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Cholestasis in newborn and infancy period

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Summary

During the newborn and infancy period, it is an important to demonstrate the condition which causes cholestatic liver diseases. If direct bilirubin level is more than 20% of total biluribin, it is defined as cholestasis. Especially early diagnosis of diseases including biliary atresia, tyrosinaemia, galactosemia is crucial for prevention of permanent damage in the future and for benefit from early treatment. Therefore, total, direct and indirect bilirubin levels should be measured in all newborns with jaundice lasting longer than two weeks. If 20% of total bilirubin is direct bilirubin, liver-related disorders should be questioned. In this review, we aimed to show which clinical and laboratory features should be considered to demonstrate the cause of cholestatic diseases. *(Turk Arch Ped 2012; 47: 1-7)*

Key words: Direct hyperbilirubinemia, cholestasis, biliary atresia

Introduction

Cholestasis in the newborn and infancy period is characterized with increase in harmful substances (for example, bile acids) which can not be excreted as a result of decrease in bile flow in the bile ducts and increase in direct bilirubin. Cholestasis is present, when direct bilirubin is is more than 20% of total biluribin. The incidence of cholestasis in the newborn is 1:2500. The fact that hepatic secretory function is not fully developed renders the newborn predisposed to metabolic and infectious factors which may lead to dysfunction of bile excretion (1).

Early recognition of cholestasis in the newborn and demonstrating the causative disorder is very significant in terms of treatment of metabolic or infectious conditions and referring patients with biliary atresia (BA) to surgical treatment. Significant difference was found between referring children with a diagnosis of BA in the first 60 days and after the first 90 days in terms of providing biliary flow in studies performed (2). Therefore, bilirubin should be tested as total, direct and indirect bilirubin in all newborns with jaundice after two weeks. If 20% of total bilirubin is direct bilirubin, disorders related to the liver should be examined.

A physiological tendency to cholestasis is present in newborns and infants due to the fololowing reasons:

1) Increased serum bile acid levels,

2) Differences in canalucilar and basolateral carrying system of bile acids,

3) Decrease in intake of bile acids into the liver,

4) No lobular difference in bile acid cycle,

5) Decrease in conjugation, sulphation and glucuronidation of bile acids,

6) Qualitative and quantitative differences in bile acid synthesis,

7) Decrease in canalicular excretion of bile acids,

8) Decrease in intraluminal bile acid intensity,

9) Decrease in ileal active transport of bile acids.

Cholestasis in the newborn and infant may be related to intrahepatic and extrahepatic causes. Extrahepatic causes leading to cholestasis include bile atresia, choledochal cyst, gallbladder stone, spontaneous perforation of the bile duct, choledocopancreatic junction anomalies, bile plug, sclerozing cholangitis of the newborn and congenital hepatic fibrosis/Caroli disease (3). The most important one among these extrahepatic causes is biliary atresia. Biliary atresia is observed with an incidence of 1:8000-12000. It develops as a result of an obstructing cholangiopathy which demages the biliary tract epithelium related to an inflammatory, toxic, infectious and immunological process. While it was considered to be a congenital abnormality previously, today it is known that it can also occur related to an acquired disorder (4). If the disease is congenital, it is usually associated with other abnormalities; in 25% of the cases it can be associated with polysplenia and cardiac, vascular and intestinal pathologies (5).

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In biliary atresia, jaundice and hepatomegaly are present clinically. Jaundice can be present from the first days of life or it may develop in the 2-3rd week of life. It is usually observed in term babies. The liver gradually gets a rigid consistence, the stool is white and the urine is dark-colored staining the napkin. Other than these findings the infants appear healthy (6,7).

In laboratory findings, conjugated bilirubin, alkaline phosphatase (AP), gamma-glutamyl transferase (GGT) and transaminases are high. The high level of cholestase enzymes is not distinctive among other cholestases (8). Ultrasonographical examination (USG) is needed to exclude choledochal cyst (9). Since radioactive substance will not be able to pass the intestines also in intrahepatic cholestases on biliary scintigraphy, finding of "no passage" is not significant, but positive passage means that biliary atresia is not present (10). In all patients in whom white-colored stool continues, liver biopsy should be performed. In all patients in whom liver biopsy reveals new bile duct formation and bile thrombi, the definite diagnosis should be made by performing "peroperatory" or "percutaneous" cholangiography (11). Biliary atresia requires surgical intervention during the first 2 months of life. Time is significant in terms of progression to cirrhosis. If biliary atresia is diagnosed, "Kasai" operation (hepato-porto-enterostomy) should be performed.

Complications including cholangitis, bacterial peritonitis and cirrhosis may be observed after Kasai operation (2).

Choledochal cysts constitute 2% of the cholestases in the newborns. Clinically, intermittent pain during this period is not possible. 18% of choledochal cysts cause symptoms below the age of one. The diagnosis and differentiation with biliary atresia is made by USG (9). Treatment include extraction and Y-shaped choledochojejunestomy.

Among metabolic diseases, galactosemia related to carbohydrate metabolism is a disease which should be diagnosed rapidly. It is a disorder of galactose metabolism, is inherited autosomal recessively and has three types: it may develop as a result of deficiency of galactokinase, epimerase or galactose 1 phosphate uridyle transferase enzyme (12). Its incidence ranges between 1:10 000 and 1:60 000 (13). In deficiency of galactose 1 phosphate uridyle transferase, acute and toxic events develop in the liver. In homozygote newborns, symptoms occur in two weeks after ingesting breastmilk. The findings of the disease include jaundice, vomiting, hypoglycemia, convulsion, cataract, hepatomegaly, cirrhosis, bleeding diathesis, renal Fanconi, mental retardation and hypergonodotropic hypogonadism. Gram negative sepsis may be observed in these patients. E. Coli infection is common in newborns with galactosemia. Lack of hypoglycemia in the infant fed with breastmilk, positive reductant substance in urine other than glucose and finding of low level of enzyme in the blood are used for diagnosis. Treatment consists of galactose-free diet for a life time (12).

In hereditary tirosinemia type 1 which is one of the amino acid metabolism disorders, there is mutation in the gene coding fumaryl acetoacetate hydrolase enzyme which is the final enzyme of tyrosine catabolism (14). Hepatic involvement starting from the birth may be present and hepatocellular carcinoma may develop in the early period (15). The levels of succinylacetone and delta aminolevulinic acid are increased in urine and serum. Phenylalanine, tirosine and methionine levels are increased in serum. Therefore, the levels of tirosine metabolites are also increased in urine. Serum alpha fetoprotein level is increased (16). The disease has three types:

1) Acute form: This form is observed in 6 months and leads to acute hepatic failure; the mortality rate is 37% below the age of 2 years.

2) Subacute form: It occurs with hepatomegaly, growth retardation and rachitis between 6 months and 1 year of age.

3) Chronic form: This form occurs with hepatomegaly and rachitis above the age of one.

Phenilalanine and tyrosine-free diet is given for treatment, but this is not enough to improve hepatic dysfunction completely

Table 1. Intrahepatic cholestatic diseases

Neonatal hepatitis
- Idiopathic
- Viral
  - Cytomegalovirus
  - Herpes virus
  - Rubella
  - Reovirus type 3
  - Adenovirus
  - Parvovirus B 19
  - Hepatit B virus
  - HIV
- Bacterial sepsis
  - Lysteriosis
  - Tuberculosis
  - Toxoplasmosis
  - Malaria

Genetic cholestatic syndromes
- Alagille syndrome
- Progressive familial intrahepatic cholestases
- Turner syndrome
- Down syndrome
- Aagenaes syndrome

Unclassified
- Ischemia, shock
- Neonatal lupus
- Congenital hepaticv fibrosis
- Caroli disease
- Bile mud
- Histiocytosis X
- Indian childhood cirrhosis

Metabolic
- Carbohydrate metabolism disorder
  - Galactosemia
  - Fructosemia
  - Glycogen storage disease
- Aminoacid metabolism disorder
  - Tyrosinemia
  - Hypermethioninemia
  - Mevolanata kinase deficiency
- Lipid metabolism diseases
  - Niemann-Pick
  - Gaucher disease
  - Wolman disease
  - Cholesterol ester depot disease
- Alpha 1 antityripsine deficiency
- Cystic fibrosis
- Urea cycle disorders
- Mitochondrial diseases
- Peroxysomal diseases
  - Zellweger sydrome
  - Infantile Refsum disease
- Endocrinopahties
  - Hypopituitarism
  - Hipothyroidism
- Iron depot disease of the newborn
- Bile acis defect
  - Citrin deficiency

Toxic
- Endotoxine
- Total parenteral nutrition
- Drug
- Aluminium

(17). In tirosinemia, NTBC (2 nitro-4-trifluoromethylbenzoyl 1-3 cyclohexanedione) treatment is being administered at a dose of 2 mg/kg/day for the last 10 years and fairly good responses have been obtained. If hepatic failure develops despite treatment or if hepatocellular carcinoma develops, liver transplantation should be performed (18).

Alpha 1 antitrypsin deficiency is inherited autosomal recessively and related to demage to the gene named "serpin 1" coded on 14q31-32 gene locus. Alpha 1 antitrypsin is a proteolytic enzyme (neutrophyle esterase) inhibitor and is produced in hepatocytes. If proteolytic activity of these enzymes is not inhibited, hepatic and lung demage occurs. This protease inhibitor (PI) system has 75 different alleles. Normal phenotype is MM. PI ZZ is associated with hepatic and lung diseases. The types associated with hepatic diseases include MS, MZ and SZ (19). The pathogenesis of the disease is not known. Abnormal antitripsine molecules are accumulated in the endoplasmic reticulum as polymers and lead to hemorrhagic disease and cholestatic demage in the liver by immunological and environmental factors (20). In 10-15% of individuals with a phenotype of PI ZZ, alpha-1-antitrypsin levels may be normal and cholastatic hepatic disease may develop in 12% (21).

The diagnosis is made by determining alpha-1-antitripsine level and by phenotyping. Granules may not be observed in the first months of life. Liver biopsy reveals PAS positive eosynophylic cytoplasmic granules (22).

Alpha-1-antiripsine deficiency has no specific tratment. In cases of cirrhosis, liver transplantation should be performed. Gene treatment seems to be promising (23).

Cystic fibrosis (CF) is an autosomal recessive disease inherited on the long arm of chromosome 7 at position 7q31. This gene codes a polypeptide named cystic fibrosis transmembrane regulator with 1480 amino acids. This polupeptide is involved in regulation of chlor channels and possibly other ion channels. Abnormal transmembrane regulator protein function is divided in 6 significant classes and shows variance in terms of the course of the disease with each mutation (24). More than 1600 mutations are known. Among these the most commonly observed is ΔF508 mutation (25).

Cystic fibrosis transmembrane regulator protein has a variable expression and shows different effects on the epithelium of differen organs. Observation of different clinical findings despite the same genotype shows that environmental and hereditary factors can change the phenotype of the disease (26).

The disease which has an incidence of 1:2000-4000 is treated according to the organ involved (27). Cystic fibrosis can present with any finding related to the gastrointestinal system; meconium ileus (partial or complete) can occur in the first 48 hours in 15-20% of the newborns with a diagnosis of cystic fibrosis. It occurs due to increase in the consistency of intestinal secretions after birth (26). Increase in the consistency of pancreatic secretions leads to obstruction in the ducts. Lipid absorption is disrupted as a result of exocrine functions and fatty stool is observed. As a consequence, deficiency of lipid soluble vitamins (A, D, E, K) develops and coagulation disorders, skin eruptions and hemolytic anemia may be observed. Pancreatic enzymes are also responsible of digestion of carbohydrates and proteins, so digestion of carbohydrates and proteins is also disrupted. Increase in the consistency of pancreatic secretions causes obstruction of the ducts and development of pancreatitis (28).

The rate of hepatic involvement in patients with a diagnosis of cystic fibrosis is not known; it has been reported to be 20-50% in different studies. In contrast to pancreatic involvement, there is no phenotype-genotype relation in hepatic diseases (29). Hepatobiliary complications of cystic fibrosis are the second reason of death after the lung and shows high variance. Hepatic diseases related to cystic fibrosis start in the biliary tract. Cystic fibrosis transmembrane regulator protein is not present in the hepatocyte; it is present in the apical surfaces of the epithelial cells in the biliary ducti and gallbladder. Plugs are formed with the increase in the biliary solute load and cause demage to the biliary tract by combining with cytotoxins and bacteriae. The condition progresses to periportal fibrosis, bridge fibrosis and focal biliary cirrhosis in order. The most common hepatic disorder is hepatic steatorrhea. It is observed in 1/3 of the patients. The reason and course of hepatic steatorrhea is not known very well (30). Normal liver enzymes and even normal biopsy findings do not exclude hepatic involvement. In patients with a diagnosis of cystic fibrosis, yearly biochemical examination of the liver is recommended. In treatment, ursodeoxycolic acid is choleretic and protects the cell. Although long-term results are not known exactly, improvement in USG findings have been observed with ursodeoxycolic acid in a 10-year follow-up period. In patients with portal hypertension, beta blockers should not be used because of bronchospasm (29). In patients with biliary involvement, biliary cirrhosis and portal hypertension, treatment is liver transplantation. For liver transplantation the most appropriate period in terms of lung function, nutritional status and cardiac function should be selected. Improvement in lung findings are observed after liver transplantation, but the reason is not known (31).

Progressive familial intrahepatic cholestasis syndromes (PFIC) are inherited autosomal recessively and is a group of diseases characterized by disruption of the carrier system which provides carriage of the bile content into the canalicules. The carrier system functions in a ATP-dependent way. Toxic substances which can not be carried are deposited in the liver and lead to hepatic demage (32). Cholestasis usually develops in the newborn period or during the first year of life. Development of cirrhosis may occur during a long period ranging from infancy to adolescence (33). Clinically, jaundice, growth retardation, recurring epistaxis and symptoms related to deficiency of lipid-soluble vitamins may be observed. Pancreatic insufficiency and related lipid absorption defect and diarrhea may develop (34). As hepatic failure develops, related complications and symptoms are observed in time (32). The disease is divivded

into three forms according to the carrier gene defect. In **progressive familial intrahepatic cholestasis-1 (PFIC-1)** which is also known as Byler disease, since it was firstly described in Byler family, mutation is present on ATP8B1 gene on the 18th chromosome. Since the same gene can be present in different tissues, intestinal absorption defect, pancreatic failure and respiratory problems may accompany (35). Despite the presence of cholestasis, serum GGT and cholesterol levels are low or normal (36). Benign recurring intrahepatic cholestasis is the point in question in conditions where the same gene region is affected and heterogeneity is present. Cholestasis attacks can occur at any age and last for weeks or months (37). Although it is thought that permanent hepatic disease does not develop, it is known that some patients progress to familial intrahepatic cholestasis (38). In **progressive familial intrahepatic cholestasis type 2 (PFIC-2),** transport defect developing due to ABCB11 mutation on BSEP gene is present. There is defect in carriage of bile acids into the bile by passing hepatocyte canalicular membrane. Gamma GT levels are normal or low (39). In **progressive familial intrahepatic cholestasis type 3 (PFIC-3)** which develops in relation to ABCB4 mutation on MDR-e gene, canalicular phospholipid transport is disrupted. Decrease in phospholipids cause the bile to be lithogenic and show detergent effect and thus demage to the bile epithelium occurs. As a result, increase in bile canaliculi, portal fibrosis and liver demage at an early period develop. It usually occurs at older ages. Hepatic failure, portal hypertension and related complications are observed more commonly. It may lead to intrahepatic cholestasis of pregnancy (40). Serum GGT and cholesterol levels are low. Bile acid synthesis defects lead to a clinical picture similar to progressive familial intrahepatic cholestasis and is also called **progressive familial intrahepatic cholestasis-4 (PFIC-4).** Serum GGT levels are low, there is no pruritus and serum primary bile acid levels are not increased as observed in progressive familial intrahepatic cholestasis (41).

Although liver biopsy reveals pathologies including bile plugs, pseudoacini, balloon degeneration, giant cell formation, fibrosis in the portal area and bridging, these findings are not specific for this disease. The diagnosis is made with the presence of classical clinical and laboratory findings and genetic analysis after excluding other conditions leading to intrahepatic cholestasis (42). Ursodeoxycholic acid used in treatment provides excretion of endogenous bile acids from the hepatocytes and inhibits their intestinal reabsorption and decreases their toxic effects on the liver. If partial external biliary diversion surgery can be performed before development of cirrhosis in PFIC-1 and PFIC-2, improvement in both clinical findings including jaundice and in hepatic histopathological findings can be obtained (39). In patients in whom hepatic failure develops despite ursodeoxycholic acid treatment and partial external biliary diversion treatment, liver transplantation should be performed (43).

The condition where bile duct can not be observed in 6 of 10 portal areas on liver biopsy is called paucity of bile ducts. This condition may be syndromic or not syndromic.

Alagille syndrome is an autosomal dominant disease. Its incidence is 1:70000. It is related to microdeletion in the 20th chromosome. Jagged 1 gene is responsible. This gene codes the protein which binds to “transmembraner NOTCH” receptor in cellular differentiation in the early phase of development (44). Jagged 1 gene mutation can be found in more than 90% of the patients. In patients with a diagnosis of Alagille syndrome in whom jagged 1 gene mutation was not found, NOTCH2 gene mutation was found (45).

The patients have a typical shape of face. The forehead is prominent, the eyes are sunken and the chin is pointed.

Bile tract aplasia and extrahepatic findings other than typical facial shape are present in the patients. Extrahepatic findings include butterfly vertebrae, posterior embriotoxone, cardiac abnormalities (especially peripheral pulmonary artery stenosis alone) and skeletal defects.

Xanthomas may develop in these patients due to high cholesterol level. Increase in bile acids are manifested with jaundice and malnutrition. Ophtalmological and renal complications may be present. Progressive hepatic fibrosis develops in these patients (46).

In non-syndromic paucity of bile ducts, alpha-1 antitrypsin deficiency, hypopituitarism, cystic fibrosis, increased trihydroxycoprostanic acid, Down syndrome, infections (CMV, rubella, syphilis, HBV), immonulogical conditions (graft versus host disease, chronic rejection) and primary sclerosing cholangitis should be considered.

In preterm infants, fluids containing lipids added to parenteral nutrition may lead to hepatocyte demage and as a result cholestatic hepatic disease may develop (47).

In newborns, primarily macrolide group antibiotics including erythromycine which is used in sepsis and other infections or for increasing intestinal motility and some other antibiotics may lead to hepatotoxicity depending on the dose and the time of usage and cause transient intrahepatic cholestasis (48).

Citrin is present in the structure of mitochondrial inner membrane and is involved in malate-aspartate NADH transport system which is responsible of calcium-dependent aspartate-glutamate transport. This is specifically present in the hepatocytes and is involved in glycolysis, gluconeogenesis and urea cycle (49). As a result of citrin defect which develops in relation to the mutation in SLC25A13 gene two clinical conditions occur. The first one is type 2 cytrulinemia which occur in adults and the second one is the type which leads to hepatocyte demage and is manifested with cholestasis in the newborn. Clinical findings in newborns include growth retardation and prolonged jaundice. Biochemically, hypoproteinemia, hemolytic anemia, ketotic hypoglycemia, increased alphafetoprotein levels, and increased serum cytrulline, arginine, treaonine, methionine and tirosine levels are found. Liver biopsy may reveal diffuse hepatosteatosis and fibrosis. Carbohydrate and lipid-rich diet is used in treatment (50).

Niemann-Pick type C is a lysosomal storage disease characterized by defect in intracellular transport of

Table 2. Diagnosis in cholestatic hepatic diseases in newborns and infants

Congenital and postnatal infections	
Toxoplasma	IgM antibodies
Rubella	IgM antibodies
Cytomegalovirus	Urine for viral culture, inclusion body Ig M antibodies, CMV DNA, cranial graphy, cranial USG
Syphilis	VDRL, FTA-ABS, long bone graphy
Herpes Simplex	Viral culture
Hepatitis B	HBs Ag, anti HBC IgM, HBV DNA
Hepatitis C	Anti HCV, HCV RNA
"Human Immundeficiency" virus	Anti HIV, immunglobulins, CD4
Parvovirus B19	IgM antibodies
Enteric viral sepsis (Echo, Coxackie A and B, adenovirus) A ve B, adenovirüs)	Serology and viral culture
Bacterial sepsis	Toxic granulation on peripheral smear, CRP, culture
E.coli urinary tract infection	Urine culture
Structural	
Bile atresia	USG, scintigraphy, liver biopsy, cholangiography
Choledochal cyst	USG
Bile stone, spontaneous perforation	USG
Metabolic	
Alpha 1 antitrypsin deficiency	Protein electrophoresis, alpha 1 antitripsine level, Phenotyping
Cystic fibrosis	Sweat test, gene analysis
Galactosemia	Blood glucose, galactose 1 phosphate uridyltransferase
Tyrosinemia	Chromatography of amino acids, serum tyrosine, methionine, alpha fetoprotein, succinylacetone in urine and blood
Fructosemia	Blood glucose, fructose 1 phosphate aldolase
Glycogen storage type IV	Liver biopsy, enzyme activity
Niemann-Pick type A	Bone marrow depot cells, sphyngomyelinase activity
Niemann-Pick type C	Bone marrow depot cells, sphyngomyelinase activity
Wollman	Imaging of adrenal glands on abdominal graphy
Zellweger	Long-chain fatty acids, liver biopsy peroxysomes
Ductular hypoplasias	No bile duct in 6 of 10 portal areas in liver biopsy
Syndromic ductular hypolasia	
Alagille syndrome	Echocardiography, posterior embriotoxone in the eye, butterfly vertebrae, specific facial appearance
Non-syndromic ductular hypoplasia	
Familial progressive cholestases	
PFIC 1 (Byler)	Low GGT, increased serum bile acids
PFIC 2	Low GGT, increased serum bile acids
PFIC 3	Increased GGT and serum bile acids
Endocrine	
Hypopituitarism	Decreased cholesterol, TSH and T4 level
Hypothyroidism	Increased TSH, decreased T4, T3 level
Genetic	
Trisomy 18, 21	Karyotyping
Immune	
Neonatal Lupus	Anti Ro antibodies (in the mother and in the infant)
Neonatal hepatitis, autoimmune hemolytic anmeia	Coombs test, giant cell in liver biopsy
Idiopathic neonatal hepatitis	Giant cell in liver biopsy

cholesterol. It generally occurs as a result of mutation in NPC-1 gene. In some patients, NPC-2 gene mutation may be present. Although it has a very wide clinical spectrum, neurological retardation and transient intrahepatic cholestasis are present in most patients. Splenomegaly and hepatomegaly develop in later phases (51).

The diagnosis in cholestatic diseases in the newborn and infancy has a very wide spectrum (Table 2). Except for infections, liver transplantation is needed in most conditions. The two conditions which should be diagnosed in the early periods of life include BA and galactosemia. In both conditions, early diagnosis is very significant in terms of prognosis. Symptomatic treatment should be performed for complications including pruritus, deficiency of vitamins A, D, E, K, cirrhosis and portal hypertension which may develop during treatment and follow-up of these conditions (Table 3 and 4).

Table 3. Physiopathological results of prolonged cholestasis and symptomatic treatment

Defect	Result	Treatment
Decrease in bile excretion		
Increased bilirubin	Jaundice	
Increased bile salts	Pruritus	Phenobarbital (5-10 mg/kg/day) Cholestiramine (1-4 g/day) Ursodeoxycholic acid (15-20 mg/kg/day) Rifampicine (5-10 mg/kg/day) Liver transplantation
Increased cholesterol	Xanthelasma	
Malabsorption of long chain triglycerides	Growth failure, diarrhea	Diet rich in moderate-chain fatty acids, adding essential fatty acids
Vitamin D	Osteoporosis, rahitis osteomalacia	Vitamin D 5 mg/ 3 months
Vitamin E	Hemolytic anemia Neuromuscular degeneration	Vitamin E 10 mg/ kg (max 200 mg /2 months)
Vitamin A	Night blindness	Vitamin A 500 000 IU/month
Vitamin K	Bleeding	Vitamin K 10 mg/15 days
Hepatocyte dysfunction	Cirrhosis Portal hypertension Hepatic failure Tendency to infections	

Table 4. Treatment in cholestatic disease in infancy

Biliary atresia	Hepatoportoenterostomy Liver transplantation
Toxoplasma	Pirimetamine, spiramycine
CMV	Gancyclovir, CMV hyperimmune globuline
Herpes virus	Acylovir, Vidarabine
Syphylisis	Penicillin
Galactosemia	Diet
Fructosemia	Diet
Tirosinemia	NTBC Liver transplantation
Glycogen storage disease type IV	Liver transplantation
Alpha 1 antitrypsin deficiency	Follow-up Liver transplantation
Cystic fibrosis	Follow-up Liver transplantation
Byler disease	Ursodeoxycholic acid, biliary diversion ? Liver transplantation
Alagille syndrome	Symptomatic, liver transplantation
Non-syndromic ductular hypoplasia	Liver transplantation
Histiocytosis X	Chemotherapy Liver transplantation
Neonatal hepatitis, autoimmune hemolytic anemia	Prednisolone + azatioprine
Related to total parenteral nutirition	Enteral nutrition, ursodeoxycholic acid, metronidazole
Primary sclerosing cholangitis	Ursodeoxycholic acid, immunoupressant, Liver transplantation
Niemann-Pick disease	Liver transplantation
Gaucher disease	Administration of enzyme Liver transplantation
Neonatal hemochromatosis	Liver transplantation

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