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Acute liver failure in newborns

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ABSTRACT

Acute liver failure is a condition that is defined as a sudden, complete, or nearly complete loss of liver functions without any previous liver disease, usually accompanied by encephalopathy, which can be reversible, but with a mortality rate of 55-70%. Acute liver failure newborns is an acute liver failure in the first 28 days of life. The Pediatric Acute Liver Failure Working Group identified the presence of coagulopathy as the main finding for the identification of acute liver failure in childhood following vitamin K administration. Although the incidence of acute liver failure is reported to be 17/100 000 in all ages, its incidence is not known exactly in newborn and childhood. The most common cause of acute liver failure in the newborn period is the gestational alloimmune liver disease that was previously known as neonatal hemochromatosis. This is followed by viral infections, metabolic diseases, hemophagocytic lymphohistiocytosis, and other rare causes. In the neonatal period, acute liver failure is a rare condition with a high mortality rate. For this reason, the vital signs of the patients should be closely monitored and supportive treatments should be planned according to the follow-up and the etiology of the disease should be clarified urgently. In this process, acyclovir treatment until herpes simplex virus infection is excluded and lactose-free feeding until galactosemia is excluded are recommended as life-saving treatments. In the literature, since there is a limited number of studies related to neonatal acute liver failure, prospective studies investigating the factors affecting treatment and prognosis are needed.

Keywords: Galactosemia, herpes simplex virus, liver failure, newborn

Introduction

Acute liver failure (ALF) is a condition that is defined as a sudden, complete, or almost complete loss of liver function without any previous liver disease, usually accompanied by encephalopathy, can be reversible, but with a mortality rate of 55-70% (1-4). It is defined as the presence of acute damage without significant fibrosis of the liver. Acute liver failure (NALF) in the newborns is ALF seen in the first 28 days of life. ALF in adults is defined as the detection of encephalopathy within eight weeks of the development of jaundice in a person without previously known liver disease (5), but it is difficult to detect hepatic encephalopathy in childhood, especially in the neonatal period. For this reason, the Pediatric Acute Liver Failure Study Group has determined the presence of coagulopathy [prothrombin time ≥20 seconds after vitamin K administration or an international normalized ratio (INR) ≥2] as the main finding for the definition of ALF in childhood. INR value may be up to 2 in healthy newborns and INR ≥2 in premature babies may be normal. Therefore, the presence of coagulopathy in the NALF definition is accepted as INR≥3 (3-7). Although the prevalence of acute liver failure at all ages is reported as 17/100 000, its prevalence in the newborn and childhood period is not fully known (2).

Infections, metabolic diseases, hypoxia, toxic substances, drugs, and mass lesions are the main problems known to cause ALF in the newborn period (2). While the factors that initiate

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the damage cause the formation of reactive oxygen radicals by primarily causing oxidative stress in liver cells, they also disrupt energy metabolism and cause oxidative phosphorylation to deteriorate. As a result, the DNAs of the liver cells are broken down and calcium accumulates within the cell. All these pathophysiological mechanisms lead to cytolysis and necrosis and serious functional disorders in hepatocytes (4, 8-10).

Liver failure that starts in the intrauterine period causes congenital cirrhosis. Congenital cirrhosis is detected at or shortly after birth and may present with stillbirth or early postnatal death. The definition of NALF includes newborns with congenital cirrhosis since liver damage starts in the intrauterine period. ALF seen in the neonatal period is clinically and etiologically different from older children and adults (5, 6). Patients may present with non-specific symptoms such as vomiting, fever, jaundice, inability to gain weight, refusal to eat, dehydration, hepatomegaly, encephalopathy, bleeding disorder, ascites, respiratory distress, sepsis, seizures (1, 2). If these clinical findings are accompanied by laboratory findings such as elevated transaminases, hyperbilirubinemia (direct/indirect), a disorder in coagulation tests, unexplained hypoglycemia, hypoalbuminemia, and hyperammonemia, NALF should be considered as the diagnosis (1, 2, 5). It is vital to evaluate patients diagnosed with ALF in the neonatal period in terms of treatable diseases such as galactosemia, hereditary fructose intolerance, and herpes simplex virus (HSV) infection (1, 2, 5, 6).

Etiology

The most common cause of ALF in the neonatal period is gestational alloimmune liver disease (GALD), formerly known as neonatal hemochromatosis (NH). This is followed by viral infections, metabolic diseases, hemophagocytic lymphohistiocytosis (HLH), and other rare causes (4-6, 10).

Gestational alloimmune liver disease

Gestational alloimmune liver disease seems as the main reason for 60-90% of NALF (6). In previous studies, it was reported that the most common cause of ALF in the neonatal period was NH. However, today it is accepted that NH is not a disease, it is a phenotype of liver disease and most frequently develops as a result of GALD. Gestational alloimmune liver disease is accepted as a cause of NH, and NH as a finding of GALD (6). Immunoglobulin Gs that pass from mother to fetus in gestational alloimmune liver disease activate the fetal complement system and fetal liver damage starts in the middle of pregnancy through the membrane attack complex. Fibrosis develops in the liver of the fetus in the second half of pregnancy. The gestational alloimmune liver disease differs from perinatal infections by the absence of liver necrosis. Splenomegaly is usually not detected because patients have patent ductus venosus. In the antenatal period, signs of portal hypertension such as cirrhosis, ascites, intrauterine growth restriction (IUGR), oligohydramnios can be detected and these cases are often born premature (6, 8).

In NH, which develops as a result of gestational alloimmune liver disease, low hepcidin levels in the liver of the fetus disrupt the transition of maternofetal iron and as a result, iron accumulation develops in various tissues of the fetus. Siderosis develops in extrahepatic tissues, especially in acinar cells of the pancreas, myocardium, thyroid follicular epithelial cells, adrenal cortex, oro-nasopharynx, and respiratory tract epithelium (9). Iron accumulation and siderosis in tissues are the main defining characteristics of NH. In newborns, patients with a diagnosis of hemochromatosis have high plasma iron levels and transferrin saturation, normal or low transferrin levels; ferritin levels are usually above 800 ng/mL, but if they are higher than 7000 ng/mL, other diagnoses should be considered.

A definitive diagnosis is made by demonstrating extrahepatic siderosis with magnetic resonance imaging and/or oral mucosa biopsy (8, 9).

Since there is no necrosis in the liver, the increase in transaminase levels is moderate (usually <100 U/L), INR values are usually >4, albumin levels are <2 g/dL. There is an 80% risk of recurrence in subsequent pregnancies and when the family history of the patients is examined, there is usually a history of sibling loss (5, 6). Recurrence of the disease can be prevented by giving the mother intravenous immunoglobulin (IVIG) starting from the 14th gestational week; therefore, accurate diagnosis of patients is important to prevent recurrence in subsequent pregnancies. In the treatment, double-volume exchange transfusion can be performed to clear the antibodies transmitted from the mother from the blood, and high-dose IVIG therapy can be given to bind antibodies transmitted from the mother. It can take months for patients to recover, and supportive treatments are important during the healing process (6, 8-10).

Viral Infections

Viral infections are held responsible for 20-30% of NALF (5, 6). Viruses are transmitted to newborns at or after birth. For this reason, patients are usually normal in the prenatal period, and present symptoms in the 1st -2nd weeks of life. Preterm babies are more susceptible to infections than term babies due to low levels of antibodies transmitted from the mother and their immune system is not yet developed. Transaminase levels are extremely high (>1000 U/L) due to massive necrosis of the liver and hepatosplenomegaly is common. Diagnosis is made by demonstrating the agent with polymerase chain reactions in blood and other body fluids, nasal swab, urine, and stool samples or by the production of the agent in fibroblast cultures (6, 11).

The most common virus that causes ALF in newborns is the Herpes simplex virus (HSV). The risk of transmission to the newborn increases in the presence of a known active primary infection in mother, so babies should be delivered by cesarean section. Herpes simplex virus can cause mucocutaneous vesicular lesions, neurological symptoms, and widespread disease in newborns. Skin findings may not always be seen in newborns infected with the virus, therefore in case of doubt, acyclovir treatment should be initiated without waiting for viral serology results, as it is necessary and life-saving (2, 5, 6, 11, 12).

Cytomegalovirus (CMV) is the most common cause of congenital viral infections and affects 0.2-2% of all newborns worldwide. Newborns can be transmitted through cervical mucus and breast milk in the perinatal period. Maternal anti-CMV antibodies protect term babies from CMV infection, but CMV infections with prenatal or perinatal transmission are encountered in preterm babies with low maternal antibody levels. CMV infection in newborns rarely causes ALF, it usually causes chronic hepatitis and cholestasis (5, 6, 11).

In newborns with acute liver failure, enterovirus should be considered as a factor if there are signs of diarrhea or respiratory tract infection in mother. Necrotizing enterocolitis may develop in patients with NALF due to enterovirus infection. High-dose IVIG use is recommended in the treatment of NALF resulting from enterovirus. The effectiveness of the antiviral drug called Pleconaril in treatment is under investigation. Herpes simplex virus-6 (HSV-6), adenovirus and parvovirus may rarely be NALF agents (2, 5-7, 10-12).

Metabolic Diseases

Amino acid metabolism disorders, bile acid biosynthesis disorders, carbohydrate metabolism disorders, glycosylation disorders, glycogen storage diseases, fatty acid oxidation defects, peroxisomal disorders, respiratory chain defects, alpha 1 antitrypsin deficiency, and Nieman-Pick type C are metabolic disorders known to cause acute liver failure. However, these metabolic disorders rarely cause NALF. Galactosemia, tyrosinemia type 1, and hereditary fructose intolerance are the main inherited metabolic diseases with autosomal recessive inheritance, easily diagnosed and treated, and can cause ALF in the newborn period (5, 13).

Galactosemia is a carbohydrate metabolism disorder. Its prevalence is between 1/40 000 and 1/60 000 all over the world, while the prevalence in our country is 1/23 775 (13, 14). The deficiency of the galactose-1-phosphate uridyltransferase (GALT) enzyme leads to classic galactosemia. This enzyme synthesis is encoded on the short arm (9p13) of chromosome 9. More than 350 mutations that cause classic galactosemia have been reported. The most common mutation in our country is Q188R mutation. The genotype does not always determine the phenotype in this disease (14). Prenatal diagnosis can be made with amniocentesis or chorionic villus sampling. Galactose, which is formed by the destruction of lactose taken with breast milk or formula, cannot be converted to glucose in GALT deficiency, and it accumulates in various organs, especially in the liver, kidney, and eye as galactose-1-phosphate and causes damage. Patients may present with jaundice, vomiting, inability to reach birth weight, feeding difficulty, lethargy, diarrhea, sepsis, cataract, hepatomegaly, liver failure, and renal tubular dysfunction in the second half of the first week of life. Patients who cannot be diagnosed early may die from liver failure, kidney failure, or sepsis (15). It was determined in a study conducted in our country that 57% of the cases were diagnosed late (14). Patients with ALF findings in the neonatal period should be evaluated for galactosemia. The diagnostic value of examining the urinary reducing substances is controversial, the definitive diagnosis is made by showing that the GALT enzyme activity decreases in erythrocytes and that the galactose-1 phosphate levels increase. (13, 16). Tests should not be repeated by giving galactose, because the galactose given can transform into galactose-1-phosphate and damage organs. Before taking blood from the patient for diagnostic tests, care must be taken to ensure that no blood transfusion has been performed. When ALF develops in the neonatal period, a lactose-free diet should be considered until the diagnosis of galactosemia is excluded (17). Galactosemia is included in the neonatal screening program in many European countries and the United States. There is no consensus on the inclusion of galactosemia in the neonatal screening program in the Cochrane database (18).

Hereditary fructose intolerance is one of the most important fructose metabolism disorders, it is autosomal recessive inheritance and is caused by the deficiency of fructose-1 phosphate-aldolase (aldolase B) enzyme in the liver, small intestine, and kidney. Nearly 40 mutations that cause the disease have been reported. Generally, babies show symptoms when they start complementary feeding and are exposed to fructose. However, due to the presence of fructose in some formulas, babies fed with formula may present with ALF in the newborn period. Therefore, it is important to obtain detailed nutritional histories of newborns diagnosed with ALF (5, 19). The enzyme is absent in leukocytes and erythrocytes. For this reason, a definitive diagnosis is made by studying enzymes in the liver and small intestine biopsy samples or by genetic study (19).

Tyrosinemia is an autosomal recessive disorder caused by enzyme deficiencies in tyrosine amino acid metabolism. Tyrosine is an amino acid involved in catecholamine, thyroid hormone, and melanocyte synthesis. There are three types of hereditary tyrosinemia. Fumaryl acetoacetate hydroxylase enzyme is deficient in type 1 tyrosinemia (hepatorenal type). The liver, kidney, and nervous system are affected as a result of this enzyme deficiency. Patients usually present with restlessness, nausea, vomiting, jaundice, growth restriction, hepatomegaly, electrolyte imbalance, metabolic acidosis, renal tubular dysfunction, hypoglycemia, bleeding diathesis, and ALF in the early childhood and neonatal period. Succinylacetone in urine in suspected newborns; Diagnosis can be made by demonstrating reduced fumaryl acetoacetate hydroxylase enzyme activity in lymphocyte, erythrocyte, or liver tissue, and patients can be treated with appropriate nutrition and vitamin support (5, 20).

Respiratory chain defects are another group of diseases that can cause NALF. Mitochondria are the organelles responsible for the energy production of cells. Mitochondrial diseases cause multiple tissue and organ system effects due to mitochondrial DNA (mtDNA) damage. Mitochondrial cytopathies can affect all tissues and organs. They show clinical signs of the structures they involve by affecting the heart, musculoskeletal system, gastrointestinal system, nervous system, eye, and ear. As the energy requirements of the brain, muscle, and liver are higher than other tissues and organs, mitochondrial diseases are most frequently encountered with neurological findings, rhabdomyolysis, and ALF. Cholestasis and cirrhosis may develop in patients immediately after birth or in the first week of life (21). When looking at the arterial blood, lactate levels, lactate/pyruvate ratios (>20, usually >30) and beta-hydroxybutyrate / acetoacetate levels (≥2) increased. Decreased respiratory chain complex activity can be demonstrated on muscle or liver biopsy. Treatment findings are aimed at alleviating the disease and supportive; vitamins, cofactors, and antioxidants are used in treatment (2, 5, 6, 22).

Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a rare cause of NALF (<%10). It may be primarily familial, or it may develop secondary to systemic infections, malignancies, metabolic disorders, and immunodeficiencies. HLH should be kept in mind in the differential diagnosis in patients whose clinical and laboratory findings do not improve despite antibiotic treatment and appropriate supportive treatment (5, 23). Five of the following

criteria as fever >38.5°C for more than 7 days, cytopenia in at least two series (hemoglobin <12 g/dL in the neonatal period, platelets <100 000/mm^3, polymorphonuclear leukocyte <1000/mm^3), splenomegaly, low fibrinogen-high triglyceride levels, high ferritin level (>500 µg/mL), high CD25 level (>2400 U/mL), low natural killer cell activity, and demonstration of hemophagocytosis in tissues are sufficient for diagnosis. Various chemotherapeutic drugs are used in the treatment (10, 23, 24).

Other rare causes

Perinatal asphyxia, hypoxia, sepsis, drugs toxic to the liver, maternal overdose of paracetamol, low cortisol (pituitary insufficiency, adrenal insufficiency), and genetic cholestasis are also rare causes known to cause NALF (5, 6, 10).

Diagnostic Approach

Although coagulation disorder is prominent in acute liver failure, there is usually no tendency to bleeding in children and adult patients due to the decrease in the synthesis of both procoagulant and anticoagulant proteins in the liver, but this situation is different in the neonatal period. In the neonatal period, patients may present with bleeding diathesis due to missing coagulation factors, especially vitamin K-related coagulation factors. Patients with high transaminases should be evaluated in terms of coagulation disorder even if their general condition is good, vitamin K should be given to the patient in the presence of prolonged prothrombin time (PT) and INR, and the failure to improve coagulation disorder after vitamin K should suggest ALF (10). In acute liver failure, transaminases are usually excessively high (>1000 U/L), conjugated hyperbilirubinemia and vitamin K-resistant coagulation disorder are present, and unexplained hypoglycemia is common. Transaminases are slightly increased in chronic liver failure lasting more than eight weeks; albumin levels are variable. Hypoglycemia and vitamin K-resistant coagulation disorder are common findings of both acute and chronic liver failure. It is possible to see parenchymal changes with ultrasonography in chronic cases (5, 7, 8, 24).

Taking detailed antenatal, natal, and postnatal history from the families of the newborns diagnosed with acute liver failure is very important in terms of diagnosis. Parvovirus B19, bile acid synthesis disorders, and hemophagocytic syndromes, especially GALD, should be considered in the presence of findings suggestive of liver failure starting in the intrauterine period such as antenatal cirrhosis, ascites, and IUGR (1, 6, 7, 10, 23). If ALF has developed in a newborn who is born at term and looks healthy when born, primarily viral diseases (such as HSV, Hepatitis A, B, C, E, Varicella zoster virus, Enteroviruses, Echovirus, Coxsackie viruses, Adenovirus, CMV, Epstein–Barr virus), vascular diseases such as vein thrombosis, and neoplasms such as neuroblastoma, leukemia should be kept in mind in the differential diagnosis (7, 10, 11). Findings in NALF secondary to metabolic diseases can occur both in antenatal and postnatal periods (7, 13, 19, 20).

The existence of consanguinity between parents, history of sibling loss, birth history, medications used by the mother, and diseases of the mother should be questioned in detail in evaluating the development process of liver failure. In a baby diagnosed with ALF in the neonatal period, the examinations should be planned according to the clues obtained from the patient's history and physical examination. The first level examinations that should be requested are presented in Table 1. To reach the correct diagnosis, the results of detailed history, clinical evaluation, and laboratory tests should be evaluated together, especially when a disease is suspected, second and third level examinations should be requested for that disease (Table 1). The differential diagnosis of the diseases that most commonly cause ALF in newborns is presented in Table 2.

Table 1. Diagnostic approach to acute liver failure in the newborn (2, 5-7, 10)

First Level Examinations		**Original studies**	
Biochemical tests	Transaminase levels, plasma glucose, electrolytes, calcium, phosphorus, magnesium, ferritin, amylase, cholesterol, triglyceride, blood gas, lactate, pyruvate ammonia, plasma amino acids, alpha 1 antitrypsin, plasma acylcarnitines, GALT, AFP	Biochemical tests	When HLH is suspected: Soluble IL-2R alpha levels
Hematologic tests	Complete blood count, reticulocyte, prothrombin time, INR, fibrinogen, blood group, direct Coombs test	Hematologic tests	When malignancy or HLH is suspected: Bone marrow biopsy When HLH is suspected: Natural killer cell activity
Microbiological tests	**Cultures:** Blood, urine, stool, throat swab, culture from the lesion if there is a skin lesion, acid fluid culture	Microbiological tests	**Cultures:** Urine and viral culture on skin lesions if present, vaginal swab culture for HSV from the mother
	Serological tests: Anti-HAV IgM, HBsAg, HBcAb (IgM), HBcAg, anti HCV, HCV PCR, anti-hepatitis D antigen-antibody, anti-hepatitis E antigen-antibody, CMV, EBV, HIV		**Serological tests / viral PCR:** HSV, Adenovirus, Echovirus, measles, toxoplasma, listeria
Urine tests	Toxicology, osmolarity, electrolytes, amino acids, organic acids, succinylacetone	Tissue samples	Buccal mucosa biopsy, muscle biopsy, skin fibroblast cultures
Ultrasonography	Imaging of liver, portal and hepatic veins, inferior vena cava, biliary system, spleen	Genetic tests	Mutation analysis

AFP, alpha-fetoprotein; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GALT, galactose-1-phosphate uridyltransferase; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBcAg, hepatitis B core antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSV, Herpes simplex virus; INR, International normalized ratio

Table 2. Differential diagnosis of acute liver failure in the newborn (5, 6)			
	Gestational Alloimmune Liver disease	**Viral hepatitis**	**Metabolic Disorders**
Medical history			
Prematurity	+	-	-
Oligohydramnios	+	-	-
Intrauterine growth restriction	+	-	+
Clinical findings			
Patent ductus venosus	+	-	-
Hepatomegaly	+/-	+	+/-
Splenomegaly	-	+	+/-
Other organ involvement	-	Meningoencephalitis, skin involvement	Depends on the disease
Laboratory tests			
Total bilirubin (mg/dL)	8-17,6	60-170	120-320
Direct bilirubin (mg/dL)	2,3-6,4	20-80	40-140
ALT/AST (IU/L)	Normal x 1-2	Normal x 20-30	Normal x 4-5
GGT (IU/L)	Normal	Normal x 2-3	Normal x 1-2
INR	≅3	≅4	≅2.5
High Lactic Acid Level	-	-	+

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, International normalized ratio

Table 3. General management of acute liver failure in the newborn (2, 10)
Vital signs and urine output should be closely monitored.
Patients with encephalopathy or INR >4 should be monitored in the neonatal intensive care unit.
Lactose-free formulas should be used until Galactose-1-phosphate uridylttransferase enzyme activity is seen.
High-dose acyclovir therapy should be given until the herpes simplex virus infection is excluded.
Fluid therapy should be 90-95% of the maintenance fluid and plasma glucose should be kept in the range of 90-110 mg/dL.
Electrolyte monitoring should be done at intervals of at least 12 hours.
Prophylactic broad-spectrum antibiotic therapy and antifungal therapy should be initiated if necessary.
It should be considered to give ranitidine as a gastric defense.
Sedation should be avoided even if mechanical ventilation is required.
PaCO2 level should be kept at 4.5 Kpa and pH between 7.35 and 7.45 in patients on mechanical ventilators.
Seizures should be stopped with anticonvulsant drugs such as phenytoin, midazolam, phenobarbital, levetiracetam, and topiramate.
Protein intake should be restricted to 0.5-1 g/kg/day, and the necessary calorie support should be provided.

Treatment

It is necessary to investigate the etiology of NALF on the one hand and to manage the disease and the problems it brings in newborns diagnosed with acute liver failure. First of all, it is necessary to remember that these patients are at risk in terms of increased fluid volume burden and fluid restriction is necessary (daily fluid = 90-95% of the maintenance fluid). Blood sugar should be kept in the range of 90-110 mg/dL. Hypoglycemia is observed in 40% of patients due to decreased gluconeogenesis and increased insulin levels. Therefore, newborns diagnosed with ALF may need fluids with high glucose perfusion rate and central catheters for normal blood glucose values. In newborns with liver failure, electrolyte monitoring should be performed with an interval of at least 12 hours, protein intake should be restricted to 0.5-1 g/kg/day and necessary calorie support should be provided (1-3). Since the first clinical findings of ALF in the neonatal period can be confused with sepsis and infection can frequently accompany NALFs developing based on metabolic disease, it is appropriate to add antibiotics, especially gram-negative bacteria, to the treatment until sepsis is excluded (10). Fungal infections should be kept in mind in the presence of fever, leukocytosis, and worsening of the clinical condition unresponsive to antibiotic treatment. Candida species are the most common fungal sepsis agent in acute liver failure. It can be difficult to breed the agent in culture, so antifungal therapy should be initiated in case of clinical suspicion (2, 10).

The hemodynamic status of newborns with liver failure should also be closely monitored. Inotropic support should be given, if necessary, along with appropriate fluid support so that the blood pressure is within the normal range. Noradrenaline is a preferred drug in ALF since it increases peripheral vascular resistance. Hydrocortisone therapy should be considered in the presence of inotrope-resistant hypotension (5, 7, 10). General management of ALF in newborns is presented in Table 3.

Since the international normalized ratio value is a criterion for the patient to be included in the liver transplant list, it is recommended not to correct the coagulation disorder in patients who do not have bleeding and are not scheduled for an invasive procedure in their follow-up. In case of bleeding or if the patient is being prepared for an interventional procedure; vitamin K, fresh frozen plasma (FFP) (10 mL/kg, in 30 minutes), cryoprecipitate (5-10 mL/kg if fibrinogen <1 g/L, in 30 minutes), thrombocyte suspension (keeping platelet values >75×109/L) or factor VII (if INR value does not improve despite FFP) support should be given. If the blood product will be given to the patient, the necessary samples should be reserved for the diagnostic tests before the blood product is given (9, 10, 12, 25).

Table 4. Etiology-specific treatments in acute liver failure in the newborn (5, 6, 10)	
Gestational alloimmune liver disease	Whole-blood exchange, intravenous immunoglobulin
Herpes simplex virus	Acyclovir
Cytomegalovirus	Ganciclovir, valganciclovir
Enterovirus	Pleconaril
Galactosemia	Galactose-free diet
Hereditary fructose intolerance	Fructose-free diet
Tyrosinemia	Nitisinone
Respiratory chain defects	Antioxidants, vitamins
Hemophagocytic lymphohistiocytosis	Chemotherapeutic drugs

Acute hepatic encephalopathy (HE) with acute onset, another complication of acute liver failure, can be completely recovered when liver dysfunction is restored. It is difficult to evaluate the HE findings in the neonatal period, the first findings may be excessive crying, feeding difficulties, behavioral change, and these findings may be followed by lethargy, drowsiness, seizures, and coma. Monitoring patients by intubation may be considered when they are thought to develop hepatic encephalopathy, but unnecessary sedation should be avoided. If there is a seizure, it should be treated. Anticonvulsant drugs such as phenytoin, midazolam, phenobarbital, levetiracetam, topiramate can be used for seizures (2, 5, 7). Symptoms such as systemic hypertension, bradycardia, hypertonicity, hyperreflexia, and hyperventilation due to increased intracranial pressure are mostly seen in older children. In the presence of bulging in the fontanel or sudden neurological deterioration, intracranial bleeding and sepsis should be kept in mind in the differential diagnosis. In the treatment of increased intracranial pressure due to cerebral edema, fluid therapy should be adjusted by keeping the serum sodium level in the range of 145-150 mEq/L. Regulation of cerebral perfusion pressure with inotrope support is another treatment option in severe cases. Serum ammonia levels are not often associated with the severity of liver dysfunction and the degree of encephalopathy. However, ammonia-lowering treatment should be initiated in the presence of progressive HE accompanied by hyperammonemia (2, 10, 25).

Hypoalbuminemia, excessive fluid therapy, or ascites secondary to infections may develop in patients. Fluid restriction should be applied in acid treatment, albumin infusion should be performed in patients with albumin <2.5 g/dL or with an albumin level below the 25th percentile. Diuretic therapy can be given if the fluid load causes respiratory distress or is very common, but diuretics should be used with caution as excessive diuresis may trigger the development of hepatorenal syndrome (2, 5, 25, 26). Hepatorenal syndrome is a dreaded complication of ALF and is characterized by sudden impairment of renal function without a risk factor such as bleeding, hypotension, sepsis, or nephrotoxic drug intake. Hemodiafiltration or dialysis is required in treatment (2, 26, 27). Treatments specific to the etiology of ALF in newborns are presented in Table 4.

Liver transplantation is another treatment option for newborns who do not respond to treatment. The main indications for liver transplantation in the neonatal period are biliary atresia and metabolic diseases. Survival after liver transplantation in the first three months of life is the same as for older child recipients; however, the risk of reoperation requirement is higher due to bleeding, wound complications, sepsis, and biliary complications, and it has been reported that the need for intensive care and hospitalization periods are longer (28). Therefore, liver transplantation should not be considered before the etiology is clear (1, 5, 6, 28-30). Before liver transplantation, the factors that increase the death rate are the patient's being younger than one year old, having advanced stage encephalopathy, having INR> 4, and needing dialysis. The risk of death increases five times if the ammonia level is >200 µmol/L (1, 25, 29, 30). Zozaya Nieto et al. (4) found that ischemia is the most common cause of ALF in the first two months of life. They showed that the prognosis of ALF due to ischemia is better than other causes of ALF (NH, viral infections, metabolic diseases, etc.), but high INR and ALT levels are associated with increased death and transplant requirement.

As a result, NALF is a rare condition with a high mortality rate. For this reason, the vital signs of the patients should be closely monitored and the etiology of the disease should be immediately clarified while planning the necessary supportive treatments according to the follow-ups. In this process, acyclovir treatment until HSV infection is excluded and lactose-free nutrition initiation until galactosemia is excluded are recommended as life-saving treatments. Since the number of studies on NALF in the literature is limited, there is a need for prospective studies, especially examining the effective factors in treatment and prognosis.

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