect
(iii) Hemolysis leading to biliary inspissation/sludge/stones
(iv) Sickle liver
(v) Transfusion-related iron overload
(vi) Transfusion-related infectious hepatitis
(vii) Budd-Chiari
(a) Hypercoagulable states
(b) Myeloproliferative disorders
(c) Paroxysmal nocturnal hemoglobinuria
(viii) Leukemia and lymphoma
(ix) Langerhans cell histiocytosis
(x) Liver tumors
(xi) Stem cell transplantation
(a) Graft versus host disease
(b) Sinusoidal obstruction syndrome
(c) Opportunistic liver infections
(D) Pulmonology
(i) Cystic fibrosis liver disease
(ii) Sarcoidosis
(iii) Tuberculosis
(E) Nephrology
(i) Polycystic kidney disease, nephronophthisis
(ii) Alagille syndrome
(iii) Membranoproliferative glomerulonephritis associated with portal hypertension
(F) Endocrine
(i) Nonalcoholic steatohepatitis
(ii) Diabetic glycogen hepatopathy (Mauriac syndrome)
(iii) Hypopituitarism
(iv) Autoimmune polyendocrine syndrome type 1
(v) McCune-Albright syndrome
(vi) Generalized lipodystrophy (Berardinelli-Seip syndrome)
(G) Immunology
(i) Immunodeficiencies associated with sclerosing cholangitis or hepatic abscess
(ii) Granulomatous hepatitis in chronic granulomatous disease (CDG)

(continued)

Table 6.14 (continued)

(iii) Wegener's granulomatosis
(iv) Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX)
(v) Hyper-IgM syndrome (CD40 ligand deficiency)
(vi) HIV particularly congenitally acquired
(H) Rheumatology
(i) Systemic lupus erythematosus
(ii) Systemic juvenile idiopathic arthritis (JIA)
(iii) Juvenile dermatomyositis
(iv) Macrophage activation syndrome
(v) Secondary amyloidosis
(I) Genetics
(i) Liver abnormalities as part of multisystem syndromes

Table 6.15 Differential diagnosis for clinical signs that may suggest liver disease presenting without jaundice, hepatomegaly, or elevated transaminases

(a) Isolated splenomegaly
(i) Portal hypertension (causes of portal hypertension, see Table 6.15)
(ii) Anemia
(iii) Infection
(iv) Sequestration, e.g., sickle-cell disease
(v) Metabolic storage diseases
(vi) Cancer
(vii) Immune, e.g., Felty syndrome, macrophage activation
(b) Ascites
(i) Portal hypertension
(ii) Fontan circulation, heart failure, constrictive pericarditis
(iii) Infection – peritonitis, tuberculosis
(iv) Cancer
(v) Lymphatic dysplasia
(vi) Nephrotic syndrome
(vii) Trauma – lymphatic, urinary
(viii) Vasculitis, serositis
(ix) Kwashiorkor
(x) Pseudo-ascites, e.g., giant omental cyst (Fig. 6.2)
(c) Pruritus
(i) Anicteric cholestasis
(ii) Acute and chronic dermatological conditions
(iii) Cutaneous allergic reactions
(iv) Drug reaction
(v) Opiate withdrawal
(vi) Psychological
(vii) Renal failure
(d) Gastrointestinal bleeding
(i) Varices (usually esophageal or gastric)
(ii) Peptic ulcer

Table 6.15 (continued)

(iii) Mallory-Weiss tear
(iv) Hemorrhoids
(v) Inflammatory bowel disease
(vi) Meckel's diverticulum
(vii) Polyps
(viii) Cancer
(ix) Trauma/ingestion
(x) Intestinal vasculitis, e.g., Henoch-Schönlein purpura
(xi) Angiodysplasia
(e) Metabolic bone disease/hypocalcemia
(i) Nutritional vitamin/calcium/phosphorus deficiency
(ii) Fat-soluble vitamin malabsorption
1. Anicteric cholestasis
2. Bile acid deficiency
(a) Ingestion of bile acid binders
(b) External biliary drainage
(c) Bile acid synthesis and conjugation defects
3. Celiac disease
4. Pancreatic insufficiency
5. Lymphangiectasia
(iii) Hypoparathyroidism

present with the notable exception of defects of bile acid amidation (see chapter 8).

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