Liver Disease

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Key Facts

- Liver disease is a common and important sequel of inherited metabolic diseases.
- Defects of the following major pathways of intermediary metabolism can lead to significant liver disease: degradation of fatty acids, fructose, galactose, and glycogen as well as of gluconeogenesis, ketogenesis, urea cycle including citrin deficiency, or oxidative phosphorylation.
- Hints to diagnosis can be specific symptoms of these disorders reflecting the demand on the pathway affected; a detailed history as well as pathological alterations of blood ammonia, glucose, lactate, ketone bodies, and pH can lead the path.
- Specific metabolic symptoms can be obscured by consequences of rather nonspecific responses of the liver to hepatocellular damage, decreased liver function, cholestasis, and hepatomegaly.
- Inherited diseases interfering primarily with hepatic cell integrity are Wilson disease, tyrosinemia type I, transaldolase deficiency, RALF syndrome caused by mutations in NBAS, cystic fibrosis, α-1-antitrypsin deficiency, and deficiencies of biosynthetic pathways, such as of cholesterol biosynthesis, bile acid synthesis, peroxisomal disorders, and CDG syndromes. Very striking physical involvement of the liver with relatively little functional derangement is seen in lysosomal storage disorders.
- The diagnostic laboratory evaluation of liver disease must be broad, especially in neonates, and initiated early. Successful outcome depends very much on early institution of specific therapy. In addition to the increasing therapeutic options for individual metabolic disorders, pediatric liver transplantation has developed into a well-established procedure, with the best outcome rates of ≥90 % in liver-based metabolic disorders.

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24.1 General Remarks

Despite the complex interrelated functions of the liver in intermediary metabolism, the hepatic phenotype resulting in inherited metabolic disease is limited and often indistinguishable from that resulting in acquired causes, such as infections or intoxications. The corollary is that acquired liver diseases affect many metabolic processes. The diagnostic laboratory evaluation of liver disease must therefore be broad. Careful evaluation of the history and clinical presentation should include a detailed dietary history as well as a list of all medications, the general appearance of the patient, somatic and psychomotor development, signs of organomegaly, neurological signs, and an ophthalmologic examination. In combination with the results of routine laboratory investigations (Table 24.1), this should lead to the suspicion of an inborn error of metabolism, the initiation of specific metabolic tests (Table 24.2), and a provisional grouping into one of the four main clinical presentations (A, jaundice/cholestatic liver disease; B ,liver failure/hepatocellular necrosis; C, cirrhosis; or D, hepatomegaly).

The family and personal history of the patient may be informative in either acquired or inherited liver disease. Routes of infection may become obvious. Linkage of symptoms to oral intake of food or drugs may almost be diagnostic in fructose intolerance, paracetamol intoxication, or accidental poisoning.

Another important key to diagnosis is the age at presentation. During the first 3 months of life, the majority of patients with liver disease, including those with inherited metabolic diseases, present with conjugated hyperbilirubinemia. Later in infancy, the presentation becomes broader (Fig. 24.1).

Only a few well-defined inherited diseases cause unconjugated hyperbilirubinemia: hemolytic anemias or impaired conjugation of bilirubin resulting in recessive deficiency of UDP-glucuronyl transferase in Crigler–Najjar syndrome types 1 and 2 or in the milder *Gilbert syndrome* (bilirubin, 1–6 mg/dL). The latter is a benign condition manifesting in neonates only if they are afflicted by a second hemolytic disorder, such as glucose-6-phosphatase deficiency. In later life, mild jaundice aggravated by fasting or intercurrent illness is the only symptom, and the condition is often discovered accidentally. *Crigler–Najjar syndrome type 1*, usually defined as bilirubin >20 mg/dL or >360 μmol/L that does not respond to phenobarbitone therapy, leads to severe nonhemolytic jaundice. Severe neurological damage and death due to kernicterus are a common sequel. Patients with *Crigler–Najjar type 2* have bilirubin levels of up to 20 mg/dL. Both orthotopic and auxiliary liver transplant have proven highly successful. Crigler–Najjar syndrome type 1 has been ameliorated by

Table 24.1 First-line investigations in disease of the liver

Alanine and aspartate aminotransferases (transaminases)
Lactate dehydrogenase
Cholinesterase
Alkaline phosphatase
γ-Glutamyl transpeptidase
Bilirubin, conjugated and unconjugated
Bile acids
Coagulation studies: INR, PT, and PTT, and factors V, VII, and XI
Albumin, prealbumin
Urea nitrogen, creatinine, uric acid, CK
Glucose
Ammonia
Hepatitis A, B, C, E
Cytomegalovirus, EBV, herpes simplex, toxoplasmosis, HIV
Viral cultures of stool and urine
Abdominal ultrasound (gall bladder before and after meal, hepatic tumor)
Ultrasound of the heart (vitium cordis, peripheral pulmonary stenosis)
In infancy
Rubella, parvovirus B19, echovirus, and a variety of enterovirus subtypes
Bacterial cultures of blood and urine

INR international normalized ratio, *PT* prothrombin time, *PTT* partial thromboplastin time, *EBV* Epstein–Barr virus, *HIV* human immunodeficiency virus

Table 24.2 Second-line investigations in suspected metabolic liver disease

Plasma/serum
Copper, ceruloplasmin
α-Fetoprotein
Cholesterol, triglycerides
Serum iron and ferritin, transferrin, and transferrin saturation
Free fatty acids, lactate, pyruvate, 3-hydroxybutyrate, acetoacetate
Chitotriosidase
Amino acids
Free and total carnitine, acylcarnitines profile
α-1-Antitrypsin activity and PI phenotyping
Lysosomal enzymes
Blood spots
Acylcarnitines profile
Acid lipase
Urine
Amino acids
Ketones
Reducing substances/sugars (galactosemia, fructose intolerance)
Organic acids (incl. specific assays for orotic acid and succinylacetone)
Individual bile acids (bile acid synthesis defects)
Copper in 24-h urine
Sweat chloride(cystic fibrosis)
In infancy
Galactose-1-phosphate uridyl transferase (galactosemia)
Chromosomes (especially when liver disease is accompanied by malformations suggesting trisomy 13 or 18)
Free T_4 and TSH (hypothyroidism)
Transferrin isoelectric focusing (CDG syndromes)
Very long-chain fatty acids (peroxisomal disorders)

hepatocyte transplantation in a few cases and is an attractive candidate for gene therapy (Table 24.3).

Pediatric liver transplantation has developed into a well-established procedure. Patients with cholestatic or liver-based metabolic diseases have the best outcome with 5-year survival ≥90% and high-quality long-term survival. Auxiliary transplantation is an option when there is no significant fibrosis, and the objective of treatment is the replacement of the missing enzyme, e.g., in Crigler–Najjar syndrome type 1 or urea cycle disorders.

24.2 Cholestatic Liver Disease

24.2.1 Cholestatic Liver Disease in Early Infancy

Cholestatic liver disease may aggravate or prolong physiological neonatal jaundice. It becomes obviously pathological when conjugated hyperbilirubinemia is recognized (conjugated bilirubin >15% of total). Normal infants pass colorless urine. An important early warning sign is finding colored urine which may vary from only faintly yellow to distinctly yellow or even brown. The significance of this finding is often missed, as this color is similar to adult urine. Of course, by this time the sclerae are yellow – with chronic direct hyperbilirubinemia, the skin becomes yellow and may have a greenish hue. Cholestasis frequently causes pale or acholic stool. A colored stool, however, does not exclude cholestasis.

Remember

A stool specimen should always be looked at in the first visit of jaundiced neonates with conjugated hyperbilirubinemia.

Transient conjugated hyperbilirubinemia can be observed in neonates, especially premature infants, after moderate perinatal asphyxia. It is associated with a high hematocrit and a tendency to hypoglycemia and has an excellent prognosis, if the pathological conditions described below have been excluded.

Remember

Cholestatic liver disease in infancy may be the initial presentation of cystic fibrosis, Niemann–Pick disease type C, and tyrosinemia type I. In East Asians citrin deficiency has to be considered.

Biliary obstruction. Infants with cholestatic liver disease often appear well. Early differentiation between biliary atresia, a choledochal cyst, and a "neonatal hepatitis syndrome" is most important. Biliary atresia accounts for 20–30% of neonatal cholestasis syndromes. Structural cholestasis can also be due to intrahepatic bile

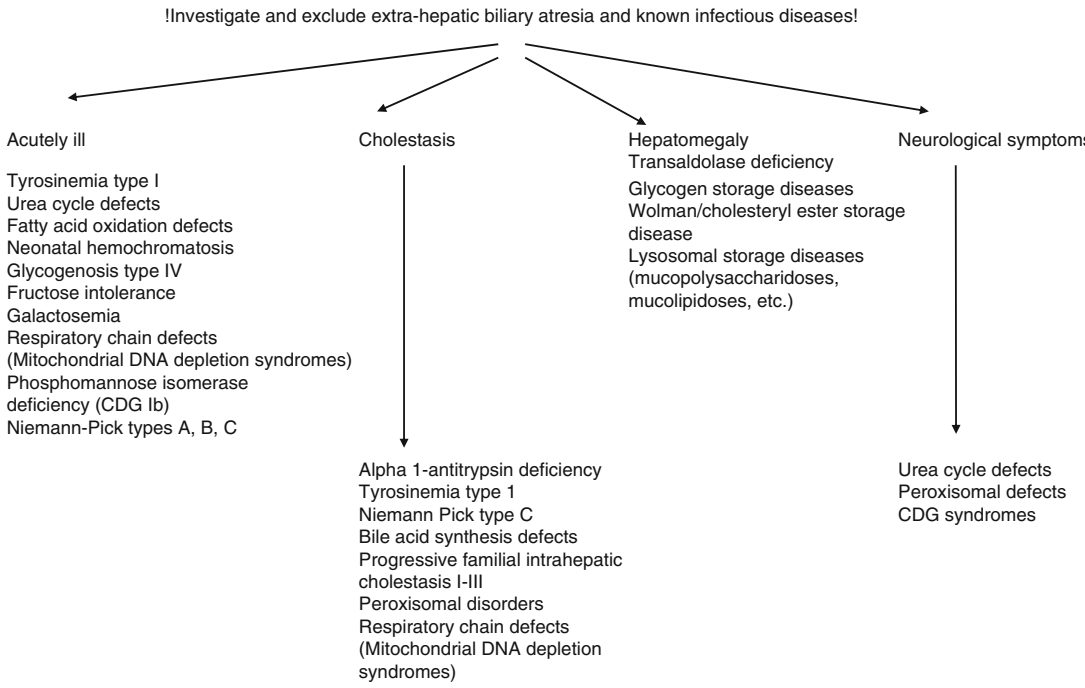

Fig. 24.1 Differential diagnosis of metabolic liver diseases in infants

duct paucity. The syndromal form is *Alagille syndrome*, in which a dominantly inherited dysplasia of the pulmonary artery occurs with distinctive dysmorphic features and paucity of intrahepatic bile ducts resulting in cholestatic liver disease. Intrahepatic bile duct paucity can be an isolated finding. Routine clinical chemical investigations can seldom differentiate between biliary obstruction and neonatal hepatitis syndrome, although low or normal γ-GT suggests a disorder of bile acid synthesis or transport. Impaired coagulation unresponsive to vitamin K points to the development of liver failure and should prompt referral for consideration of liver transplantation.

Remember

The differentiation between biliary obstruction and neonatal hepatitis syndrome must be vigorously pursued by a structured protocol so that biliary atresia, or other surgical causes, can be confirmed within 1 week as late surgery affects survival.

Disease Info: α-1-Antitrypsin Deficiency

α-1-Antitrypsin is one of the most important inhibitors of proteases (e.g., elastase, trypsin, chymotrypsin, thrombin, and bacterial proteases) in plasma. Different protein variants of α-1-antitrypsin are differentiated by isoelectric focusing. The Z variant is characterized by a glutamine to lysine exchange at position 342 in the protein. It alters the charge and tertiary structure of the molecule and is associated with reduced enzyme activity. The frequency of this particular allele is very high in Caucasians; 5 % of the population of Sweden are MZ heterozygotes and 2 % of the United States. The frequency of the homozygous Pi-ZZ phenotype is 1 in 1,600 in Sweden and 1 in 6,000 in the United States. Normal serum levels of α-1-antitrypsin are from 20 to 50 μmol/L and, in the ZZ phenotype, 3 to 6 μmol/L. Patients with values below 20 μmol/L should have PI phenotyping.

Table 24.3 Hepatic diseases that may be cured by liver transplantation

Disease	Timing
Acute Wilson disease	If acute liver failure or if no response to therapy
Neonatal hemochromatosis	Soon if no response to antioxidant cocktail
α-1 Antitrypsin deficiency	In early infancy if cholestasis deteriorates
Urea cycle disorders	Early in the course to prevent further crises
Tyrosinemia type I	Early in the course if no response to therapy or if hepatocellular carcinoma is suspected
PFIC I–III	If pruritus and portal hypertension develops
Primary hyperoxaluria	Liver transplantation before development of renal impairment
	Combined liver/kidney TX when GFR <20
Crigler–Najjar type 1	Before school age, consider liver cell or auxiliary transplantation
Cystic fibrosis	If cholestasis deteriorates or portal hypertension is resistant to therapy
Glycogenosis type I	In childhood if poor metabolic control (non-A) or later if risk of malignancy
Glycogenosis type IV	If decompensated liver disease
Maple syrup urine disease	If poor metabolic control

Cholestatic liver disease occurs in 10–20 % of infants with the Pi-ZZ α-1-antitrypsin phenotype, which in turn accounts for 14–29 % of the neonatal hepatitis syndrome, once infectious and toxic causes have been excluded. Bleeding may occur as a result of deficiency of vitamin K with prompt response to intravenous vitamin K. The stool may be acholic. Low serum α-1-antitrypsin and genetic phenotyping usually lead to the diagnosis. In the acute stages, liver biopsies of infants with α-1-antitrypsin deficiency may show giant cell hepatitis but may mimic biliary atresia.

Some patients with α-1-antitrypsin deficiency, who had no history of neonatal cholestasis, develop cirrhosis eventually and may present with unexplained liver failure. These patients have had the Pi types ZZ, MZ, and M (Malton). In addition, hepatocellular carcinomas have been described in ZZ and MZ phenotypes.

A major proportion of patients with α-1-antitrypsin deficiency remain free of liver disease throughout their life. In adulthood, 80–90 % of patients with the Pi-ZZ phenotype develop destructive pulmonary emphysema. α-1-Antitrypsin is protective of the lung, because it is an effective inhibitor of elastase and other proteolytic enzymes, which are released from neutrophils and macrophages during inflammatory processes. Children with the rare Pi null variant may have severe emphysema early in their life. Intravenous infusions of α-1-antitrypsin have been shown to impede the development of emphysema but are not indicated for liver disease.

In *dysmorphic infants with cholestasis*, very long-chain fatty acids, as well as chromosomes, should be investigated as peroxisomal diseases, and trisomies 13 and 18 are associated with the neonatal hepatitis syndrome and biliary atresia (trisomy 18). Alagille syndrome has been discussed earlier.

A group of inherited metabolic diseases characterized by *progressive familial intrahepatic cholestasis* (PFIC) starting in infancy are increasingly recognized. These include *defects in bile acid biosynthesis*. Unfortunately the necessary laboratory facilities to diagnose these latter treatable disorders are only available in a few laboratories worldwide. Multiple enzyme defects in the modification of the steroid nucleus of bile acids and in conjugation of bile acids have been elucidated. Malabsorption of fat-soluble vitamins is pronounced and results in spontaneous bleeding and rickets. The level of alkaline phosphatase is often highly elevated and γ-GT disproportionally low. Determination of total bile acids is not helpful. More widespread availability of fast atom bombardment mass spectrometry for rapid analysis

of urine samples will hopefully result in a quicker recognition of these disorders in the future. After diagnosis, there is a good clinical and biochemical response to supplementation with bile acids such as cholic or chenodeoxycholic acids. Ursodeoxycholic acid may have some nonspecific benefits in cholestasis but does not address the underlying metabolic defect.

Remember

After exclusion of other diseases, infants with cholestatic liver disease should be examined for the treatable defects of bile acid biosynthesis, which requires determination of individual bile acid metabolites.

24.2.2 Cholestatic Liver Disease in Later Infancy and Childhood

After 3 months of age, the initial clinical and biochemical presentation usually allows a clearer suspicion and differentiation of inherited metabolic liver disease than in neonates. In patients with α-1-antitrypsin deficiency, cholestatic liver disease gradually subsides before 6 months of age. In later infancy, three distinct metabolic diseases present with cholestatic liver disease (Table 24.4).

Disease Info: Progressive Familial Intrahepatic Cholestasis (PFIC) (Byler Disease)

PFIC is a genetically heterogeneous group of autosomal recessive liver disorders, characterized by cholestasis that frequently progresses to cirrhosis and liver failure before adulthood. There are at least four types of PFIC recognized and in approximately 30 % of cases no genetic cause has been identified. The term Byler disease is generally used for PFIC type 1 caused by a deficiency of a P-type ATPase that is required for ATP-dependent amino phospholipid transport and encoded by the *ATP8B1* gene. Other PFIC types are linked to the *ABCB11* gene (PFIC2), the *ABCB4* gene (PFIC3), and the *TJP2* gene. Symptoms may start anytime in infancy with jaundice, pruritus, growth failure, and conjugated hyperbilirubinemia. Liver function slowly deteriorates, and terminal liver failure usually occurs before 15 years. All types except PFIC3 have a low/normal γ-glutamyltransferase (γ-GT). Partial biliary diversion can have a dramatic effect in some types if used early, with liver transplantation as the treatment of choice for advanced liver disease. Transplantation

Table 24.4 Differential diagnosis of metabolic cholestatic liver disease (conjugated hyperbilirubinemia)

Age of presentation	Diseases to be considered	Additional findings
<3 months	α-1-Antitrypsin deficiency	⇓ α-1-Globulin, ⇓ α-1-antitrypsin
	Cystic fibrosis	⇑ Sweat chloride
	Tyrosinemia type I	⇑ AFP
	Niemann–Pick type	Foam cells in marrow
	Peroxisomal diseases	Encephalopathy
	Bile acid synthesis defects	Prominent malabsorption
	Citrin deficiency	Failure to thrive, ⇑ alpha-fetoprotein
>3 months	Progressive familial intrahepatic cholestasis (e.g., Byler disease)	Progressive cirrhosis
	Rotor syndrome	Normal liver function
	Dubin–Johnson syndrome	Normal liver function

Known infectious diseases should have been ruled out by laboratory tests listed in Table 24.1 and extrahepatic biliary disease by imaging techniques

may be complicated by postoperative intractable diarrhea, progressive liver disease in the graft and pancreatitis in PFIC1, and, more rarely, immune-mediated recurrence in PFIC2.

PFIC3 is due to mutations in *ABCB4* which encodes for MDR3 and can be distinguished from the other disorders by high-serum γ-GT activity and liver histology that shows portal inflammation and ductular proliferation at an early stage. MDR3 acts to translocate phosphatidylcholine across the canalicular membrane where it neutralizes the detergent effect of bile acids. In the absence of phosphatidylcholine, canalicular bile acids cause a chemical cholangitis. Heterozygous mutations in *ABCB4* are associated with some types of intrahepatic cholestasis of pregnancy and with gallstone disease.

Disease Info: Dubin–Johnson and Rotor Syndromes

Dubin–Johnson and Rotor syndromes are both autosomal recessively inherited disorders characterized by isolated conjugated hyperbilirubinemia. Patients are usually asymptomatic except for jaundice. Bilirubin levels can range from 2 to 25 mg/dL (34–428 μmol/L). Both the conditions are rare and can be differentiated by urinary porphyrins and appearance of the liver, which is deeply pigmented in Dubin–Johnson syndrome and unremarkable in Rotor syndrome. Excretion of conjugated bilirubin is impaired in both the disorders. Rotor syndrome requires mutations in both of the adjacent genes *SLCO1B1* and *SLCO1B3*, encoding organic anion-transporting polypeptides OATP1B1 and OATP1B3, respectively. Dubin–Johnson syndrome is due to mutations in *ABCC2* which encodes the canalicular multispecific organic anion transporter.

24.3 Liver Failure

24.3.1 Fulminant Liver Failure in Early Infancy

The differential diagnosis in this age group is wide, ranging from toxic or infectious causes to several inherited metabolic diseases (Table 24.5). Mortality is high. The age of presentation (Table 24.6) as well as associated features (Table 24.7) may be helpful in directing the investigations. Jaundice is usually present, but more important and characteristic features are elevated liver transaminases and markers of hepatic insufficiency, such as hypoglycemia, hyperammonemia, hypoalbuminemia, and vitamin K-unresponsive coagulopathy. Failure to thrive is usually present. Deranged liver function may result in spontaneous bleeding or neonatal ascites, indicating end-stage liver disease.

Remember

Encephalopathy associated with severe liver failure may not be obvious in neonates and young infants.

Acute disease may progress rapidly to hepatic failure. In severely compromised infants, routine clinical chemical measurements often do not distinguish acutely presenting inherited metabolic diseases from severe viral hepatitis or septicemia, although disproportionate hypoglycemia, lactic acidosis, and/or hyperammonemia all point to a primary metabolic disease. Furthermore, it is not uncommon for septicemia to complicate and aggravate inherited metabolic diseases. Help in the differential diagnosis may come from the judgment of liver size. Decompensated inherited metabolic diseases are often accompanied by significant hepatomegaly due to edema, whereas rapid atrophy can develop in fulminant viral hepatitis or toxic injury.

In babies with acute hepatocellular necrosis, rapid diagnosis of the inherited metabolic diseases listed in Tables 24.5 and 24.7 is essential as specific therapy is available for most and must be initiated as soon as possible. Metabolites accumulating in galactosemia

(galactose-1-phosphate) and hereditary fructose intolerance (fructose-1-phosphate) have a similar toxicity particularly for the liver, kidneys, and brain but are usually differentiated by different clinical settings (different age groups) in which first symptoms occur. Determination of amino acids in plasma and urine and analysis of organic acids in urine (particularly succinylacetone, dicarboxylic acids, and orotic acid) should elucidate the presence of hepatorenal tyrosinemia, fatty acid oxidation defects, and urea cycle disorders.

Disease Info: Galactosemia

Galactosemia is caused by a deficiency of galactose-1-phosphate uridyltransferase (GALT). Clinical symptoms usually start after the onset of milk feeds on the third or fourth day of life and include vomiting, diarrhea, jaundice, disturbances of liver function, or sepsis and if untreated may progress to death from hepatic and renal failure. Whenever galactosemia is suspected (and in all neonates with liver failure), adequate blood and urine tests should be initiated (galactose and galactose-1-phosphate in serum, erythrocytes, or dried blood spots; enzyme studies in erythrocytes) and a lactose-free diet should be started immediately. Galactose in urine is not detected by standard stix tests based on the glucose oxidase method (Clinistix® and Tes-tape®), and there is a strong argument for the continued use of the older methods of screening urine for reducing substances (Benedict or Fehling test and Clinitest®), which also detect galactose. Urinary excretion of galactose depends on the dietary intake and will not be detectable 24–48 h after discontinuation of milk feedings. On the other hand, babies with severe liver disease from any cause may have impaired galactose metabolism and gross secondary galactosuria. After discontinuing galactose for 2–3 days, a baby with galactosemia begins to recover. Cataracts may have developed in only a few days (Fig. 30.2) and slowly clear in early infancy after removal of the toxic sugar.

Remember

In any baby who has received milk and developed liver disease, the investigation should include determination of the enzymatic activity of galactose-1-phosphate uridyl transferase in erythrocytes, regardless of the results of newborn screening.

Remember

Elevations of succinylacetone in urine may be small in young infants, and repeated analyses with special requests for specific determination by stable isotope dilution may be warranted in patients in whom clinical suspicion is strong.

Genetic defects of fatty acid oxidation and of the respiratory electron transport chain have become recognized as causes of rapidly progressive hepatocellular necrosis in infancy. Defects of fatty acid oxidation are suggested in prolonged intermittent or subacute presentations by myopathy, cardiomyopathy, hypoketotic hypoglycemia, hyperuricemia, elevation of CK, lactic acidosis, and dicarboxylic aciduria (see also Chap. 16). Defects of the respiratory chain causing hepatocellular necrosis are characterized by additional variable multiorgan involvement, especially, of the bone marrow, pancreas, and brain, moderate to severe lactic acidosis, and ketosis (see also Chaps. 14 and 42). During acute hepatocellular necrosis in infancy, these differentiating features may be masked by generalized metabolic derangement. Repeated determinations of metabolites such as lactate, pyruvate, 3-hydroxybutyrate, acetoacetate, free and total carnitine, and acylcarnitines in addition to determinations of amino acids in blood and organic acids in urine should be performed in any baby with progressive hepatocellular

Table 24.5 Differential diagnosis of liver failure (acute or subacute hepatocellular necrosis)

Age of presentation	Diseases to be considered	Additional findings
<3 months	Neonatal hemochromatosis	⇑ ⇑ ⇑ Ferritin, ⇑ ⇑ ⇑ AFP
	Galactosemia	Cataracts, urinary reducing substance
	Tyrosinemia type I	⇑ ⇑ AFP
	Urea cycle defects	⇑ ⇑ ⇑ Ammonia
	Respiratory chain defects	⇑ ⇑ Lactate
	Long-chain fatty acid oxidation defects	⇑ Lactate, ⇑ urate, ⇑ CK, ⇑ ammonia, (cardio)myopathy, myoglobinuria, abnormal acylcarnitines
	Niemann–Pick types A, B, C	Foam cells in marrow
	Phosphomannose isomerase deficiency (MPI-CDG, formally type Ib)	°Pattern of transferrin isoforms
3 months–2 years	Fructose intolerance	⇓ Glucose
	Tyrosinemia type I	⇑ ⇑ AFP
	Fatty acid oxidation defects	⇓ Glucose, ⇑ uric acid, ⇑ CK, ⇓ ketones, ⇑ lactate, ⇑ ammonia, abnormal acylcarnitines
	Respiratory chain defects	⇑ Lactate
	Urea cycle defects	⇑ ⇑ ⇑ Ammonia
	Wolcott–Rallison syndrome	Diabetes
	RALF syndrome	Recurrent episodes precipitated by fever
>2 years	Wilson disease	Corneal ring, hemolysis, renal tubular abnormalities, neurologic degeneration
	α-1-Antitrypsin deficiency	⇓ α-1-Globulin, ⇓ α-1-antitrypsin
	Respiratory chain defects	⇑ ⇑ Lactate
	Fatty acid oxidation defects	⇓ Glucose, ⇑ uric acid, ⇑ CK, ⇓ ketones, ⇑ lactate, ⇑ ammonia
	Urea cycle defects	⇑ ⇑ ⇑ Ammonia
	Glycogenoses type VI/IX	± ⇓ Glucose, ⇑ transaminases, ⇑ lactate, ⇑ CK
	Phosphoglucomutase 1 deficiency or PGM1-CDG	Bifid uvula ± ⇓ Glucose, ⇑ transaminases, ⇑ CK
	RALF syndrome	Recurrent episodes precipitated by fever
	Urea cycle defects	⇑ ⇑ ⇑ Ammonia

Known infectious diseases should have been ruled out by laboratory tests listed in Table 24.1 and extrahepatic biliary disease by imaging techniques

necrosis. If the clinical and biochemical presentation is suggestive of a defect of fatty acid oxidation or of the respiratory chain, appropriate enzymatic confirmation in the muscle and liver, or molecular studies of nuclear or mitochondrial DNA, should be sought (see also Chaps. 14, 16, and 42). If results are negative, those suspected of fatty acid oxidation should then have a defect of the respiratory chain excluded and vice versa. Small infants with primary defects of fatty acid oxidation may present with overwhelming lactic acidosis and infants with severe liver disease due to defects of the respiratory chain with hypoketotic hypoglycemia and dicarboxylic aciduria.

Table 24.6 Age at presentation as a clue to the cause of hepatic failure in infancy

0–7 days	Herpes simplex types 1 and 2
	mtDNA depletion
	Neonatal hemochromatosis
1–4 weeks	Infections including enteroviruses
	Galactosemia
	Tyrosinemia
4–8 weeks	Hepatitis B (vertical transmission)
	Familial hemophagocytic lymphohistiocytosis
2–6 months	Bile acid synthesis defects
0.5–1 year	Hereditary fructose intolerance
	Ralf syndrome
	mtDNA depletion
	Wolcott–Rallison syndrome
	Viral hepatitis
	Autoimmune disease

Table 24.7 Neonatal liver failure

Disorder	Additional clinical features
Mitochondrial hepatopathy, often mtDNA depletion	Muscular hypotonia, multisystem disease, encephalopathy, ↑↑ lactate
Neonatal hemochromatosis	Hepatocellular necrosis, cirrhosis, ↑↑ ferritin, ↑↑ AFP, transaminases may be low
Galactosemia	Onset after milk feeds, jaundice, renal disease, cataracts
Fatty acid oxidation disorders	(Cardio)myopathy, hypoketotic, hypoglycemia, ↑↑ lactate
Urea cycle disorders	↑↑ Ammonia, encephalopathy
Niemann–Pick type C	Jaundice, hypotonia, hepatosplenomegaly
Glycosylation disorders (CDG, especially MPI-CDG, formally type Ib)	Hepatomegaly, hepatocellular dysfunction, protein losing enteropathy, multisystem disease

Rarely: α_1-antitrypsin deficiency, bile acid synthesis disorders

Remember

When cardiomyopathy is present, lactic acidosis may be due to heart failure and poor perfusion.

Disease Info: Neonatal Hemochromatosis

Neonatal hemochromatosis is the commonest cause of rapidly progressive hepatocellular necrosis in infancy. While neonatal hemochromatosis may be a phenotype rather than a single entity, in the majority of cases, it appears to be alloimmune in origin. Maternal antibodies to an uncharacterized fetal antibody have been detected, the recurrence pattern is characteristic of other gestational alloimmune diseases, and early (<18 weeks of gestation) prenatal maternal immunoglobulin treatment modifies the disease. Diagnosis is by exclusion of other causes and demonstration of increased concentrations of serum iron, ferritin (>2,000 μg/L), and α-fetoprotein as well as decreased concentrations of transferrin with complete or near-complete saturation of iron-binding capacity. Demonstration of extrahepatic siderosis is pathognomic. This can be assessed by minor salivary gland biopsy or abdominal MRI. Exchange transfusion in combination with immunoglobulin treatment is the first-line treatment, but liver transplantation is often required and all cases should be discussed with a transplant center (Table 24.3). Iron storage is not permanently disturbed as survivors with and without transplantation do not develop permanent iron storage disease.

24.3.2 Hepatic Failure in Later Infancy and Childhood

Fulminant hepatic failure in later infancy or early childhood may present in a similar fashion to that in neonates with elevated transaminases, hypoglycemia, hyperammonemia, decrease of coagulation factors, spontaneous bleeding, hypoalbuminemia, and ascites. Mortality is high and most will die without liver transplantation (Table 24.3). On liver biopsy hepatocellular necrosis is obvious. Renal tubular dysfunction or rickets is indicative of an

inherited metabolic disease. In combination with early infancy insulin-dependent diabetes mellitus, *Wolcott–Rallison syndrom*e (OMIM #226980) should be looked for by mutation analysis. The association of acute hepatocellular necrosis with a prominent noninflammatory encephalopathy suggests a diagnosis of Reye syndrome; most patients with this syndrome are now found to have inherited metabolic disease.

Most cases of acute hepatocellular necrosis in older children are unexplained and labeled as seronegative hepatitis. A small or rapidly decreasing liver size and deep jaundice is a strong argument against an inherited metabolic disease. Autoimmune disease must also be taken into consideration; autoantibodies are present in the majority of affected children, and there usually is an increase in IgG.

Disorders of fatty acid oxidation and urea cycle defects should be high on the list of differential diagnosis of children presenting with acute hepatocellular necrosis. If disproportionate hyperammonemia or hypoketotic hypoglycemia has been observed, vigorous emergency measures should be promptly initiated and diagnostic confirmation sought by specialized metabolic investigations (Chaps. 16 and 17). Both are potentially lethal in the acute episode.

The recently described recurrent acute liver failure (RALF) syndrome is caused by mutations in NBAS which encodes for a protein involved in transport between endoplasmic reticulum and Golgi apparatus. Haack et al. (2015) Children present with bouts of liver failure consisting of very high transaminases, severe coagulopathy, and encephalopathy starting in infancy. Bouts are self-limiting, and recovery may be hastened by antipyresis, aggressive support, and the use of intralipid infusion. There is complete recovery between episodes, which persist throughout childhood but diminish in adulthood.

Tyrosinemia type I and fructose intolerance are usually diagnosed in infancy or early childhood; urea cycle and fatty acid oxidation defects can cause acute hepatic dysfunction at any age.

Hepatopathy with increased liver transaminases, intermittent hypoglycemia, short stature, and bifid uvula with or without cleft palate are characteristics of phosphoglucomutase 1 deficiency or PGM1-CDG. Patients with this disorder, which is eminently treatable with oral galactose supplementation, often develop exercise intolerance, increased muscle glycogen content, and increased serum creatine kinase.

In later childhood, Wilson disease and α-1-antitrypsin deficiency are important metabolic causes of severe hepatocellular necrosis. Courses may be subacute or chronic, and initial presentation is variable, ranging from isolated hepatomegaly, jaundice, or ascites to a chronic active hepatitis-like picture or acute liver failure. Hemolysis, when present, may be an important clue to Wilson disease.

Disease Info: Tyrosinemia Type I

Tyrosinemia type I (fumarylacetoacetase deficiency) usually presents with pronounced acute or subacute hepatocellular damage and only occasionally with cholestatic liver disease in infancy. Patients who have an acute onset of symptoms very quickly develop hepatic decompensation. They may have jaundice and ascites along with hepatomegaly. There may be gastrointestinal bleeding. Several infants have been noted by their mothers to have a peculiar sweet cabbage-like odor. Generalized renal tubular dysfunction occurs, leading to glucosuria, aminoaciduria, and hyperphosphaturia. Very low levels of phosphate in serum are common findings, as are hypoglycemia and hypokalemia. In some patients the diagnosis of tyrosinemia type I can be difficult, as increases of tyrosine and methionine occur in many forms of liver disease but may be missing in tyrosinemia type I. A highly elevated α-fetoprotein is sensitive but not specific for tyrosinemia. Very high elevations of α-fetoprotein are also seen in neonatal hemochromatosis, which should be differentiated on the basis of gross elevations of iron and ferritin. Diagnostic proof of tyrosinemia type I comes from the demonstration of succinylacetone in urine and subsequently by detection of pathogenic mutations.

If tyrosinemia type I does not become symptomatic until later in infancy, patients usually follow a less rapid course. Vomiting, anorexia, abdominal distension and failure to thrive, rickets, and easy bruising may be the presenting features, and there is usually hepatomegaly. Although transaminases may be normal or only slightly elevated, prothrombin time and partial thromboplastin time are usually markedly elevated, as is α-fetoprotein, which may range from 100,000 to 400,000 ng/mL. Individual patients may present with different clinical pictures, such as with acute liver disease and hypoglycemia as a Reye-like syndrome. They may present with isolated bleeding and undergo initial investigation for coagulation disorders before hepatic disease is identified.

Renal tubular disease in tyrosinemia type I is that of a renal Fanconi syndrome with phosphaturia, glucosuria, and aminoaciduria (Chap. 26). There may be proteinuria and excessive carnitine loss. Renal tubular loss of bicarbonate leads to systemic metabolic acidosis. The affected infants have been observed to develop vitamin D-resistant rickets at less than 4 months of age.

Beyond infancy, neurological crises very similar to those of acute intermittent porphyria are a more common cause of admission to the hospital than hepatic decompensation. Succinylacetone inhibits porphobilinogen synthase (the enzyme affected in acute intermittent porphyria); increased urinary excretion of delta-aminolevulinate and porphobilinogen occurs during neurological crises. About half of the patients experience such crises, starting with pains in the lower extremities, followed by abdominal pains, muscular weakness, or paresis and paresthesias. The head and trunk may be positioned in extreme hyperextension, suggesting opisthotonus or meningismus. Systemic signs include hypertension, tachycardia, and ileus. Symptoms can continue for up to a week and slowly resolve. Intellectual function has been thought to be normal in tyrosinemia type I but recent reports suggest that educational difficulties are relatively common.

In the natural disease course, most children with tyrosinemia type I die in early life, most of them before 1 year of age. Survivors have chronic liver disease with macronodular cirrhosis. Splenomegaly and esophageal varices develop and are complicated by bleeding. A common complication is hepatocellular carcinoma, which may first be suspected because of a secondary rise in the level of α-fetoprotein. Liver or combined liver–kidney transplantation was the only promising option of treatment until the advent of 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). Currently, liver transplantation in tyrosinemia type 1 is only necessary in nonresponders to NTBC therapy. The drug is a potent inhibitor of *p*-hydroxyphenylpyruvate dioxygenase, thus preventing the formation of the highly toxic fumarylacetoacetate, and its products succinylacetoacetate and succinylacetone. Treatment is combined with tyrosine and phenylalanine restriction, and compliance is crucial as hepatic malignancy or neurological crises may develop rapidly after even a short interruption of or inconsistent treatment. If the treatment is instituted early, hepatic and renal function slowly improves to normal, and neurological crises are prevented. Concentrations of succinylacetone, α-fetoprotein, and delta-aminolevulinate gradually decrease to near-normal values. If treatment is started preemptively following newborn screening, significant liver disease can be avoided.

The differential diagnosis of the patient with elevated levels of tyrosine in the blood includes tyrosinemia types II and III and transient neonatal tyrosinemia. *Tyrosinemia type II* (tyrosine aminotransferase deficiency), known as the Richner–Hanhart syndrome, results in oculocutaneous lesions, including corneal erosion, opacity, and plaques. Pruritic or hyperkeratotic lesions may develop on the palms and soles. About half of the patients described have had low-normal to subnormal levels of intelligence, but this may reflect bias of ascertainment.

The phenotype of *tyrosinemia type III* (*p*-hydroxyphenylpyruvate dioxygenase deficiency) is less well defined. It may include neurological manifestations such as psychomotor

retardation and ataxia but also remain asymptomatic. As treatment with NTBC in patients with tyrosinemia type I shifts the metabolic block from fumarylacetoacetate hydrolase to *p*-hydroxyphenylpyruvate dioxygenase or from tyrosinemia type I to tyrosinemia type III, treatment with NTBC must be supplemented by dietary treatment with a phenylalanine- and tyrosine-reduced diet, which is the rational approach to treatment in tyrosinemia types II and III.

Metabolic investigations or newborn screening, particularly in premature infants, sometimes detects tyrosinemia and hyperphenylalaninemia not due to a defined inherited metabolic disease. The protein intake is often excessive, especially when an evaporated milk formula is being used. This form of tyrosinemia is thought to result from physiological immaturity of *p*-hydroxyphenylpyruvate dioxygenase and is a warning that protein intake should be moderate during the first weeks of life. Relative maternal vitamin C deficiency may play a role. This condition is sometimes associated with prolonged jaundice and feeding problems and can cause diagnostic confusion.

Disease Info: Hereditary Fructose Intolerance

Symptoms develop in hereditary fructose intolerance when fructose or sucrose is introduced into the diet. The recessively inherited deficiency of fructose-1-phosphate aldolase results in an inability to split fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate. Fructose-1-phosphate accumulates in the liver, kidney, and intestine. Pathophysiological consequences are hepatocellular necrosis and renal tubular dysfunction, similar to what occurs in galactosemia. There is an acute depletion of ATP caused by the sequestration of phosphate and direct toxic effects of fructose-1-phosphate.

Depending on the amount of fructose or sucrose ingested, infants may present with isolated asymptomatic jaundice or with rapidly progressive liver failure, jaundice, bleeding tendency, and ascites, suggesting septicemia or fulminant viral hepatitis; hepatosplenomegaly, if present, argues against the latter diagnosis. Postprandial hypoglycemia develops in 30–50 % of the patients affected with fructose intolerance and may progress to coma and sudden death. Most patients present subacutely with vomiting, poor feeding, diarrhea, or sometimes failure to thrive. Pyloric stenosis and gastroesophageal reflux are common initial diagnoses. The clinical picture may be more blurred in later life, and laboratory findings may be unrevealing. Hereditary fructose intolerance deserves consideration as a cause of renal calculi, polyuria, and periodic or progressive weakness or even paralysis. A major clue to diagnosis may be an accurate dietary history that will reveal an aversion to fruits and sweets.

Characteristic clinical chemical laboratory features include elevated transaminases, hyperbilirubinemia, hypoalbuminemia, hypocholesterolemia, and a decrease of vitamin K-dependent, liver-produced coagulation factors. There is an occasional pattern of consumptive coagulopathy. In addition, patients may have hypoglycemia, hypophosphatemia, hypomagnesemia, hyperuricemia, and metabolic acidosis in a renal Fanconi syndrome with proteinuria, glucosuria, aminoaciduria and loss of bicarbonate, and high urine pH despite acidosis. In these circumstances detecting fructose in the urine is virtually diagnostic of the disease, but it may be absent. Elevated plasma levels of tyrosine and methionine in combination with markedly elevated excretion of tyrosine and its metabolites in urine may misleadingly suggest a diagnosis of tyrosinemia type I.

The prognosis in hereditary fructose intolerance depends entirely upon the elimination of fructose from the diet. After withdrawal of fructose and sucrose, clinical symptoms and laboratory findings quickly reverse. Vomiting stops immediately and the bleeding tendency within

24 h. Most clinical and laboratory findings become normal within 2–3 weeks, but hepatomegaly takes longer to resolve.

The excellent response to treatment supports a presumptive diagnosis of fructose intolerance. Confirmation of diagnosis should first be attempted by molecular analysis. Several frequent mutations are known, such as A149P in Caucasians. An intravenous fructose tolerance test can usually not be performed any longer in diagnostically difficult cases as there are no i.v. preparations of fructose available. Demonstration of the enzyme defect in biopsied liver or intestine may be necessary in exceptional circumstances.

Mitochondrial DNA depletion syndromes are increasingly identified as causes of rapidly progressive liver disease. Forms known so far are caused by defects in the deoxyguanosine kinase (DGUOK), polymerase-γ (POLG), MPV17, recessive Twinkle helicase (PEO1) genes, as well as in the EIF2AK3 gene.

Disease Info: Wilson Disease

Wilson disease, or hepatolenticular degeneration, is characterized by the accumulation of copper in various organs and low serum levels of ceruloplasmin. Clinical manifestations are highly variable, but hepatic disease occurs in ≈80 % of affected individuals. This is usually manifested at school age, rarely before 4 years of age. About half of the patients with hepatic disease, if untreated, will develop neurological symptoms in adolescence or adulthood. In older patients with Wilson disease, neurological manifestations may be the presenting symptoms.

Liver transplantation is also usually contraindicated in liver failure due to mutations in *Twinkle* and *DGUOK* with neurological involvement. In contrast, older children with mutations in *MPV17* may have good quality long-term survival following liver transplantation. Disease due to mutations in *TRMU* is particularly important to identify as spontaneous recovery may occur.

Disease Info: Alpers Disease

In patients with Alpers disease, liver failure mostly occurs later in the course of disease, often triggered by the use of valproic acid. Mutations in the *POLG* gene result in defects in respiratory chain complexes I and IV. Despite fulminant liver failure, aminotransferases typically are only mildly elevated. Most patients with Alpers disease present at preschool or school age with neurological symptoms like seizures or even epileptic status and epilepsia partialis continua. Patients' history usually reveals mild and then progressive psychomotor development. However, liver failure may develop before significant neurological disease. If in an unclear situation a therapeutic liver transplantation is being considered, mutation analysis of the *POLG* gene should be pursued as soon as possible. Alpers syndrome due to mutations in the *POLG* gene is a contraindication for transplantation as the neurological disease progresses post transplantation.

One extreme of the clinical spectrum of Wilson disease is a rapid fulminant course in children over 4 years of age progressing within weeks to hepatic insufficiency manifested by jaundice, ascites, clotting abnormalities, and disseminated intravascular coagulation. This is followed by renal insufficiency, coma, and death, sometimes without diagnosis.

Wilson disease can also present with a picture of acute hepatitis. Nausea, vomiting, anorexia, and jaundice are common presenting complaints, and the episode may subside spontaneously. In the presence of splenomegaly, the diagnosis may mimic infectious mononucleosis. Recurrent bouts of hepatitis and a picture of chronic active hepatitis in children above the age of 4 years are suggestive of Wilson disease.

These patients experience anorexia and fatigue. Hepatosplenomegaly is prominent. In some patients isolated hepatosplenomegaly may be discovered accidentally. Any hepatic presentation of Wilson disease implies the development of cirrhosis; the disease may present as cirrhosis. The histological picture is indistinguishable from chronic active hepatitis. Terminally there may be hepatic coma or a hepatorenal syndrome.

Hemolytic anemia may be a prominent feature of Wilson disease in children, and its presence is very suggestive of the diagnosis. Renal tubular disease is subtle; a generalized aminoaciduria often displays an unusually high excretion of cystine, other sulfur-containing amino acids, and tyrosine. Later there may be a full-blown Fanconi syndrome, and patients may develop renal stones or diffuse nephrocalcinosis.

In adults, the onset of Wilson disease is classically neurological, predominantly with extrapyramidal signs. Choreoathetoid movements and dystonia reflect lenticular degeneration and are frequently associated with hepatic disease. This picture has been associated with poor prognosis. Progression tends to be much slower in patients presenting with parkinsonian and pseudosclerotic symptoms, such as drooling, rigidity of the face, and tremor. Speech or behavior disorders, and sometimes frank psychiatric presentations, can occur in children. The lack of overt liver disease can make diagnosis difficult. Dementia develops ultimately in untreated patients.

Wilson disease is treatable by copper-chelating agents making early diagnosis crucial. A key finding is the demonstration of Kayser–Fleischer rings around the outer margin of the cornea as gray–green to red–gold pigmented rings (Fig. 24.2). Slit lamp examination may be required. The rings are difficult to be seen in green–brown eyes. They are pathognomonic in neurological disease, but they take time to develop and are absent in most children who present with hepatic disease.

Biochemical diagnosis of Wilson disease may sometimes be difficult. The diagnosis is usually made on the basis of an abnormally low serum ceruloplasmin, liver copper content, and urine copper content plus mutation analysis. In 95 % of patients, ceruloplasmin is below 20 mg/dL (200 mg/L) (control children 25–45 mg/dL). However, intermediate and even normal values have been reported. Levels of copper in the serum are usually elevated, but measurement of urine copper is more reliable. Urinary excretion of copper is increased to >100 µg/day (1.6 µmol/day in about 65 % of patients) (control children <30 µg/day (0.5 µmol/day)). Further increase in urinary copper excretion can be provoked by loading with 500 mg of D-penicillamine 12 h apart while collecting urine for 24 h. Controls excrete less than 600 µg (9.4 µmol)/day, whereas in Wilson disease, excretion ranges from 1,600 µg (25 µmol) to 3,000 µg (47 µmol)/day. The most sensitive test is the measurement of the concentration of copper in the liver, and this test may be required for diagnosis. Disposable steel needles or Menghini needles should be used. Patients with Wilson disease usually have highly elevated concentrations of copper in the liver (>250 µg (4 mmol) of copper per gram of dry weight, heterozygotes 100–200 mg/g, controls <50 µg (0.8 µmol)). Elevated concentrations of copper in the liver may also be found in children with extrahepatic biliary obstruction or cholestatic liver disease.

Liver histology is not specific. Rhodamine or other staining techniques for copper are not sensitive in childhood Wilson and therefore do not

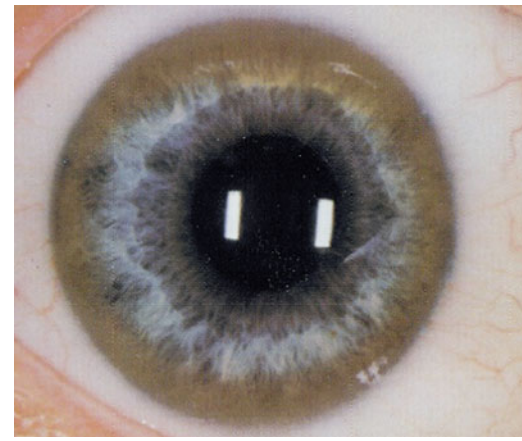

Fig. 24.2 Kayser–Fleischer ring in Wilson disease (Courtesy of Prof. Dr. Wolfgang Stremmel, Heidelberg, Germany)

contribute to the diagnosis. As 80 % of patients with Wilson disease show at least one of the 200 known mutations in the ATP7B gene, molecular diagnosis of Wilson disease is a helpful tool in confirming the diagnoses.

Once the diagnosis of Wilson disease is established, family members (particularly sibs) should be thoroughly examined. This is much easier when known diseases causing mutations have been recognized. Where the mutation status is unknown, liver biopsy may be necessary in the case where an asymptomatic sibling has a low ceruloplasmin level, elevated liver enzymes, and high copper urine, which can be consistent with heterozygosity as well as homozygosity. Stable isotopic ^{65}Cu studies may help to avoid liver biopsy in selected cases. Following oral administration ^{65}Cu enrichment peaks at 1–2 h. ^{65}Cu enrichment then falls to a minimum at about 6 h as ^{65}Cu is taken up by the liver. Thereafter there is a secondary rise over 72 h as ^{65}Cu is excreted from the liver in ceruloplasmin. In Wilson disease this secondary rise does not occur. Early diagnosis must be vigorously pursued, as the best prognosis has been demonstrated following early treatment of asymptomatic patients.

Remember

The association of liver disease with intravascular hemolysis and renal failure is highly suggestive of Wilson disease as are bouts of recurrent hepatitis and a picture of chronic active hepatitis in children above the age of 4 years.

24.4 Cirrhosis

Cirrhosis is the end stage of hepatocellular disease. The list of diseases that can result in cirrhosis and failure of the liver is extensive and includes infectious, inflammatory, and vascular diseases, biliary malformations, as well as toxic and finally metabolic disorders. Cirrhosis can result from most of the diseases discussed in different places of this chapter. Exceptions are primary defects of bilirubin conjugation and some of the storage disorders that lead to isolated hepatomegaly.

Glycogenosis type IV, branching enzyme deficiency, can cause primarily cirrhotic destruction of the liver. In Wilson disease and even more frequently in α-1-antitrypsin deficiency, a cirrhotic process may be quiescent for a long period with no evidence of signs or symptoms of liver disease. Patients may be recognized following family investigations, during investigations of an unrelated disease, or the disease may remain unrecognized until decompensation leads to full-blown liver failure. Specific metabolic diseases leading to cirrhosis are listed in Tables 24.8 and 24.9.

Table 24.8 Differential diagnosis of cirrhosis

Age of presentation	Diseases to be considered	Additional findings
<1 year	Glycogenosis type IV	Myopathy
	Galactosemia	Cataracts, urinary reducing substance
	Neonatal hemochromatosis	⇑⇑⇑ iron, ⇑⇑ ferritin, ⇑⇑ AFP, ⇓ transferrin
	Tyrosinemia type I	⇑⇑ AFP
	Transaldolase deficiency	Dysmorphic features, pancytopenia, cardiac defects
>1 year	α-1-Antitrypsin deficiency	⇓ α-1-Globulin, ⇓ α-1-antitrypsin
	Wilson disease	Corneal ring, hemolysis, renal tubular abnormalities, neurologic degeneration
	Tyrosinemia type I	⇑ AFP

Known infectious and autoimmune diseases should have been ruled out by laboratory tests listed in Table 24.1 and extrahepatic biliary disease by imaging techniques

Table 24.9 Chronic hepatitis or cirrhosis in older children

Disorder	Clinical features
Wilson disease	Neurological and renal disease, corneal ring
Hemochromatosis	Hepatomegaly, cardiomyopathy, diabetes mellitus, diabetes insipidus, hypogonadism
α_1-Antitrypsin deficiency	Failure to thrive, ↓ α_1-antitrypsin
Tyrosinemia type I	Coagulopathy, renal disease, failure to thrive, ↑ AFP
Hereditary fructose intolerance	Symptoms after fructose intake: hypoglycemia, renal disease, failure to thrive, ↑ urate
Transaldolase deficiency	Hepatosplenomegaly, dysmorphic features, pancytopenia
Cystic fibrosis	Failure to thrive, recurrent airway infections
Celiac disease	Failure to thrive, diarrhea, small stature

Table 24.10 Signs and symptoms of liver cirrhosis

General	Malnutrition, failure to thrive, muscle wasting, hypogonadism, elevated temperature, frequent infections
CNS	Lethargy progressing to coma, behavioral changes, depression, intellectual deterioration, pyramidal tract signs, asterixis
Gastrointestinal tract	Nausea and vomiting, splenomegaly, caput medusa, hemorrhoids, epistaxis hematemesis, abdominal distension, steatorrhea, ascites
Kidney	Fluid and electrolyte imbalance, progressive renal insufficiency
Skin	Jaundice, flushing, pruritus, palmar erythema, spider angiomata, digital clubbing

Remember

α-1-Antitrypsin should be quantified in any child, adolescent, or adult in the differential work-up of cirrhosis.

As cirrhosis progresses, signs and symptoms of decompensation eventually emerge. Regardless of the primary disease, patients develop weight loss, failure to thrive, muscle weakness, fatigue, pruritus, steatorrhea, ascites, or anasarca, as well as chronic jaundice, digital clubbing, spider angiomatoma and epistaxis, or other bleeding (Table 24.10). Complications of cirrhosis include portal hypertension, bleeding varices, splenomegaly, and encephalopathy. Terminally there may be hepatic coma. Liver transplantation provides the only realistic therapy. In some cases bridging to transplantation with albumin dialysis may be indicated.

Glycogenosis type IV is due to a deficiency of the branching enzyme α-1,4-glucan: α-1,4-glucan-6-glucosyl transferase that leads to a decrease in the number of branch points making for a straight chain of insoluble glycogen like starch or amylopectin. The content of glycogen in liver is not elevated, but the abnormal structure appears to act like a foreign body causing cirrhosis. The diagnosis can be established by enzyme assay of leucocytes, cultured fibroblasts, or the liver.

Disease Info: Glycogenosis Type IV

Infants with this rare form of glycogen storage disease often present around the first birthday with findings of hepatic cirrhosis, an enlarged nodular liver, and splenomegaly. Hypotonia and muscular atrophy are usually present and may be severe. Treatment is symptomatic and palliative. Transplantation of the liver is curative in predominant liver disease; untransplanted patients usually succumb to complications of cirrhosis before the age of 3 years. Cardiomyopathy and myopathy are often present.

α-1-Antitrypsin deficiency (see textbox Chap. 24 page 4) is an important cause of neonatal

cholestasis as well as of chronic active hepatitis (v. r.). In patients with α-1-antitrypsin deficiency manifesting cholestatic liver disease in infancy, cholestasis gradually subsides before 6 months of age and patients become clinically unremarkable. However, 20–40 % of these children go on to develop hepatic cirrhosis in childhood.

Remember

About 50 % of apparently healthy children with the homozygous Pi-ZZ phenotype have subclinical liver disease, as indicated by elevated levels of aminotransferases and γ-glutamyl transpeptidase.

In the presence or absence of a history of neonatal cholestasis or hepatitis, α-1-antitrypsin should be quantified in any child, adolescent, or adult with unexplained liver disease.

24.5 Hepatomegaly

Hepatomegaly is often the first clinical sign of liver disease. Two clinical aspects are helpful to the diagnostic evaluation of the patient: first, the presence or absence of splenomegaly and, second, the consistency and structure of the enlarged liver.

Remember

Splenomegaly, especially hepatosplenomegaly, is the hallmark of storage diseases.

Functional impairment of the liver, such as decreases of coagulation factors and serum albumin or impaired glucose homeostasis, is usually absent in lysosomal storage diseases, and aspects of liver cell integrity are unremarkable. Exceptions are Niemann–Pick diseases, both the types A/B and C (Table 24.11). In lysosomal storage diseases, the liver and spleen are firm but not hard on palpation. The surfaces are smooth and the edges easily palpated. The liver is not tender. There may be a protuberant abdomen and umbilical hernias. Hepatosplenomegaly may lead to late hematological complications of hypersplenism. A presumptive diagnosis of lysosomal storage disease is strengthened by involvement of the nervous system and/or mesenchymal structures resulting in coarsening of facial appearance and skeletal abnormalities. Macroglossia makes a storage disorder virtually certain. In addition, slow gradual progression is evident.

The diagnostic work-up for lysosomal storage disorders in a patient with hepatosplenomegaly may start with the investigation of mucopolysaccharides and oligosaccharides in urine. Positive results are followed up with confirmatory enzymatic studies. If mucopolysaccharides and oligosaccharides are negative, lymphocytes are investigated for vacuoles (D5 – Chap. 43, Pathology). If negative, bone marrow is investigated for storage cells. If storage cells are found, corneal clouding is sought with a slit lamp. If both are present, *N*-acetylglucosaminylphosphotransferase is determined to make a diagnosis of mucolipidoses II or III. If corneal clouding is not present, potential enzymes to be determined are sphingomyelinase (Niemann–Pick type I, A and B), acid lipase (Wolman), and cholesterol uptake and storage (Niemann–Pick type II or C). The demonstration of an elevated activity of chitotriosidase reinforces the suspicion of a lysosomal storage disorder in ambiguous cases. It is clearly elevated in Gaucher disease, Niemann–Pick types A and B and often in Niemann–Pick type C, and other lysosomal storage disorders. However, about 5 % of the population have very low and uninterpretable levels of chitotriosidase, and false-positive values may result from chronic inflammatory disease. If there are neither pathological urinary screening results nor storage cells but peripheral neuropathy, the activity of ceramidase is determined seeking a diagnosis of Farber disease. Histological, histochemical, electron microscopical, and chemical examinations may be required of biopsied liver (D5 – Chap. 43, Pathology).

Disease Info

Transaldolase deficiency is a disorder of the pentose phosphate pathway presenting in infancy with hepatosplenomegaly, pancytopenia, and bleeding tendency which can progress to liver failure. Growth

Table 24.11 Differential diagnosis of hepatomegaly

Age of presentation	Diseases to be considered	Additional findings
<3 months	Lysosomal storage diseases, specifically	Splenomegaly
	Wolman disease	Adrenal calcifications
	CDG syndromes (PMM2-CDG, MPI-CDG, ALG8-CDG)	Lipodystrophy, inverted nipples
	Defects of gluconeogenesis	⇓ Glucose, ⇑ lactate
	Transaldolase deficiency	Splenomegaly, dysmorphic features, wrinkly skin, pancytopenia, and abnormal urinary polyols
	Mevalonic aciduria	Severe failure to thrive, splenomegaly, anemia
3 months–2 years	Glycogen storage diseases	± ⇓ Glucose, ⇑ lactate, ⇑ lipids, myopathy
	Defects of gluconeogenesis	⇓ Glucose, ⇑ lactate
	Lysosomal storage diseases	Splenomegaly
	α-1-Antitrypsin deficiency	α-1-Globulin, ⇓ α-1-antitrypsin
>2 years	Hemochromatosis	Diabetes mellitus, hypogonadism
	Cystic fibrosis	Pulmonary involvement, malnutrition, ⇑ sweat chloride
	Lysosomal storage diseases, specifically Niemann–Pick, type B	Splenomegaly
	Niemann–Pick, type B	Pulmonary infiltrates
	Cholesterol ester storage disease	Hypercholesterolemia
	Glycogenosis type VI/IX	± ⇓ Glucose, ± ⇑ lactate, ± ⇑ CK
	Fanconi–Bickel syndrome	Fanconi syndrome, ± ⇓ glucose

retardation, dysmorphic features, cutis laxa, and congenital heart disease are also common. While liver involvement is prominent, other phenotypic manifestations are variable and the psychomotor development usually normal. Urine analysis for polyols identifies elevated excretions of erythritol, ribitol, arabitol, sedoheptitol, perseitol, sedoheptulose, mannoheptulose, and sedoheptulose-7-phosphate consistent with transaldolase deficiency. Diagnosis is confirmed by detection of mutations in *TALDO1*.

Any acutely developing liver disease due to infectious, inflammatory, toxic, or metabolic origin may cause hepatomegaly as a result of edema and/or inflammation. In these disorders, other manifestations of the disease have usually led to consultation, and hepatomegaly is discovered during physical examination. On palpation, the liver may feel firm but not hard and the surface is smooth. The liver may be tender. Clinical or routine clinical chemical studies (Table 24.1) are likely to reveal abnormalities which direct further diagnostic evaluation. Inherited metabolic diseases considered in this category have been discussed under acute or subacute hepatocellular necrosis (Table 24.5).

If the enlarged liver feels hard, is not tender, and has sharp or even irregular edges, a detailed evaluation of causes of cirrhosis should be performed even in the presence of unremarkable liver function tests. A hard irregular or nodular surface is virtually pathognomonic of cirrhosis. Metabolic causes of silent liver disease associated with hepatomegaly, which may lead to quiescent cirrhosis, are Wilson disease and α-1-antitrypsin deficiency. Another important metabolic disorder is hemochromatosis, in which

hepatomegaly may be the only manifestation in adolescence and young adulthood. Although this disease usually does not progress to hepatic failure, as does Wilson disease, early recognition and initiation of treatment allow the prevention of irreversible sequelae.

In patients with persistent isolated hepatomegaly, additional findings are helpful in the differential diagnosis and should be specifically sought (Table 24.12). Defects of gluconeogenesis result in severe recurrent fasting hypoglycemia and lactic acidosis (Table 24.13). Of the three enzymatic *defects of gluconeogenesis*, hepatomegaly is a consistent finding in fructose-1,6-diphosphatase deficiency, while patients with deficiency of pyruvate carboxylase or phosphoenolpyruvate carboxykinase tend to present with lactic acidemia and multisystem disease without hepatomegaly.

Table 24.12 Differential diagnosis of metabolic causes of hepatomegaly

Additional findings	Suggestive disorder
Cardiomyopathy	Glycogenosis III, hemochromatosis, phosphoenolpyruvate carboxykinase deficiency, disorders of fatty acid oxidation and of oxidative phosphorylation
Muscular weakness	Glycogenoses III, IV, VI, and IX, fructose intolerance, disorders of fatty acid oxidation and of oxidative phosphorylation
Enlarged kidneys	Glycogenosis I, Fanconi–Bickel syndrome
Renal Fanconi syndrome	Glycogenoses I and III, Wilson disease, fructose intolerance, tyrosinemia type I, Fanconi–Bickel syndrome, mitochondrial disorders
Hemolytic anemia	Wilson disease, fructose intolerance
Fasting intolerance, hypoglycemia	Glycogenoses I and III, fructose-1,6-diphosphatase deficiency, disorders of fatty acid oxidation and of oxidative phosphorylation
Diabetes mellitus, hypogonadism	Hemochromatosis
Neurologic deterioration (Kayser–Fleischer ring)	Wilson disease
Early onset emphysema	α-1-Antitrypsin deficiency
Susceptibility to infections	Glycogenoses I non-A
Malnutrition	Cystic fibrosis
Lipodystrophy, inverted nipples	CDG syndrome type I
Isolated	Glycogenosis type IX

Confronted with an infant or young child with a moderately enlarged smooth, soft liver and otherwise completely unremarkable history and physical examination, investigations may be postponed until confirmation of persistence of hepatomegaly on repeat clinical examinations a few weeks later. If unexplained hepatomegaly persists, first-line investigations should be undertaken as in Table 24.1. Subsequent second-line investigations should measure red blood cell glycogen, glycogen phosphorylase, phosphorylase kinase, and debranching enzyme as well as acid lipase, sphingomyelinase, and β-glucosidase. In hepatic glycogen storage disorders (types I, III, VI, and IX and Fanconi–Bickel syndrome), biotinidase activity is usually significantly elevated. Suspected glycogen storage disease can be confirmed with high accuracy by mutation analysis using next-generation screening. As a result, liver biopsy can be reserved for when no specific disorder can be confirmed or where there is evidence of structural liver disease. If liver biopsy is undertaken, histological and electron microscopic

Table 24.13 Hepatomegaly plus hypoglycemia

Disorder	Clinical features
Glycogen storage disease I	Hepatocellular dysfunction, large kidneys, ↑↑↑ triglycerides, ↑ urate, ↑ lactate
Glycogen storage disease III, IX	Short stature, skeletal myopathy
Fanconi–Bickel disease	Tubulopathy, glucose/galactose intolerance
Disorders of gluconeogenesis	↑ Lactate
Glycosylation disorders (CDG, e.g., PMM2-CDG)	Hepatomegaly, hepatocellular dysfunction, protein losing enteropathy, multisystem disease

analysis should be performed with additional tissue frozen at −80 °C for biochemical analyses. Patients with hepatomegalic glycogenoses may present with a moderately enlarged smooth, soft liver and otherwise completely unremarkable history and physical examination in infancy and early childhood.

Disease Info: Juvenile Hemochromatosis

Juvenile hemochromatosis is a rare multisystemic disease which usually presents in the second decade with nonspecific symptoms including abdominal pain, fatigue, and delayed puberty. Hepatomegaly is the most frequent early manifestation. Additional manifestations include diabetes mellitus, hypogonadism, skin pigmentation, cardiac arrhythmias, and congestive heart failure.

Laboratory investigations of symptomatic patients reveal increased serum iron and ferritin and markedly elevated saturation of transferrin of 77–100 %.

The disease is caused by mutations in *HJV* (90 %) and *HAMP* (10 %). Increasingly hepatic siderosis can be quantified and monitored by quantitative MRI. Liver biopsy is still necessary when chronic liver disease is suspected.

Management consists of regular phlebotomy which can be titrated by hemoglobin, ferritin, and liver iron content. Hormone replacement and symptomatic treatment of heart failure may be required.

Children with the much more common hereditary hemochromatosis due to mutations in *HFE* may be detected by family screening. There is rarely any clinical or significant laboratory abnormality during childhood although lifelong monitoring is required.

24.5.1 The Glycogenoses

Isolated hepatomegaly is found in several glycogen storage diseases. The combined frequency varies considerably according to the ethnic background and approximates 1:50,000–1:100,000 in Europe. The original description was by von Gierke in 1929, and hepatic glycogenoses were the first inborn errors of metabolism defined enzymatically by Cori and Cori in 1952. The current classification of the glycogenoses has been extended to fifteen entities. Glycogenosis type 0, also referred to as glycogenosis, is the deficiency of glycogen synthetase. As the glycogen content in the liver is actually reduced, it is not a storage disorder but a disorder of gluconeogenesis (see also Chap. 15). The symptoms of glycogenoses types II, V, VII, X, XI, XII, XIII, and XV and sometimes IV and XIV are primarily those of muscle disease.

The results of advances in enzymatic and molecular diagnosis mean liver biopsy is rarely necessary.

Disease Info: Glycogen Storage Disease Type I

Glycogen storage disease type I results in a deficiency of any of the proteins of the microsomal membrane-bound glucose-6-phosphatase complex. In classic Ia glycogen storage disease (von Gierke disease), glucose-6-phosphatase is deficient. Type I non-A is due to defective microsomal transport of glucose-6-phosphate. A variant type Ia results from a deficiency of the regulatory protein; this has so far only been reported in a single patient.

The hallmark of von Gierke disease is severe fasting hypoglycemia with concomitant lactic acidosis, elevation of free fatty acids, hyperlipidemia, elevated transaminases, hyperuricemia, and metabolic acidosis. Lactic acidosis may be further aggravated by ingestion of fructose and galactose, as the converted glucose is again trapped by the metabolic block in the liver. Affected patients may be symptomatic in the neonatal period, when there may be hypoglycemic convulsions and ketonuria but sometimes

no hepatomegaly yet. The condition often remains undiagnosed until hypoglycemic symptoms reappear in the course of intercurrent illnesses or, at about 3–6 months, when the infant begins to sleep longer at night. Infants are then chubby in appearance, but linear growth usually lags. The liver progresses slowly in size. An immense liver down to the iliac crest is generally found by the end of the first year when the serum triglycerides reach very high levels. Because of the accumulation of lipid, the liver is usually soft and the edges may be difficult to palpate. With increasing activity of the child at around the first birthday, the frequency of hypoglycemic symptoms tends to increase. As in any of the diseases that cause severe hypoglycemia, convulsions and permanent brain injury or even death may occur. However, many children are quite adapted to low glucose levels, and in the untreated state, the brain may be fuelled by ketone bodies and lactate. Unusual patients may remain clinically asymptomatic of hypoglycemia until up to 2 years of age. Increased bleeding tendency may result in severe epistaxis and multiple hematomas, and abnormal hemostasis and persistent oozing may complicate traumatic injuries or surgery.

Patients with glycogen storage disease type I non-A develop progressive neutropenia and impaired neutrophil function during the first year of life. Recurrent bacterial infections result including deep skin infections and abscesses, ulcerations of oral and intestinal mucosa, and diarrhea. In the second or third decade, inflammatory bowel disease may develop.

In the clinical setting, diagnosis is usually confirmed by detection of mutations with liver biopsy reserved for where uncertainty remains.

Several late complications have been observed in patients with type I glycogen storage diseases despite treatment. Most patients develop osteoporosis and some have spontaneous fractures. Hyperuricemia may result in symptomatic gout after adolescence. Xanthomas may develop. Pancreatitis is another consequence of hypertriglyceridemia. Multiple hepatic adenomas develop, sometimes to sizable tumors. They are usually benign; however, malignant transformation has occurred. Renal complications include Fanconi syndrome, hypercalciuria, nephrocalcinosis, and calculi. Microalbuminuria may be followed over time by proteinuria, focal segmental glomerulosclerosis, interstitial fibrosis, and renal failure. Pulmonary hypertension is a rare, although very serious, complication in adult patients.

Disease Info: Glycogen Storage Disease Type III

Glycogen storage disease type III results in a deficiency of the debranching enzyme, amylo-1,6-glucosidase. The physical and metabolic manifestations of liver disease are usually less severe than in type I glycogenosis, and fasting intolerance gradually diminishes over the years. The predominant long-term morbidity of this disease is myopathy. In infancy it may be impossible to distinguish types I and III on clinical grounds. Hypoglycemia and convulsions with fasting, cushingoid appearance, short stature, and nosebleeds characterize either disease. However, in contrast to type I glycogenosis, concentrations of uric acid and lactate are usually normal. Transaminases are elevated. Creatine phosphokinase level is elevated as well. This may be the earliest evidence of myopathy.

In glycogen storage disease type III, glycogen accumulates in muscle as well as in the liver. In approximately 85 % of patients, both the liver and muscle are affected, and this is referred to as glycogenosis type IIIa. When the deficiency is only found in the liver, it is referred to as IIIb.

With time in many patients, the major problem is a slowly progressive distal myopathy. It is characterized by hypotonia, weakness, and muscle atrophy. It is often notable in the interossei and over the thumb. Some patients have

muscle fasciculations, suggestive of motor neuron disease, and storage has been documented in peripheral nerves. Weakness tends to be slowly progressive. Ultimately the patient may be wheelchair bound. Rarely, the myocardium may be involved as well with left ventricular hypertrophy or even clinical cardiomyopathy.

Several functional tests have been designed to differentiate glycogen storage disease type I from type III, although in the era of rapid genetic diagnosis these are rarely necessary. Following a glucose load, the initially elevated blood lactate will decrease in glycogenosis type I. In type III, lactate levels are usually normal but rise postprandially. In type I gluconeogenesis is blocked and alanine concentration is increased. In type III, gluconeogenesis is overactive, resulting in significantly lowered concentrations of alanine. One of the most useful tests is a glucagon challenge 2–3 h after a meal, which will yield a good response in GSD type III (but no increase in glucose in GSD type I). After a 14-h fast, glucagon will not usually provoke a rise in blood glucose in GSD type III, as all the terminal glycogen branches have been catabolized (see Chap. 41) – Function Tests, Monitored Prolonged Fast, and Glucagon Stimulation). Finally, the diagnosis of glycogenosis type III is proven by demonstrating the deficiency of the debranching enzyme amylo-1,6-glucosidase in leukocytes, fibroblasts, the liver, or muscle. Prenatal diagnosis is possible through enzyme analysis in amniocytes or chorionic villi.

Defects of the phosphorylase system define three separate groups of glycogen storage diseases. Type VI describes primary defects of hepatic phosphorylase, type VIII impaired control of phosphorylase activation, and type IX deficient activity of the phosphorylase kinase complex. The phosphorylase kinase complex consists of four different tissue-specific subunits. By far the most common of these defects is an X-linked recessive defect of the α-subunit of phosphorylase kinase, which affects ≈75 % of all patients with defects of the phosphorylase system (type IXa).

Disease Info: Glycogen Storage Diseases, Types VI, VIII, and IX

The clinical symptoms of defects of the phosphorylase system, types VI, VIII, and IX glycogenoses, are similar to, but milder than in, type III or I. Hepatomegaly is a prominent finding and may be the only indication of a glycogen storage disease. Muscle hypotonia, tendency to fasting hypoglycemia, lactic acidosis, elevation of transaminases, and hypercholesterolemia are mild and may be normalize after childhood.

Following a glucose or a galactose load in glycogenoses types Vl, VIII, and IX, blood lactate will show pathological increase from normal or only moderately elevated levels. Overactive gluconeogenesis results in lowered concentrations of plasma alanine. The response to the administration of glucagon even after a 12–14-h fast is usually normal. Diagnosis of glycogenoses types Vl, VIII, and IX can be proven by demonstration of the enzyme deficiency in the affected tissue, liver, or muscle. Primary molecular diagnosis has greatly facilitated the diagnostic process.

The rare hepatic glycogenosis with renal Fanconi syndrome (Fanconi–Bickel syndrome) was shown to be due to a primary defect of the liver-type facilitated glucose transport. Hepatomegaly with glycogen storage, intolerance to galactose, failure to thrive, and consequences of full-blown Fanconi syndrome are usually obvious in early childhood.

Remember

Type I glycogenosis is the most serious of all hepatic glycogenoses because it leads to a complete blockage of glucose release from the liver, impairing both glucose production from glycogen and gluconeogenesis.

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