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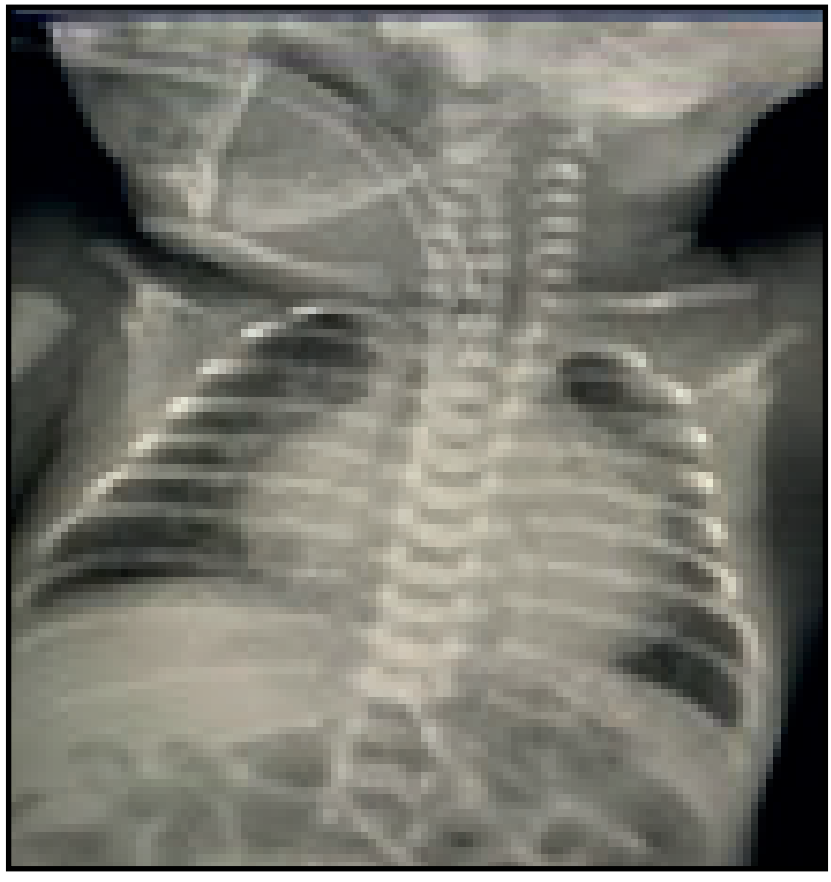

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Review

Liver transplantation in pediatric monogenic metabolic diseases

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ABSTRACT

Monogenic diseases are the results of a single gene mutation leading to alterations or defects in a single enzyme causing severe metabolic derangements causing multi-systemic systemic disease and even death Current management strategies include diet to reduce the accumulation of metabolic waste products and treatment to increase the excretion of the toxic metabolites and to induce the activity of the mutant enzyme. However, liver transplantation is the only therapeutic strategy that offers a chance of cure to children with certain genetic diseases.

Keywords: Liver transplantation, pediatric liver diseases, pediatric monogenic diseases

INTRODUCTION

Monogenic diseases are the results of a single gene mutation and are very rare diseases, occurring in 10 neonates per 1000 births according to the data of the World Health Organization.[1] Liver transplantation (LT) is the only therapeutic strategy that offers a chance of cure to children with certain genetic diseases. LT can significantly improve the quality of life of pediatric patients who suffer from congenital metabolic diseases. Advances in patient care, surgical technique, post-transplant surgical care, and immunosuppression have resulted in a 95% postoperative survival rate in the first year and 85% in the 5th year following liver transplantation.[2] In 1978, for the first time, a patient with tyrosinemia was transplanted for the first time which was followed by a liver transplantation for ornithine transcarbamylase (OTC) deficiency in 1989. These two events were evolutionary because LT became the new hope for the treatment of patients with monogenic diseases.[3,4]

Monogenic diseases are the results of single gene mutation causing alteration or defect in a single enzyme causing severe metabolic derangements causing multi-systemic systemic disease and even death. Currently, the strategies of management include diet to reduce the accumulation of metabolic waste products and treatment to increase the excretion of the toxic metabolites and to induce the activity of the mutant enzyme. The patients have to comply with a strict diet and have the risk of decompensation with every infectious process that is encountered. LT is the only means of cure that can provide a better quality of life for these patients.[5]

There are many monogenic diseases of the amino acid, lipid, and elemental metal metabolism; as well as mitochondrial disorders that can be cured by LT. According to the data of the study group for pediatric liver transplant (SPLIT) between 1995 and 2008 446 pediatric transplants were performed and 14.9%of these procedures were performed for metabolic liver diseases. Urea cycle disorders (UCD), the most common metabolic disease requiring liver transplantation, accounted for 25.6% of patients with metabolic diseases. Other frequent metabolic diseases that require liver transplantation are α-1anti-trypsin deficiency (19.7%), cystic fibrosis (10%), Wilson's Disease (7.6%),

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tyrosinemia (7.4%), maple syrup urine disease (MSUD) (6.5%), glycogen storage disease (GSD) (5.2%) and miscellaneous minor diseases (17.2%).[6]

The donors of these patients are usually the parents who are also the carriers of these autosomal recessive diseases. The data regarding living-related liver transplantation from heterozygous donors have been limited. Kasahara and colleagues have analyzed the Japanese Transplant registry and more than 95% of the donors were carriers for the monogenic diseases of the recipients. The most common disease reported in this cohort was Wilson's disease (30.4%). This was followed by OTC (20.6%), methylmalonic acidurias (MMA) (10.3%), GSD (7.7%), tyrosinemia (6.7%), propionic acidemia (4.6%), and primary hyperoxaluria (4.6%). The long term survival and better results were observed in Wilson's disease and UCD. In OTC, female donor candidates who were asymptomatic should be evaluated with thorough metabolic evaluation. Female donor candidates who are symptomatic should be excluded from donor evaluation.[7] The risk-benefit assessment should be performed with great care and a follow-up of the recipients in the postoperative period should be performed with great care. The monogenic diseases that are treated with liver transplantation are divided into two classes: those that cause liver parenchymal damage and those that do not cause any liver parenchymal damage (Table 1).

I-Monogenic Diseases that Cause Liver Parenchymal Damage

Ia) Hereditary Tyrosinemia Type 1

This is an autosomal recessive disease that is caused by fumarylacetoacetate hydrolase (FAH) deficiency in the liver and kidneys. Usually, it presents as a multisystemic disease with a mild elevation of transaminases during infancy together with severe coagulopathy. In older children and adults it can present itself as chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Associated components of the disease can be hypertrophic cardiomyopathy, renal tubulopathy, neuropathy, and porphyria-like symptoms. Pathognomonic biochemical changes are hypertyrosinemia, hypermethioninemia, elevated blood and urine succinyl acetone, and elevated serum alpha-fetoprotein.[5] The indications for liver transplantation are progressive liver disease despite phenylalanine and tyrosine restricted diet and 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) (NTBC) treatment, alpha-fetoprotein elevation during NTBC treatment, solitary hepatic nodule with a diameter greater than 10 mm or increase in the size and number of hepatic nodules or confirmation of HCC during follow-up.[5,8] Data from the United Network for Organ Sharing (UNOS) database suggests that 1- and 5 -year survival following LT for Hereditary Tyrosinemia Type 1 is 90.4% and 90.4%, respectively. The 1- and 5-year graft survival following LT is reported to be 78.1-84.4% and 63.3%-75.2%. Graft survival rates increased over time with advances in surgical and postoperative care, including immunosuppressive treatment.[9]

Acute metabolic decompensation is very rare in hereditary tyrosinemia type 1; however, fasting and catabolism associated with surgery may adversely affect the liver functions and may exacerbate porphyria-like episodes in patients. Therefore, it is recommended that preoperative fasting should be minimized and that patients be continuously infused with 10% dextrose solution. In the post-transplant period, succinyl acetone can still be detected in the serum and urine of the patients. Urinary succinyl acetone levels should be monitored in the post-transplant period due to the risk of tubulopathy; on the other hand, NTBC treatment is not recommended.[5]

Ib) Wilson's Disease

Wilson's disease is a congenital autosomal recessive disease which is characterized by a mutation in ATP7B, which encodes an intracellular transmembrane copper transporter. This results in abnormal copper accumulation in various tissues and results in tissue damage due to copper-related toxicity.[10]

Table 1. Monogenic diseases that are treated with liver transplantation

Diseases with Parenchymal Liver Damage	Diseases without Parenchymal Liver Damage
Hereditary Tyrosinemia Type I	Urea Cycle Defects
Wilson's Disease	Organic Acidemia
Alagille Syndrome	Defects of Fatty Acid Oxidation Pathway
Progressive Familial Intrahepatic Cholestasis	Primary Hyperoxaluria Type I
Disorders of Bile Acid Synthesis	Mitochondrial Hepatopathy and Systemic Mitochondrial Disease
Alfa-1 Antitrypsin Deficiency	Crigler-Najjar Type I
Glycogen Storage Disease	Acute Intermittent Porphyria
Cystic Fibrosis	Factor VII Deficiency
Ductal Plate Malformations	Protein C Deficiency
Erythropoietic Protoporphyria	

Wilson's disease-related end-stage liver disease can present as different disease spectrums which can be summarized as acute liver failure, acute/chronic hepatitis, cirrhosis, portal hypertension.[11] Copper chelating agents or zinc sulfate are used to prevent copper absorption from the gastrointestinal tract. Acute liver failure, chronic liver disease unresponsive to treatment and decompensated cirrhosis are the main indications for LT in patients with Wilson's disease. In other liver diseases and acute liver failure, Nazer's Wilson Index can be used for the decision-making process for LT. The component of this index bilirubin, AST, white blood cell count and albumin; and any patient with a score > 7 suggests proceeding with liver transplantation because the mortality without intervention is high. The sensitivity and specificity of this scoring system in predicting LT are 93% and 98%, respectively.[12] The efficacy of LT in patients with neuropsychiatric symptoms is controversial. The pathophysiology of neuro-Wilson includes tissue damage due to copper elimination, and it can be hypothesized that reversal of the process by LT can prevent further tissue damage and promote timely recovery of neural tissue. This hypothesis has been supported by various studies.[13,14] On the other hand, it has been shown that the existing central nervous system damage and cerebral dysfunction do not recover sooner than 6 months following the transplant procedure.[5] It has been reported that full recovery is possible in 56-77% of the cases. On the contrary, there are reports that suggest a worsening of the neuropsychiatric symptoms following transplant procedure, and it is known that patients with neuropsychiatric symptoms have lower survival rates than patients with isolated liver failure. For this reason, in patients who present with combined liver failure and neuropsychiatric symptoms require thorough neurologic and psychiatric evaluation before the decision to proceed with liver transplantation is made.[1,5] Specific metabolic follow-up is not required in these patients in the post-transplant period, and the medical management strategy is the same as in the patients without any metabolic defect.[5] The 1- and 5-year survival rates of the patients with Wilson's disease following liver transplantation are 91.9% and 88.2%, respectively.[15]

Ic) Alagille Syndrome

Alagille syndrome is a congenital autosomal dominant multisystemic disease that primarily affects the liver and the heart of the individuals. The main diagnostic criteria of Alagille syndrome are chronic cholestasis, congenital malformations of the heart, vascular system, eyes, and the kidneys along with a characteristic facial morphology. Severe cholestasis, intractable pruritus, growth retardation, hypercholesterolemia and osteodystrophy are some of the complications of the disease that can be reversed by LT.[16] Before the transplant procedure, patients should be thoroughly evaluated for extrahepatic manifestations of the disease, and the vascular system should be evaluated by imaging studies for cerebral aneurysm, carotid artery stenosis, coarctation of the abdominal aorta, and renal artery stenosis. Any vascular anomaly should be corrected before the liver transplantation. Patients with complications such as intractable pruritus and deformed xanthoma which are not life-threatening, non-transplant surgical alternatives such as biliary diversion or ileal bypass should also be considered.[8] Current series in the literature show that the median survival following liver transplantation is 79%. Early experience with liver transplantation for Alagille syndrome showed a 1-year survival of 57%; however, current high-volume studies suggest that 1-year survival of the patients following liver transplantation ranges from 71 to 100%.[17] In 2019, Valamparampil and colleagues reported the results of their study showing 100% patient and graft survival rates during a median of 32 (3-72) months follow-up period in patients with Alagille syndrome who underwent liver transplantation.[18]

Id) Progressive Familial Intrahepatic Cholestasis

Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of autosomal recessive diseases that cause cholestasis and liver failure. It has many subtypes that result from different genetic mutations. PFIC type 1 results from a mutation in the ATP8B1 gene. Typically, there is severe cholestasis in the early years of infancy together with normal serum gamma-glutamyl transferase (GGT) levels. Associated symptoms may include chronic diarrhea and asthma-like respiratory complaints. Pathologic analysis may reveal giant cell transformation, canalicular cholestasis with biliary plugs, ductular degeneration, and structural lobular irregularities.[19] In PFIC type 1, partial external biliary diversion or ileal bypass can provide clinical, biochemical and histologic improvement along with prevention of disease progression and support for patient growth if it can be performed before the development of cirrhosis.[20] Progressive steatohepatitis that may lead to cirrhosis in liver allograft in the post-transplant period has been reported.[8]

PFIC type 2 results from a mutation in the ABCB11 gene that encodes BSEP. Similarly, serum GGT levels are normal and the patient has cholestasis. PFIC type 2 is a more rapidly progressing disease that presents with higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, cholelithiasis and giant cell hepatitis. Furthermore, there is a high risk of hepatocellular carcinoma. Giant cell hepatitis in pathologic analysis is typical for this disease.[19,21] In mild forms of the disease, ursodeoxycholic acid and biliary diversion may result in good clinical response. In contrast to PFIC type 1, a successful liver transplantation is curative in PFIC type 2.[8,20] However, auto-antibodies may develop against the mutant BSEP protein

encoded by the defective ABCB11 gene, which may result in cholestatic disease in the transplanted liver graft that may resemble the original disease in the native liver.[22] There is no specific treatment to prevent the recurrence of the disease after liver transplantation. However, studies have shown that Rituximab which is a chimeric monoclonal anti-CD20 antibody may be effective in preventing recurrences.[23]

PFIC type 3 develops as a result of a mutation in the ABCB4 gene, which encodes the MDR glycoprotein. Its clinical course is usually different from the previous two PFIC types that we have mentioned. Biochemically, the patients have high serum GGT levels. Usually, individuals carrying the heterozygous alleles of the ABSB4 gene present with transient neonatal cholestasis. However, the onset of the disease is usually in the late adolescence and early adulthood. Cholelithiasis, intrahepatic cholestasis of pregnancy, and drug-induced cholestasis may be seen during the course of the disease. The initial findings of the disease are jaundice, pruritus and the biochemical signs of the liver failure. Pathologic analysis shows mild giant cell hepatitis, portal fibrosis and proliferation of the biliary canaliculi.[19] Treatment with ursodeoxycholic acid usually results in clinical and biochemical recovery; however, 15% of patients do not respond to treatment and the disease progresses rapidly. In patients who do not respond to medical therapy, LT can be considered for the treatment of the disease.[8,24]

PFIC type for is a congenital autosomal recessive disease that results from a mutation in the TJP2 gene. Liver failure is prominent, and develops early, and progresses rapidly. Patients usually need liver transplantation in the first few years after birth. There have been reports of the hepatocellular carcinoma development on initial admission of the patients. Extrahepatic manifestations of the disease may involve the nervous and respiratory system of the patients.[25] The GGT levels are usually normal in these patients. Histopathologic analysis shows giant cell transformation and intracellular cholestasis is also common.[19,21]

PFIC type 5 is an autosomal recessive disease resulting from a mutation in the NR1H4 gene that encoding FXR. The disease presents early in infancy and children have normal GT levels and severe cholestasis. In addition, the liver enzymes are normal but serum bile acids and alpha-feto-protein levels are elevated. Patients have vit K-independent coagulopathy and hyperammonemia. Liver failure develops very rapidly and progresses to end-stage liver failure that requires liver transplantation. Pathological analysis shows hepatocellular ballooning, giant cell transformation and micronodular cirrhosis.[19,21]

The mutation in the MYO5B gene results in microvillus inclusion disease and can also present as isolated liver disease.[19,21] Patients present around the first year of life with low serum GGT, cholestasis, hepatomegaly, and normal or elevated serum transaminases. Histopathologic analysis shows giant cell transformation, hepatocellular damage, portal and lobular fibrosis.[19]

Currently, LT offers the only means of cure for PFIC-related end-stage liver disease. However, LT may worsen the extrahepatic manifestations of PFIC type 1. The recipients who have PFIC type 2 may have recurrence of the disease in the liver allograft and the postoperative surveillance of these patients are mandatory and the immunosuppressive treatment should be given with great care.[26] A recent meta-analysis showed that a total of 131 patients from all subtypes had a graft and patient survival rate of 76.6% and 85.2%, respectively; and the longest follow-up period was 19 years.[27]

Ie) Defects of Bile Acid Synthesis

This spectrum of disease usually presents as neonatal cholestasis or hepatitis. However, it may also present as chronic liver disease in older children. Usually, the serum bile acid levels are normal or low, serum GGT levels are normal and pruritus is not observed in this disease, which is quite different from other cholestatic diseases of the liver. Usually, administration of cholic acid and chenodeoxycholic acid is effective in treating patients, if the disease is diagnosed early. LT is indicated in patients in whom the disease has progressed and end-stage liver disease has developed.[8,28]

If) Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) is a protease inhibitor found in the serum of healthy individuals and it protects the tissue from neutrophil-derived proteases such as elastase.[5,29] The presentation of AAT-related liver disease is highly variable. Generally, AAT rarely presents as a rapidly progressive, lethal liver disease that requires liver transplantation in early infancy. PiZZ is a severe form of AAT that has an autosomal co-dominant trait. Seven percent of the affected individuals have long-term obstructive jaundice, and 80% of the patients do not exhibit signs of chronic liver disease until the age of 18. Hepatocellular carcinoma may develop in children with AAT-related cirrhosis.[8,30] Pulmonary involvement is prominent, and even though liver functions improve following liver transplantation, pulmonary functions continue to deteriorate.[5,31] For this reason, strict monitoring of the pulmonary system after liver transplantation is mandatory even in patients with normal preoperative pulmonary functions.[5] The 1-, 3-, 5-, and 10- year overall survival

rates of the patients following liver transplantation are 90%, 88%, 85%, and 78%, respectively.[31]

Ig) Glycogen Storage Disease

The most common indication for LT among inborn errors of carbohydrate metabolism are the Glycogen Storge Diseases (GSD). It is a spectrum of diseases caused by defects in the enzymes that take part in glycogen synthesis, breakdown, or glycolysis, and the presentation of the disease may be isolated liver involvement, isolated muscle involvement, or involvement of both.[5] The enzymes of glycogen metabolism are present in many organ systems and tissues. For this reason, the extent of extrahepatic manifestations varies from one patient to other. Liver transplantation is frequently performed in patients with GSD types I, II, and IV.[32] Poor metabolic control, multiple adenomas, and/or suspicion of hepatocellular cancer in GSD type I; poor metabolic control, progressive liver failure or presence of complicated cirrhosis or suspicion of hepatic malignancy in GSD types III and IV are the main indications for LT in this spectrum of disease.[8]

GSD type I accounts for 25% of the cases and LT is therapeutic in a selected group of patients. GSD type Ia is also known as the von Gierke disease, is caused by defects in glucose-6-phosphatase and glucose-6-phosphorylase enzyme complex, mainly affects the liver and the kidneys.[33] It is the most common variant of GSD type I. Glucose-6-phosphorylase deficiency in GSD type Ia causes severe hypoglycemia, lactic acidosis, hypertriglyceridemia, uric acidemia, hepatomegaly, “doll’s face” and failure to thrive. One of the most common complications observed during adolescence is the development of hepatic adenomas.[5] In GSD type Ib, symptoms resemble those of GSD type Ia, in addition to neutropenia and inflammatory bowel disease. Dietary modification can normalize the blood glucose levels and reduce the lactic acid levels in patients with GSD type Ia. In patients with GSD type Ia with poor metabolic and biochemical control or in patients with large hepatic adenomas that cannot be resected, LT may be a therapeutic option. Indications for LT in GSD type Ib are similar, but also includes recurrent infections due to neutropenia.[34] Important perioperative concerns in GSD type I are lactic acidosis and hypoglycemia. Stress-induced lactic acidosis may be life-threatening. Surgical stress may lead to a severe lactic acidosis which may cause multiple organ failure and death.[5] The stress-induced hormones and glucose-6-phosphate accumulation due to the metabolic defect cause a robust of glycogenolysis and the glycolysis is induced, which causes an excess of lactic acid production. To prevent hypoglycemia and lactic acidosis, it is recommended that the preoperative fasting period should be minimized, and dextrose infusion should be started at rate of 4-9 mg/kg/min adjusted according to the age of the patient.[5,35] Intraoperatively, close monitoring of glucose, lactate and pH is required and the dextrose infusion rates should be carefully adjusted especially during hepatic dissection and anhepatic phase in order to achieve glycemic control in the patients. Infusion solutions live lactated ringer should be avoided because of the lactate content. In patients with lactic acidosis, sodium bicarbonate infusion is required to correct the deficit. Results from a cohort of 80 patients with GSD type I who received LT showed that metabolic control and tolerance to fasting improved after the transplant procedure.[34] LT reverses the liver dysfunction, growth retardation, and neutropenia. LT was also shown to cure the inflammatory bowel disease in patients with GSD type Ib. However, it is recommended that strict surveillance should be performed for neutropenia, neutrophil dysfunction, and inflammatory bowel disease in the postoperative period.[35] GSD type I is associated with progressive renal disease; and unfortunately, LT cannot reverse the progression of the renal disease. For this reason, renal functions should be monitored regularly after LT.[5]

Ih) Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease that is cause by a mutation in the CFTR gene, which encodes a transmembrane conductance regulator protein.[36] Only 35% of the patients with CF present with a liver disease. However, 5-10% of the patients with liver disease develop cirrhosis.[37] LT for CF constitute 3.5% of the transplants performed in the pediatric age group.[38] Esophageal variceal bleeding is the most prominent component of the presentation of end-stage liver disease due to CF. Recurrent episodes of variceal bleeding are indications for LT.[38] Furthermore, the biliary cirrhosis that develops in these patients may lead to accumulation of ascites and may compromise the respiratory dynamics of the patients. The optimal timing of LT depends on the suitability of cardiopulmonary functions, the presence of active acute or chronic infection, and the nutritional status of the patient. LT should be performed before the forced expiratory volume in first second (FEV 1) decreases below 50%.[39] The presence of certain microbial agents in the respiratory tract of individuals is a complex and a controversial subject in patients with CF for whom LT is being considered as a treatment option. The presence of *Aspergillus species* in the sputum of the individual is not a contraindication to LT.[38] However, colonization of the respiratory tract with resistant strains of *Pseudomonas Aeruginosa* or *Burkholderia Cepacian* is a risk factor for the development of lethal postoperative infections. The presence of these resistant strains is considered an absolute contraindication to LT by many experienced transplant centers. LT should not be performed in patients with active lung disease. The contraindications for LT in patients with CF are (i) presence of a long-term history of recurrent intermittent pulmonary infections

that compromise pulmonary functions, (ii) colonization of the respiratory tract with Burkholderia Cepacia and other resistant microbial organisms, (iii) high resting partial carbon dioxide pressure on arterial blood gas analysis, (iv) presence of extensive pulmonary fibrosis determined by imaging techniques, (v) presence of severe pulmonary fibrosis with right ventricular dysfunction. Satisfactory results have been obtained with combined lung-liver or heart-lung-liver transplantation in patients with CF-associated cirrhosis and severe pulmonary disease or pulmonary hypertension.[40]

LT should be performed early in the course of CF-related end-stage liver disease. Molmenti and colleagues[38] have analyzed the timing of LT in CF-related liver disease in pediatric patient; and their results suggest that the results of early LT led to better outcomes than the patients who waited longer before the transplant procedure. In patients who died, there was failure to thrive, poor nutritional status, severe pancreas exocrine insufficiency, and higher meconium ileus incidence.[38] The long-term survival rate after LT in patients with CF was reported to be around 75%. Pulmonary infections and sepsis are very lethal complications encountered after LT and the most common cause of mortality in the post-transplant period is the pulmonary complications in these patients. Pediatric patients have better survival when compared to adults.[40]

Ij) Ductal Plaque Malformations

In pediatric patients, this group of diseases includes autosomal recessive polycystic renal disease, Caroli disease, isolated hepatic fibrosis. LT is indicated in patients with recurrent cholangitis, biliary sepsis, portal hypertension causing hepatopulmonary syndrome or variceal bleeding. Treatment options include isolated LT, combined liver-kidney transplantation, and isolated renal transplantation. Isolated liver transplantation depends on the severity of renal failure in the patients.[8]

Ik) Erythropoietic protoporphyria

The most common form of porphyria is erythropoietic protoporphyria (EPP), which is caused by a defect in the activity of ferrochelatase (FECH), the enzyme in the last step of the heme biosynthesis.[41] Protoporphyrin is the precursor of porphyrin, and in patients with EPP, it starts to accumulate in the bone marrow and is then taken up by the liver. EPP causes edema of the skin, erythema; and occasionally, it can lead to severe photosensitivity characterized by tender vesicular and bullous lesions of the skin. In addition, in some patients, it can lead to severe protoporphyrin related liver failure that requires LT.[42] Although the first LT for EPP was reported in 1980, LT is not curative in this disease because protoporphyrin is continuously produced leading to liver allograft damage.[43,44] Bone marrow transplantation is required before LT to prevent the development of liver allograft dysfunction. Before LT, protoporphyria levels should be reduced by administration of intravenous hemin, plasma exchange, or ursodeoxycholic acid and cholestyramine treatment. Neuropathy has been reported after the transplant procedure and should be monitored closely because it may lead to pulmonary insufficiency and pulmonary functions should be supported in these patients following LT.[5] In the post-transplant period, 1-, 5-, 10-year survival rates are 77%, 66% and 66%, respectively. The recurrence rate of the disease in the liver allograft is reported to be 69%.[44]

II- Monogenic diseases that do not cause liver parenchymal damage

IIa) Urea Cycle Defects

The urea cycle is a vital pathway that produces urea as the end product of protein catabolism. It facilitates the detoxification and excretion of nitrogenous metabolites from the body.[5] Urea cycle defects (UCD) result from defect in major enzymes in the metabolic pathway that disrupt the detoxification of nitrogenous compounds and the synthesis of arginine synthesis. The major enzymes that are defective in UCD are carbamoyl phosphate synthetase 1 (CPS 1), ornithine transcarbamylase (OTC), arginosuccinate synthetase (ASS), arginosuccinate lyase and arginase 1 (ARG1). In this section, we will try to summarize the clinical and physiopathological characteristics of the functional defects of these enzymes. OTC deficiency is an X-linked trait, while others are autosomal recessive diseases. Clinical signs can be seen in any age group, but are frequently observed in the neonatal period of life. Typically, affected neonates present with decreased feeding, lethargy, nausea, and tachypnea starting from hours to days after birth. It progresses rapidly and may lead to death. Irreversible neurological damage can be seen in UCD and therefore, LT should be considered early in the evaluation of treatment options.[1,5,8] The goal of UCD treatment is to minimize ammonia production while maintaining the nitrogen balance. For this reason, dietary modification, control of plasma ammonia and arginine by administering sodium benzoate and sodium/glycerol phenylbutyrate, and supplementing essential amino acids are necessary in the management of these patients. Nevertheless, patients with UCD experience episodes of hyperammonemia crisis during the periods of catabolic stress.

In UCD, OTC deficiency is the most common indication for LT. LT has been successfully performed for citrullinemia, CPS1, arginosuccinate lyase, and argininemia deficiencies. In

patients with UCD, hyperammonemia episodes are completely cured following LT, and dietary protein restriction is no longer necessary after the transplant procedure.[45]

Heterozygous individuals can be living donors for LT in patients with UCD. Only in OTC, asymptomatic female donors can be living donors after through metabolic evaluation. Symptomatic females should not be evaluated as living donors.[45]

In the perioperative period, fasting and surgical stress may result in excessive protein catabolism and hyperammonemia. Strict surveillance of nitrogen balance is necessary in order to provide metabolic complications and associated morbidity in patients. Preoperative lipid solutions and glucose infusion and minimization of the fasting period are recommended. Hyperammonemia should be corrected and ammonia- excreting medication should be administered whenever necessary. Close monitoring of ammonia levels in the perioperative and postoperative periods is recommended to support metabolic balance in patients.[46]

In patients with OTC and CPS1 deficiency, extrahepatic citrulline is insufficient and monitorization of plasma citrulline level is recommended and any deficiency should be supplemented.[5] The 1- and 5- year survival rates of patients following LT for UCD are reported to be 97% and 89%, respectively.[47]

IIb) Organic Acidemia

This is a group of metabolic disorders in which the metabolism of amino acid (especially the branched-chain amino acids) is disrupted and there is an excessive accumulation of organic acids in the urine or blood of the individuals.[48] It is classified into 5 subtypes: branched-chain organic acidemia, multi-carboxylase deficiencies, glutaric acidemia, fatty acid oxidation defects, and inborn errors of energy metabolism. The most common forms of the disease are methylmalonic acidemia (MMA), propionic acidemia (PA), and isovaleric acidemia. Other forms of the organic acidemia are maple syrup urine disease (MSUD), homocystinuria, biotin-resistant 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) lyase deficiency and ketothiolase deficiency and glutaric acidemia type I (GA I). The typical clinical presentation includes toxic encephalitis-related neurologic symptoms such as vomiting, reduced feeding and seizures, abnormal tonus and lethargy that can progress to coma. In older children, deterioration of intellectual function, ataxia, or other focal neurologic symptoms can be observed. Prolonged fasting can trigger a catabolic state that may exacerbate the metabolic crisis. Therefore, in patients with organic acidemia, if a procedure requiring fasting is planned, than the patients should be hospitalized and strict metabolic surveillance along with intravenous glucose infusion is recommended. LT may be considered in the treatment of patients with organic acidemia who have intractable hyperammonemia, failure to thrive, or severely reduced quality of life.[8]

In classic MMA and PA, the infants usually present with lethargy that can progress to coma or death, vomiting, metabolic acidosis, hyperammonemia, and encephalopathy. Medical and dietary modifications include protein restriction, supplementation of nutritional formulations, maintenance of acid base balance, carnitine supplementation, and antibiotic therapy to reduce enteric propionic bacteria. There is a continuous systemic production of toxic metabolites resulting in an inability to control the disease despite aggressive medical therapy. Typically, during the natural course of organic acidemia, metabolic decompensation can be seen during prolonged periods of catabolic stress, which may be life-threatening if the episodes are recurrent. Mental retardation, hypotonia, cardiomyopathy, pancreatitis, and osteopenia are common in PA. MMA has similar findings in addition to renal insufficiency. Patients remains at risk for progression of neurologic symptoms and progressive renal failure despite a successful liver transplantation.[1,5,8] In patients with MMA, serum MMA concentrations and the protein intolerance are corrected after LT, but not completely reversed. Dietary restriction should continue and strict monitorization of the toxic metabolites, acid/base balance, and the renal functions is recommended following LT. Renal dysfunction is progressive and central nervous system damage is irreversible once it develops; therefore, LT should be considered early in the course of the disease.[5]

MSUD is the result of a disorder of branched-chain amino acid (BCAA) metabolism. It is an autosomal recessive disease and the defective enzyme is branched-chain α-ketoacid dehydrogenase (BCKAD), which is the enzyme of the rate-limiting second step of branched-chain amino acids such as leucine, isoleucine, and valine. The affected infant has a sweet odor to the urine hence the name maple syrup urine disease has been given.[49] The affected individuals have neurocognitive deterioration and catabolic stress induces metabolic decompensation in the patients. Although, LT does not reverse the existing damage that has occurred, it reverses the metabolic effects and results in prevention of progression of neurological damage and reduces the need for protein restriction in the diet.[50,51]

Episodes of metabolic decompensation create a risk factor for the patients. For this reason, it is necessary to minimize the fasting period before surgery and monitorization of the serum leucine, acid/base balance, serum glucose, and fluid-electrolyte

levels.[52] Plasma BCAA can be monitored perioperatively; studies have shown that isoleucine levels have return to normal 6 hours after the liver transplant procedure. Nutritional support can be modified according to the serum levels of the BCAA.[5]

Since LT does not cure the underlying enzymatic defect, metabolic decompensation has been reported after liver transplantation under severe physiological stress.[51] The explanted liver of the patients with MSUD can be used for domino liver transplantation to non-MSUD recipients because the extrahepatic tissue of the recipient will have a fully functional enzyme and it will not create a potential risk.[1,5,8]

IIc) Defects of Fatty Acid Oxidation

Fatty acid oxidation is a critical energy supply for high energy-consuming tissues such as heart and skeletal muscle. Furthermore, it is the only metabolic pathway that supplies the necessary energy during the periods of fasting. Defects in the fatty acid oxidation pathway are a serious congenital disease that leads to hypoketotic hypoglycemia, acute encephalopathy, cardiomyopathy, rhabdomyolysis, metabolic acidosis, and disturbances in liver functions. Fever, nausea and vomiting, and prolonged fasting may lead to lethal complications. Hypoketotic hypoglycemia and symptoms resembling Reye syndrome can be seen in infancy, and this condition can persist through childhood and adolescence.[8] There may be recurrent episodes of acute liver failure. Dietary modification is the main treatment modality. Treatment of acute episodes includes infusion of 10 mg/kg/min to maintain the serum glucose levels above 100 mg/dl. Dietary modification reverses acute liver failure episodes and controls almost all the symptoms. Strict dietary modification can reduce the need for LT. Liver transplantation is the treatment of choice in patients with fulminant hepatic failure who are unresponsive to suitable dietary modification.[53]

IId) Primary Hyperoxaluria Type 1

Primary hyperoxaluria type 1 is an autosomal recessive metabolic disorder that results from a defect in a hepatic peroxisomal enzyme; alanine-glyoxylate aminotransferase which is encoded by the AGXT gene. Overproduction of oxalate and excessive urinary excretion causes recurrent nephrolithiasis, nephrocalcinosis, which may lead to end-stage renal failure. Accumulation of calcium oxalate can be seen in the blood vessels, retina, heart, peripheral nerves, bone and bone marrow and the synovial fluid. Liver is the organ that detoxifies glyoxylate and prevents calcium oxalate accumulation, for this reason LT is curative in these patients. Planning LT early in the course of the disease prevents progression of damage to the kidneys and other organs.[1,5,8] Patients with renal failure should receive combined liver-kidney transplantation. In patients with mild to moderate renal damage that does not require dialysis, isolated liver transplantation can be considered for the treatment of the metabolic disease.[54,55] If combined liver and renal transplantation is not possible, staged transplantation can be a therapeutic choice. Liver transplantation should be chosen as the first transplant procedure in patients with even minimal renal function. Heterozygous healthy living related donors can be chosen for partial liver transplantation and good results have been reported. Renal oxalate accumulation can be seen after combined liver-kidney transplantation, and a multidisciplinary approach is required for the management of these patients.[5]

IIe) Familial Hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant disease that caused by a mutation in the gene encoding the low-density lipoprotein (LDL) receptor. Hypercholesterolemia, atherosclerosis, and ischemic heart disease have been reported to present in childhood. Xanthomas are yellow skin lesions and are common in these patients. Mutations in *LDLR*, *APOB,* or *PCSK9* genes have been identified in patients with familial hypercholesterolemia. Patients with *LDLR* homozygous mutations have very high LDL levels, severe atherosclerosis that is unresponsive to standard anti-hyperlipidemic therapy.[56] Failure to control LDL levels with accurate medical therapy is an indication for LT. LT reverses the xanthoma and also, causes a rapid decline in the plasma LDL levels. Effective treatment with statins and treatment modalities such as plasmapheresis have significantly decreased the need for LT in hypercholesterolemia. Currently, hypercholesterolemia is a treatment option for individuals with homozygous *LDLR* mutations.[56,57]

Before LT, a comprehensive and thorough cardiac evaluation is required to assess the level of atherosclerosis. Coronary artery bypass surgery is required in patients with severe atherosclerosis. Liver transplantation early in the course can minimize the incidence of cardiovascular disease and is associated with better outcomes.[58]

The long-term effects of LT on cardiovascular diseases are not clear, and statin treatment continues despite a significant decrease in plasma LDL levels.[56,59] In patients with familial hypercholesterolemia and ischemic heart disease, combined liver-heat transplantation has excellent results.[60,61] Ten-year patient survival rates have been reported to exceed 70%.[62]

IIf) Mitochondrial Hepatopathies and Systemic Mitochondrial Diseases

Mitochondrial diseases are a spectrum of diseases that include acute liver failure, severe neuromuscular deficits, multiorgan involvement or isolated liver disease. Medical therapy includes coenzyme Q10 and a vitamin cocktail to support the electron transport chain. The effect of medical therapy on mitochondrial hepatopathy is undetermined.[63,64] The clinical characteristics of mitochondrial hepatopathies are well defined and there is no definitive treatment for these patients which leads to poor outcomes.[65,66] Currently, the role of LT in the treatment of mitochondrial hepatopathy is controversial. LT is not suitable for pediatric patients with severe extrahepatic mitochondrial disease with multiorgan involvement. Extrahepatic mitochondrial disease can develop after LT, and the relatives of the patients should be informed of this possibility.[8]

IIg) Crigler-Najjar Type I

Crigler-Najjar Type I syndrome is an autosomal recessive disease resulting from the deficiency of uridine diphosphate glucuronosyltransferase. It presents as unconjugated hyperbilirubinemia during infancy. The initial therapy of the patients aims at preventing kernicterus; and to achieve this, treatment options include exchange transfusion and long-term phototherapy. During hyperbilirubinemia crisis, the optimal duration of phototherapy is 20-24 hours. Furthermore, the optimal duration of phototherapy to maintain acceptable bilirubin levels is 8-12 hours. LT is the gold standard and the only treatment option before irreversible brain damage develops.[1,5,8] The reason for this is because of the fact that bilirubin levels normalize after LT and if LT can be performed before irreversible brain damage, neurological damage can be stopped and the existing deficits may be reversed.[5] It is important to maintain the bilirubin-albumin balance before liver transplantation and drugs that affect bilirubin and albumin conjugation should be avoided.

IIh) Acute Intermittent Porphyria

Acute intermittent porphyria (AIP) is a rare metabolic disorder including the heme biosynthesis. AIP results from the deficiency of the enzyme hydroxymethylbilane synthase (HMBS), which is also known as porphobilinogen deaminase (PBGD). Once the heme biosynthesis is disrupted, porphobilinogen starts to accumulate in the cytoplasm of the cells. Acute episodes are characterized by abdominal pain and tachycardia which are neurovisceral crises that are seen during the natural course of the disease. Treatment includes avoidance of agents that trigger the acute attacks. Treatment of the patients during the acute attacks includes hydration of the patients and administration of glucose and hemin. LT is therapeutic for patients with recurrent and lethal acute attacks. LT prevents the development of irreversible neurological damage.[5] Renal dysfunction is a common complication of AIP in the long term. Combined liver-kidney transplantation has been reported to be successful in these patients.[67-69] Renal dysfunction is very important for the perioperative period during LT. The transplant surgeons should be aware that the patients with AIP may have subtle renal dysfunction, and fluid-electrolyte balance and the blood pressure of the patients should be closely monitored.[5]

IIj) Factor VII Deficiency

Factor VII deficiency is treated with fresh frozen plasma, cryoprecipitate, and recombinant Factor VIIa.[8,70]

IIk) Protein C Deficiency

Purpura fulminans is the severe form of Protein C deficiency that is seen in the neonates and it is usually life-threatening. In older children, its clinical characteristics are heterogeneous. The risk of vascular thrombosis is high.[8,71] Medical therapy is usually the treatment of choice for both Protein C and Factor VII deficiencies. LT is indicated in patients with complications or in individuals whom the medical therapy option has failed.[8]

Author contribution

Concept: FİV; Design: FİV; Data Collection or processing: FİV; Analysis or interpretation: FİV; Literature Search: FİV; Writing: FİV. All authors reviewed the results and approved the final version of the article.

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Original Article

The effects of early nutritional contents in premature infants on the development and severity of retinopathy: A retrospective case-control study

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ABSTRACT

Objectives: Poor weight gain during the first weeks of life in preterm infants is associated with the risk of developing retinopathy of prematurity (ROP). Our study aimed to evaluate the effect of energy, macronutrient intake, and weight gain during the first 4 weeks of life on the risk of ROP.

Methods: This study was designed as a single-center, retrospective, and case-control trial. Premature babies, born before the 30th week of gestation, were included in our study. The infants were divided into three groups: control (without ROP), mild ROP, and severe ROP groups. Possible nutritional risk factors for ROP were compared.

Results: ROP was found in 32 (29.5%) of 108 infants included in this study. The first enteral feeding day, full enteral feeding day, and total duration of parenteral nutrition were significantly higher in infants with level 3-4 ROP than the others ($p < 0.05$). The risk of severe ROP increased in infants who gained less than 8 g/day and who received less than 91 kcal/kg of calories ($p < 0.05$). It was found that infants with severe ROP received statistically ($p < 0.05$) less breast milk, but there was no difference in formula intake ($p > 0.05$).

Conclusions: We showed that low energy intake during the first 4 weeks of life is an independent risk factor for severe ROP. This implies that the provision of adequate energy from parenteral and enteral sources during the first 4 weeks of life may be an effective method to reduce the risk of severe ROP in preterm infants.

Keywords: Retinopathy of prematurity, total parenteral nutrition, weight gain, premature

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading causes of morbidity in preterm infants. As a preventable condition, the diagnosis and monitoring of ROP are especially important. ROP is defined as abnormal vascular proliferation in the vascular-avascular junction of the immature retina, which has not completed vascularization.[1] The reported prevalence of ROP among preterm infants under 27 weeks of gestational age is between 10% and 35% in developed countries.[2] In a multicenter study conducted by the TR-ROP Study Group including 6115 infants at 69 neonatal intensive care units in Türkiye, the prevalence of ROP regardless of the stage was 27% and that of severe ROP was 6.7%.[3]

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Although the etiopathogenesis of ROP has not been fully elucidated, certain mechanisms have been proposed and numerous risk factors have been identified.[4-9] Risk factors for ROP have been studied in detail and identified risk factors include gestational age, low birth weight, hypoxia, oxygen therapy, hypercapnia, asphyxia, hypothermia, acidosis, mechanical ventilation longer than a week, bronchopulmonary dysplasia (BPD), intracranial bleeding, transfusion, hyperglycemia, erythropoietin (EPO) use, and multiple pregnancies.[7-9] In addition, in recent years, there has been a focus on the possible link between nutrition and ROP. Among other risk factors, malnutrition and late initiation of feeding have been examined.[10-12] It has been determined that in preterm infants with low caloric intake or delayed feeding after birth, vascularization is interrupted due to a decrease in the synthesis of growth factors, especially insulin-like growth factor 1 (IGF-1). A comparison of infants with ROP showed that those with lower energy intake had more advanced ROP.[10] Based on the hypothesis that ROP is less prevalent or less severe in infants who are well and aggressively fed during the first 28 days of life, this study was conducted to identify risk factors for ROP and to investigate the relationship between ROP and nutrition.

METHODS

This single-center, retrospective, case-control study included preterm infants born before 30 weeks of gestation in the Hacettepe University Faculty of Medicine Neonatal Unit between the years 2000 and 2016. The infants were divided into 3 groups: the non-ROP healthy control group, the early-stage ROP group, and the advanced ROP group. Variables that may influence the development of ROP, such as energy intake in the first 28 days, drugs used, procedures performed, and duration of mechanical ventilation, were compared among the groups.

Study population

The study included preterm infants born before 30 weeks of gestation and admitted to Hacettepe University Faculty of Medicine for treatment between 2000 and 2016. Infants born before 2000, those with congenital anomalies, those whose files did not include information on caloric intake in the first 28 days or had missing drug and weight data, and those who died were excluded.

Data collection

Data were collected by retrospective chart review. Clinical data related to the patient included sex, date of birth, gestational age at birth, birth weight, length, and head circumference, mode of delivery, presence of meconium aspiration, premature rupture of the membranes (PROM), complications of prematurity (e.g., necrotizing enterocolitis [NEC], ROP, intracranial hemorrhage), positive blood culture, sepsis, pneumonia, pneumothorax, patent ductus arteriosus (PDA) and history of medical/surgical PDA treatment, retinopathy, age at retinopathy diagnosis (days), and total hospital length of stay. Respiratory data included the presence of perinatal hypoxia, Apgar score, need for neonatal resuscitation, a number of surfactant treatments in the intensive care unit, duration and mode of mechanical ventilation (e.g., high-frequency oscillatory ventilation [HFOV], synchronized intermittent mandatory ventilation [SIMV], nasal continuous positive airway pressure [CPAP]), and presence of apnea requiring medical treatment. Nutritional data included amounts of parenteral and enteral feeding during the first 28 days, calorie, protein, and fat intake in the first 28 days, duration of total parenteral nutrition (TPN), and rate of weight gain. Maternal data were collected on gravity and parity, diseases, pregnancy-related conditions, and history of drug use. These parameters were evaluated both in patients diagnosed with ROP and in the control group.

ROP staging was done according to the definition in the TR-ROP study.[3] NEC was diagnosed in the presence of excessive gastric residual volume, abdominal distention, positive fecal occult blood test, radiological findings of pneumatosis intestinalis or portal vein gas, and discontinuation of oral intake for these reasons.[11] Patients who received more than 30% oxygen and were given surfactant were evaluated as having respiratory distress syndrome (RDS)[12], and those who needed oxygen for at least 28 days were evaluated as bronchopulmonary dysplasia (BPD).[13] Patients were classified as having PDA if evaluated as hemodynamically significant by a cardiologist and received medical treatment/ligation. Sepsis was diagnosed in patients exhibiting clinical signs and elevated acute phase reactants, with or without a positive culture.

After collecting the data, enteral protein, lipid, and calorie intake were calculated based on the following values per 100 ml: 1.4 g protein, 3.9 g lipids, and 67 kcal for breast milk; 2.2 g protein, 3.9 g lipids, and 82 kcal for fortified breast milk, and 1.4 g protein, 3.9 g lipids, and 80 kcal for formula.[14]

For infants on TPN, the daily energy intake was calculated as the sum of glucose and lipid intake was calculated. Calories were calculated using the following formula: (glucose infusion rate × 5.7) + (Lipids [g/kg] × 9).[15]

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY). Descriptive statistics were expressed as number (n) and percentage (%) for categorical variables, mean and standard deviation for normally distributed numerical variables, and median and (minimum–maximum) values for non-normally distributed numerical data. The Chi-square test was used to compare categorical data such as sex and the presence of comorbidities. The normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons of numerical data between groups were done with one-way ANOVA for normally distributed data and the Kruskal–Wallis test for non-normally distributed data, followed by post-hoc Dunn's test for pairwise comparisons to determine which group differed from the others. Receiver operating characteristic (ROC) curves were used for diagnostic data. Based on a 95% confidence interval, p-values less than 0.05 were accepted as significant.

RESULTS

The medical records of 745 patients born before 30 weeks of gestational age at our center between 2000 and 2016 were examined. Of these, 307 patients were excluded from the study due to mortality and 330 due to missing data or congenital anomalies. The 108 preterm infants included in the study were divided into 3 groups: 76 (70.3%) without ROP, 12 (11.1%) with early (stage 1-2) ROP, and 20 (18.5%) with advanced (stage 3-4) ROP. The median gestational age was 28 (24–29.4) weeks, the median birth weight was 1080 g (590–1750), and 51% were female.

There were no significant differences in maternal characteristics between the groups ($p>0.05$). Comparisons of patient characteristics between the groups are shown in Table 1. No significant differences were observed in gestational age at birth, sex, head circumference, small for gestational age (SGA) status, intraventricular hemorrhage (IVH), NEC, pneumonia, sepsis, positive blood culture, or C-reactive protein (CRP) level ($p>0.05$). However, the advanced ROP group had a more frequent need for resuscitation, lower Apgar scores, more frequent hypotension and need for inotropes, lower birth weight, longer duration of mechanical ventilation, and higher prevalence of RDS, hemodynamically significant PDA, and BPD ($p<0.05$).

No significant differences were found between the groups in terms of methylxanthine therapy, erythropoietin (EPO) therapy, phototherapy, platelet suspension therapy, fresh frozen plasma support, oxygen support, or discharge time. However, the stage 3-4 ROP group had significantly different rates of insulin use, intravenous immunoglobulin (IVIg) therapy, erythrocyte suspension therapy, and steroid therapy for the treatment of BPD compared to the other groups ($p>0.05$). The number of erythrocyte suspensions differed significantly between the stage 3-4 ROP group and the group without ROP, but there was no difference compared to the stage 1-2 ROP group ($p>0.05$).

The feeding characteristics and energy intake calculations of the groups are shown in Table 2. Infants in the advanced ROP group began enteral feeding later, received TPN support longer, and achieved full enteral feeding later than the other groups. The timing of first enteral feeding differed significantly between the advanced ROP and control groups only, whereas the duration of TPN and achievement of full enteral feeding differed significantly between the advanced ROP and control groups and between the advanced ROP and stage 1-2 ROP groups. There was no difference between the groups in terms of the amount of formula fed during enteral feeding, but the advanced ROP group received significantly less breast milk. Enteral protein intake (g/kg/day) was also significantly lower in the advanced ROP group, while there was no difference between the groups in terms of total (IV + enteral) protein intake (g/kg/day). Enteral and total (IV + enteral) lipid intakes (g/kg/day) were significantly lower in the advanced ROP group compared to the other groups.

The advanced ROP group also showed significantly lower total energy intake (kcal/kg/day) in the first 28 days, daily weight gain in the first 28 days, and weight on day 28 compared to the other groups.

Timing of full enteral feeding, duration of TPN, enteral total protein and lipid intake, total energy intake, daily weight gain, and weight on day 28 differed significantly between the advanced ROP group and the stage 1-2 ROP group, but not between the stage 1-2 ROP and control groups.

Comparisons of total protein and lipid intake, total daily energy intake (kcal/kg/day), weight gain, and weight on day 28 are shown in Figure 1. ROC curve analyses for the diagnostic use of the association between the development of severe ROP and daily weight gain and total daily energy intake are shown in Figure 2. Neither parameter was found to have a diagnostic value in ROP. A weight gain of 8.3 g/day had a 60% sensitivity and a 75% specificity for advanced ROP. When patients were grouped according to weight gain of 8.3 g/day, it was found that the risk of severe ROP was significantly increased in those with weight gain <8.3 g/day ($p=0.004$). A daily caloric intake of 91.4 kcal/kg/day had a 70% sensitivity and a 61% specificity for the development of advanced ROP.

Table 1. Comparison of neonatal characteristics between the groups				
Variable	**No ROP (n=76)**	**Stage 1-2 ROP (n=12)**	**Stage 3-4 ROP (n=20)**	**P value**
Gestational age (weeks)*	28 (26-29)	28 (26-29)	27 (24-29)	0.184
Sex				
Male	41 (53.90)	4 (33.30)	8 (40)	0.277
Female	35 (46.10)	8 (66.70)	12 (60)	
Birth weight (g) *	1100 (600-1750)	1155 (670-1480)	895 (590-1400)[+]	**0.027**
Resuscitation	4 (5.30)	0 (0)	6 (30)[·]	**0.002**
Hypotension	14 (18.40)	1 (8.30)	11 (55)[+]	**0.021**
Inotrope use	30 (39.50)	2 (16.70)	18 (90)[+]	**<0.001**
SGA	11 (14.50)	2 (16.70)	2 (10)	0.087
Apgar score (5-min)*	8 (2-10)	9 (7-10)	7 (3-9)[+]	**0.036**
Head circumference (cm)*	26.10 (23-30)	27 (22.50-29)	25.15 (22-28.50)	0.672
IVH	12 (15.80)	2 (16.70)	6 (30)	0.353
NEC	10 (13.20)	1 (8.30)	5 (25)	0.428
PDA	27 (35.50)	4 (33.30)	13 (65)[+]	**0.049**
Pneumonia	34 (44.70)	3 (25)	11 (55)	0.254
Sepsis	38 (50)	4 (33.30)	12 (60)	0.340
Positive blood culture	20 (36.30)	3 (25)	4 (20)	0.845
RDS	43 (56.60)	3 (25)	17 (85)[+]	**0.003**
Surfactant treatments*	1 (0-5)	0 (0-3)[+]	1 (0-6)	**0.007**
Ventilatory support (days)				
MV	4.05 (0-28)	2.08 (0-14)	13.45 (0-28)[+]	<0.001
HFOV	0.12 (0-8)	0	1.05 (0-16)[+]	0.047
CPAP	6.03 (0-21)	2.92 (0-9)	3.40 (0-9)	0.107
Free O_2	7.36 (0-26)	5.83 (0-15)	5.65 (0-21)	0.784
Total	17.55 (0-28)	10.83 (0-27)	23.55 (5-28)[+]	**0.002**
CRP (mg/dL)*	0.26 (0.01-13.50)	0.18 (0.01-5.87)	0.26 (0.01-6.82)	0.778
BPD	26 (34.20)	4 (33.30)	17 (85)	**<0.001**
Day of discharge*	39 (6-76)	41 (17-53)	61 (31-150)[+]	**<0.001**

Data are presented as *Median (minimum–maximum), other data are shown as n (%).
[+] Shows which group is significantly different.
Bold p values indicate statistical significance.

Table 2. Comparison of feeding characteristics between the groups				
Variable	**No ROP (n=76)**	**Stage 1-2 ROP (n=12)**	**Stage 3-4 ROP (n=20)**	**P value**
First day of enteral feeding*	2 (1-25)	3 (1-5)	4 (1-40)$^{+}$	**0.002**
Day of total enteral feeding*	15 (5-67)	13 (8-39)	31 (8-64)$^{+}$	**0.005**
Duration of TPN (days)*	14.50 (0-50)	12 (6-37)	27.50 (8-63)$^{+}$	**0.006**
Feeding (ml)*				
Breast milk	2084 (0-5896)	2041 (643-6319)	701 (0-6440)$^{+}$	**0.006**
Formula	19 (0-3585)	6 (0-2066)	17 (0-2852)	0.735
Enteral protein** (g/kg/day)	1.30±0.77	1.50 ±0.86	0.80±0.85^{+}	**0.006**
Enteral lipids** (g/kg/day)	3.07±1.44	3.52±1.42	1.90±1.86^{+}	**0.040**
Total protein (g/kg/day)**	3.04±0.98	3.45±0.80	2.91±1.16	0.373
Total lipids (g/kg/day)**	3.89±1.27	4.46±1.07	2.94^{+}±1.73	**0.007**
Total energy (kcal/kg/day)**	96.40±21	107.3 ±18.50	79.4±29^{+}	**0.003**
Weight gain (g/day)*	12.73 (-5.56-26.79)	13.91 (0-22.78)	6.96^{+} (-3.93-17.5)	**0.010**
Weight on day 28*	1470 (810-1860)	1535 (1010-1790)	1050^{+} (780-1850)	**<0.001**

Data are presented as *median (minimum–maximum), **mean±standard deviation values. $^{+}$ Shows which group is significantly different. Bold p values indicate statistical significance.

DISCUSSION

In this study, the effect of aggressive feeding on ROP in premature babies born less than 30 weeks was examined. It was determined that the patients' total lipid intake, total energy, and daily weight gain rate in the first 28 days were effective in the development of ROP. In addition, it is known that there are many comorbidities that affect the development of ROP. In our patient group, it would not be correct to attribute the development of severe ROP to nutritional parameters alone. What we want to draw attention to is that energy and lipid deficiency may be particularly effective in the development of severe ROP, so more caution should be taken in high-risk premature babies.

Although many risk factors for ROP have been identified, the strongest associations are with low birth weight and gestational age.[16] In a study comparing patients with active and inactive ROP, risk factors for active ROP, in particular, were birth before 26.4 weeks, low birth weight (mean 874 g), low Apgar scores, and longer duration of oxygen therapy.[7] In a study of preterm infants born before 28 weeks of gestation, low birth weight and gestational age were found to be independent risk factors for ROP. Other identified risk factors include intracranial hemorrhage, infections, BPD, hypoxia, hemodynamically significant cardiovascular conditions (e.g., PDA), transfusions, and multiple pregnancies.[17] Although the size of our sample group was acceptable compared to other studies, we were unable to perform logistic regression analysis of early and advanced ROP due to the small number of patients in the subgroup analysis. Therefore, pairwise comparisons were made between the groups. No significant difference was found between the groups in terms of gestational age. Infants with advanced ROP had higher rates of resuscitation, hypotension, inotrope use, insulin use, IVIg use, erythrocyte suspension therapy, PDA, RDS, and BPD, as well as a longer need for antibiotic therapy compared to the other groups. In general, the identified risk factors are interrelated and are common conditions in preterm infants. The prevalence of parameters such as hypoglycemia, RDS, hypotension, and infection increases with decreasing gestational age and birth weight. Although not found to be a significant factor in the present study, SGA has also been reported as a risk factor for ROP.[18]

In recent years, studies on the link between nutrition and ROP have highlighted the importance of providing breast milk, enteral nutrition, and adequate caloric support, and there is an extensive literature on this subject.[19-26] Although some studies have indicated that there is no significant link between breast milk and ROP[23-27], the protective and beneficial effects of breast milk are widely recognized. Coşkun et al.[20] reported low IGF-1 levels in 127 premature infants and emphasized that breast milk and good nutrition increase IGF-1 levels and may protect against ROP. Manzoni et al.[19] found a lower prevalence of ROP in infants who were breastfed compared to formula-fed infants (3.5% vs. 15.8%) and discussed the protective effect of breastfeeding against ROP (any stage). It is also known that premature infants

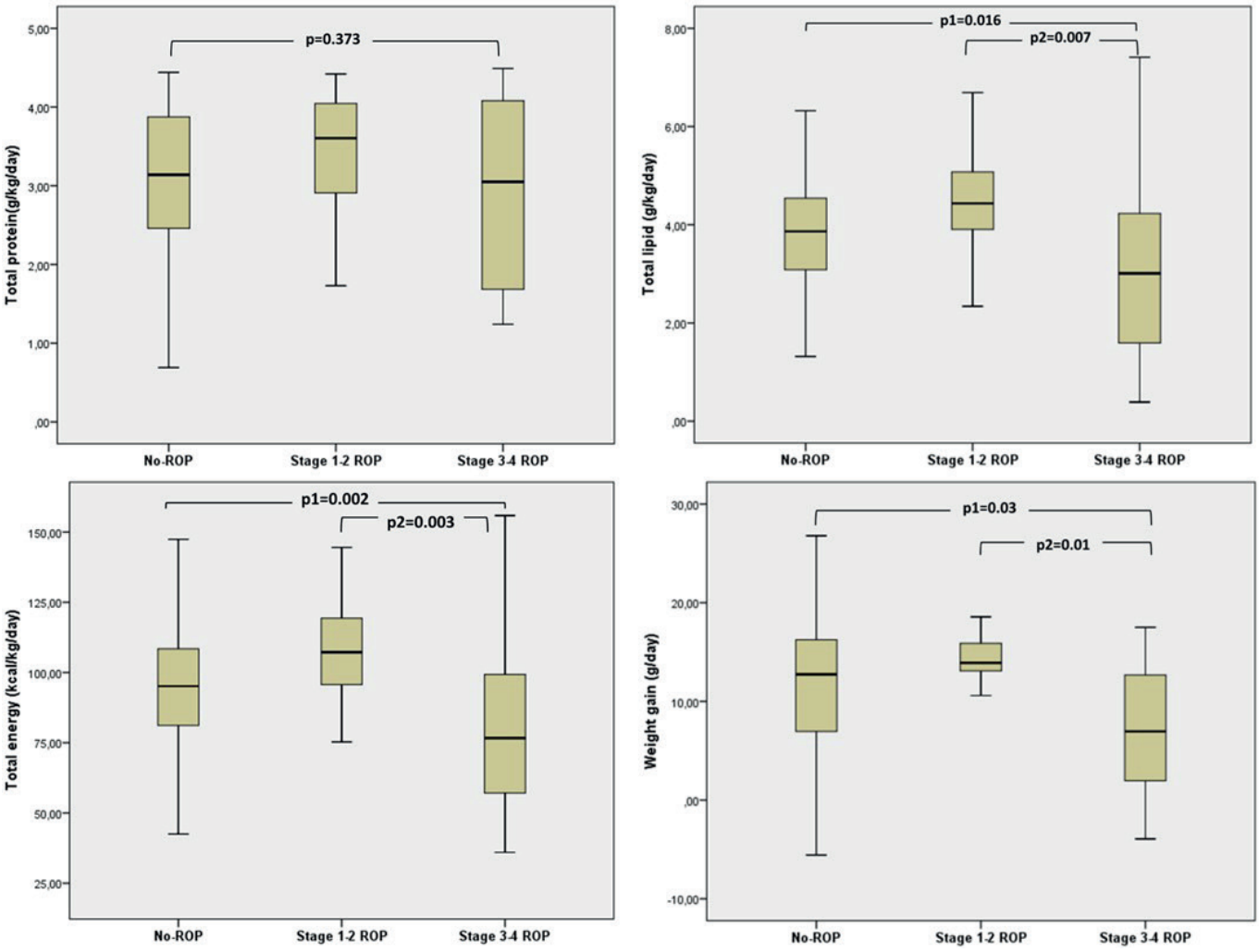
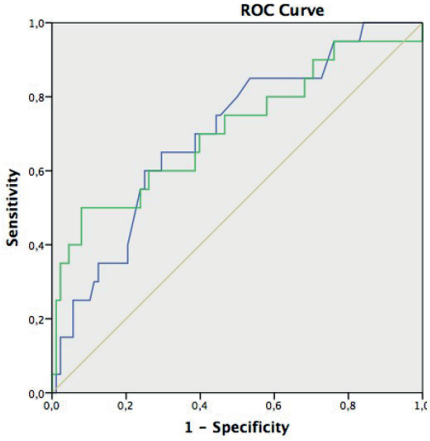


Figure 1. Comparison of total protein (g/kg/day), lipids (g/kg/day), and total calories (kcal/kg/day) and weight gain (g/day) between the groups

p1: Comparison of control group and stage 3-4 ROP group. **p2:** Comparison of stage 1-2 ROP and stage 3-4 ROP group

are exposed to oxidative stress because their antioxidant systems are still immature. Breast milk has been shown previously to provide partial protection against oxidative stress, and it has been suggested that it may also play a protective role against ROP via this mechanism.[24,25] In another study, 400 premature infants were divided into 2 groups, one fed breast milk, and the other fed formula, and rates of ROP and NEC were lower in the group that was fed breast milk.[26] In contrast, a meta-analysis including 21819 infants from 67 studies showed that breast milk was only found to be effective in observational studies and that randomized trials yielded different results.[25] In the present study, there was no significant difference between the ROP groups in terms of the number and proportion of infants who were fed enterally with breast milk. The median day of first enteral feeding was later for infants in the stage 3-4 ROP group (day 4) compared to the control group (day 2) and the stage 1-2 ROP group (day 3). Similarly, the achievement of full enteral feeding occurred later in infants with stage 3-4 ROP (day 31) compared to the control group and infants with stage 1-2 ROP (day 15 and day 13, respectively).

Determining the fluid, electrolyte, and energy requirements of preterm infants according to their birth weight and postnatal age requires precise calculations.[28] The goals of parenteral nutrition are to provide sufficient calories for energy and growth; to provide carbohydrates and lipids together in order to prevent hypoglycemia and meet energy requirements; to maintain a positive nitrogen balance to promote growth, and to this end, to provide adequate protein that also contains essential amino acids; to provide fatty acids in order to prevent essential fatty acid



	Sensitivity	Specificity	AUC	95% Cl		*p**
				Lower	Upper	
Weight gain of 8.3 g/day	60	75	0.702	0.57	0.82	**0.05**
Daily caloric intake of 91.4 kcal/kg/day	70	61	0.711	0.57	0.85	**0.03**

Figure 2. Relationship of daily weight gain and total daily energy intake (kcal/kg/day) to severe ROP development

***Green curve:** Daily weight gain, **Blue curve:** Daily calories per kg weight, **Brown curve:** Reference

deficiency and to increase non-protein-derived energy; and to provide the minerals, electrolytes, and trace elements necessary for growth.[29] Current publications demonstrate that aggressive feeding of preterm infants (earlier initiation of intravenous and enteral nutrition, earlier transition to full enteral feeding) is safe and effective.[29-33]

The literature on the relationship between aggressive nutrition and ROP includes a prospective randomized controlled trial by Can et al.[33] in which infants born before 32 weeks of gestation were divided into two groups, one that received conventional parenteral nutrition and one that received aggressive parenteral nutrition. The incidence of ROP was lower and IGF-1 levels were higher in the group that received aggressive nutrition. A meta-analysis showed that aggressive parenteral nutrition reduced the risk of ROP of any stage but did not reduce the risk of advanced ROP. The present study compared the nutritional characteristics of newborns with no ROP, early ROP, and advanced ROP. Nutritionally aggressive feeding of preterm infants has been implemented in our center since 2006. We observed that the incidence of ROP decreased in the first 4–5 years after increasing nutrition and did not change over the next 4–5 years. The decrease in mortality rate and the consistently low incidence of ROP since 2010 are related to both the improvement of other risk factors for ROP in premature infants and overly aggressive nutrition. Daily oral protein, oral lipid, total lipid, and total energy intakes, weight gain, and weight on day 28 were lower in infants with advanced ROP compared to the other groups, consistent with the literature. Preterm infants with advanced ROP have longer hospital stays and lower daily weight gain compared to other infants. In this study, weight gain in the advanced ROP group was 7.21 g/day, compared with 11.75 g/day and 13.88 g/day in the non-ROP and early ROP groups, respectively. Daily energy intake by weight was 96.4 kcal/kg/day in the control group, 107.3 kcal/kg/day in the stage 1-2 ROP group, and 79.4 kcal/kg/day in the stage 3-4 ROP group. However, we do not believe that the daily weight gain and energy intake found in this study should be compared with those in the literature, because the weight, gestational age, sex, ethnicity, and comorbidities (PDA, NEC, BPD, treatments received) of the sample groups will show substantial heterogeneity among the studies. Therefore, we believe it is more appropriate to interpret our sample group within itself.

Unlike other studies in the literature, we performed ROC curve analysis to evaluate whether daily weight gain and total energy intake could be used for diagnostic purposes in ROP. Based on our results, we concluded that these parameters are not useful in the diagnosis of ROP. On the other hand, we concluded that daily weight gain and total energy intake may play a predictive role in the diagnosis of advanced (stage 3-4) ROP. However, the sensitivity and specificity values for both parameters did not exceed 60–70%. Although the result was statistically significant, these two values alone were shown to have relatively low sensitivity and specificity for clinical use. Nevertheless, we would like to emphasize that premature infants with a daily weight gain of 8 g and a daily energy intake of less than 91.4 kcal/kg/day require closer monitoring for the development of ROP. Using daily weight gain or energy intake in combination with other risk factors may provide more reliable results. In addition, our findings need to be corroborated by studies with larger sample sizes.

Study Limitations

This study has a retrospective study design. Despite the adequate sample size compared to other studies, multivariate regression analysis could not be performed due to the small number of patients in the subgroups. The patient groups were not entirely similar in terms of comorbidities due to the clinical heterogeneity of preterm infants. There was no difference in terms of gestational age between the severe ROP group and the

other groups, but birth weights were lower in the severe ROP group, which is one of the limitations of our study. The study was planned as an analytical case-control study, and long-term follow-up results are not known. .

Ethical approval

This study has been approved by the Hacettepe University Ethics Committee (approval number 0016/137). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: MŞA, ŞY; Concept: MŞA, ŞY; Design: MŞA, ŞY; Data Collection or Processing: MŞA, ŞY; Analysis or Interpretation: MŞA, ŞY; Literature Search: MŞA, ŞY; Writing: MŞA, ŞY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of newborn screening for biotinidase deficiency from southeastern region of Türkiye

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ABSTRACT

Objective: Biotinidase deficiency (BD) is an autosomal recessive inherited metabolic disorder. Biotin plays an important role as a cofactor of carboxylases. BD is categorized into two groups as profound and partial deficiency based on serum quantitative biotinidase enzyme activity (BA). Clinical manifestations are highly variable, ranging from severe metabolic acidosis to asymptomatic.

Methods: Patients who were referred to the pediatric metabolism department due to the suspicion of BD are retrospectively retrieved. This study was conducted between 2019 to 2021 at Cengiz Gökçek Children's Hospital. The values of quantitative BA, below 30% were defined as deficiency, 10-30% were defined as partial deficiency (PBD), and below 10% were defined as profound deficiency (PFBD). Molecular analysis was performed on the patients. Quantitative analysis of the BA and BTD genes supported the diagnosis. Patients who were misdiagnosed with BD were classified as a false-positive group.

Results: A total of 255 patient files were retrospectively evaluated. 211 patients were included. The median age at presentation of the patients was 27±26,2 days (range: 10-240). 48.3% (n=102) patients in the BD group, and 51.7 % (n=109) patients in the false-positive group. Consanguinity was significantly higher in the BD group (p=0.002). The rate of patients with normal quantitative BA was 54.5% (n=115), PBD was 36.5% (n=77) and PFBD was 9% (n=19). For a variety of reasons, BTD gene analysis was carried out in 79.6% (n=168) of patients. 35.1% (n=59) of them were homozygous mutations, 13.1% (n=22) were compound heterozygous mutations, 40.5% were (n=68) heterozygous mutations, and 11.3% (n=19) were normal. Genetic analysis was consistent with BD in 26.8% (n=25/93) of patients with normal quantitative BA.

Conclusion: BA measurement may be affected by technical reasons. Because sensitivity and specificity of quantitative BA measurement methods are still controversial and inconsistent, confirmation of results by molecular analysis may reduce the risk of misdiagnosis.

Keywords: Biotinidase deficiency, biotin, newborn screening

INTRODUCTION

Biotinidase deficiency (OMIM #253260, BD) is an autosomal recessive inherited metabolic disorder. BD causes a defect in the metabolism of the vitamin biotin, resulting in a deficiency of biotin-dependent enzymes.[1] Biotinidase (EC 3.5.1.12, *amidohydrolase biotinidase*, *BTD*) is the enzyme that enables the formation of free biotin as a result of degradation and recycling of biocytin or biotinyl-peptides as well as dietary protein-bound sources. Biotin plays an important role as a cofactor of carboxylases, which are propionyl-CoA carboxylase, methyl-crotonyl-CoA carboxylase, pyruvate carboxylase, and acetyl-CoA carboxylase.[2] These carboxylases are involved in amino acid catabolism, fatty acid synthesis, and gluconeogenesis steps. All

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the mitochondrial carboxylase activities are impaired in BD. The inability of the carboxylases to function as a result of BD leads to clinical features.[3]

BD is categorized into two groups, profound and partial deficiency based on serum quantitative biotinidase enzyme activity (BA), which is less than 10% and 10-30% of regular serum activity, respectively.[4] Clinical manifestations are highly variable, ranging from severe metabolic acidosis to asymptomatic. Clinical features of symptomatic patients include neurologic manifestations such as developmental delay, seizures, hearing loss, optic atrophy, ataxia and immunologic manifestations, and cutaneous lesions such as alopecia, conjunctivitis, and skin rash.[1] In contrast to partial deficiency, where symptoms are anticipated to be mild at any age from childhood to adulthood, profound BD is predicted to present with severe symptoms early in life. Additionally, PBD is frequently asymptomatic, but may manifest symptoms in response to stressful events such as infection.[5]

Oral biotin therapy is recommended as 5-20mg/day in BD. Biotin treatment, started in the asymptomatic period, prevents the symptoms of biotinidase deficiency and also provides improvement in affected patients.[6,7] If the treatment is not administered in time, hearing and vision problems as well as neurological damage may not be fully recovered and may persist.[1,7] In Türkiye, BD has been screened under the National Newborn Screening (NBS) Program since October 2008.[8] The aim is to diagnose the patients in the asymptomatic period and to follow them without sequelae. The incidence of biotinidase deficiency ranges from 1:4500 to 1:62500 in countries that screen for this condition.[9] In some studies, the false- positivity rates of biotinidase activity screening with NBS are high. In the Netherlands, only 7% of those identified by screening were diagnosed with a profound biotinidase deficiency.[9] This study aims to identify false-positive NBS results in order to increase awareness of accurate diagnosis and follow-up of patients identified by the screening program.

MATERIALS AND METHODS

Patients who were referred to the pediatric metabolism department in Cengiz Gökçek Children's Hospital, located in the southeastern region of Türkiye, with the suspicion of BD between 2019-2021 were included in the study. Gender, age at admission, consanguinity, dried blood spot (DBS) biotinidase activity (BA), quantitative BA, and molecular analysis results were retrieved from the medical records.

The local ethics committee of Gaziantep University approved the study protocol.

Quantitative biotinidase activity and molecular analysis were performed at the first admission of patients with biotinidase activity <65 IU in DBS. DBS BA was analyzed by fluorometric immunoassay while quantitative BA was analyzed by spectrophotometric method. The determined BA values were calculated as "%" enzyme activity. Values below 30% were defined as a deficiency, below 10% defined as a profound deficiency (PFBD), and 10-30% defined as a partial deficiency (PBD). For patients with more than one value, the mean value was calculated. The diagnosis was confirmed by the quantitative BA and BTD gene analysis. BA results of DBS and quantitative and molecular analysis results were compared. Patients who were not diagnosed with BD were considered the false-positive group.

Categorical data were expressed as numbers and percentages (%), while numerical data were expressed as medians (minimum-maximum). The Chi-square test was used to compare categorical data. When comparing the numerical data from two or more independent groups, the data were first examined for parametric properties. In this study, descriptive statistics and Shapiro-Wilk tests were used. Numerical data from two or more independent groups that did not show parametric properties, were compared using the Mann-Whitney U test or Kruskal-Wallis test. All analyses were calculated with the Statistical Package for the Social Sciences 23.0 (IBM SPSS) statistical program. A p value <0.05 was considered statistically significant.

RESULTS

A total of 255 patient files were retrospectively evaluated. Patients who were previously referred to other metabolic centers, did not have a quantitative BA result, or had a suspicious diagnosis were excluded. A total of 211 patients were included, 99 (46.9%) females and 112 (53.1%) males. The median age at the presentation of the patients was 27 days (range:10-240). When the patients were evaluated with both activity and genetic results (final result), 51.7% (n=109) were normal, and 48.3% (n=102) patients were diagnosed with BD. A total of 49.8% (n=105) patients had consanguine marriages, including 60.8% (n=62) patients in the BD group and 39.4% (n=43) patients in the false-positive group. The rate of consanguinity was significantly higher in the BD group (p=0.002) (Table 1). Median BA in DBS and quantitative BA in plasma were 52.5 IU (2-65) and 33.0% (2.3-88%), respectively. When patients were categorized based on quantitative analysis, 54.5% (n=115) had normal quantitative BA, 36.5% (n=77) had PBD, and 9% (n=19) had PFBD. For a variety of reasons, BTD gene analysis was performed in 79.6% (n=168) of the patients. Homozygous mutations were found in 35.1% (n=59) of patients, compound heterozygous mutations in %13 (n=22) of patients, and heterozygous mutations in 40.4%

Table 1. Demographic findings of patients			
Final Result	**BD (n=102)**	***Normal (n=109)**	**p**
Male/female	58 (%52.9) / 48 (%47.1)	58 (%53.2) / 51 (%46.8)	0.969
Admission Age -day (median)	23.0 (11.0-85.0)	21.0 (10.0-240.0)	0.392
Consanguinity	62 (%60.8)	43 (%39.4)	0.002
*False-positive group			

(n=68) of patients. The BTD gene was normal in 11.3% (n=19) of the patients (Figure 1).

The patients were analyzed according to molecular analysis and BA. The relationships between BA and molecular analysis and consanguinity were evaluated (Table 2-3).

Despite the activity level being normal, 26.8% (n=25) of the patients had genetic data that were consistent with the diagnosis of BD. Of these, 21.5% (n=20) had homozygous mutations and 5.3% (n=5) had compound heterozygous mutations. However, heterozygous mutations were detected in 18.6% (n=14) of PBD patients, whereas no mutation was detected in 6.6% (n=5) of them. All PFBD patients had mutations in both alleles (Table 2).

DISCUSSION

BD is an autosomal recessive metabolic disorder resulting in inadequacy of biotin. Several neurological and dermatological disorders may occur. BD was first described in 1983 by Wolf et al.[10] Heard et al. described a method to measure biotinidase activity by colorimetric assessment using a DBS card in 1984.[11] The first NBS pilot NBS program for BD was carried out in US, in 1984.[12] Since 2008, NBS for BD has been launched in Türkiye. A research found that the incidence of BD was 1:60089 within the scope of the NBS program in 14 countries between 1984-1990.[13] The incidence of BD was 1:61,000 according to the 30-year screening data in Italy[14], but it was 1:5,996 in another part of the city site.[15] Although the incidence of BD in Türkiye is 1:11614[16], a recent study in the city of Şanlıurfa in southeastern Türkiye, where consanguineous marriages are more common, found the incidence to be 1:1177.[17] These results demonstrate that there are regional differences in incidence.

The main purpose of screening is to identify profound deficiencies with irreversible severe symptoms if left untreated and to prevent the onset of symptoms through early treatment. A neonatal screening program for BD is critical because of the

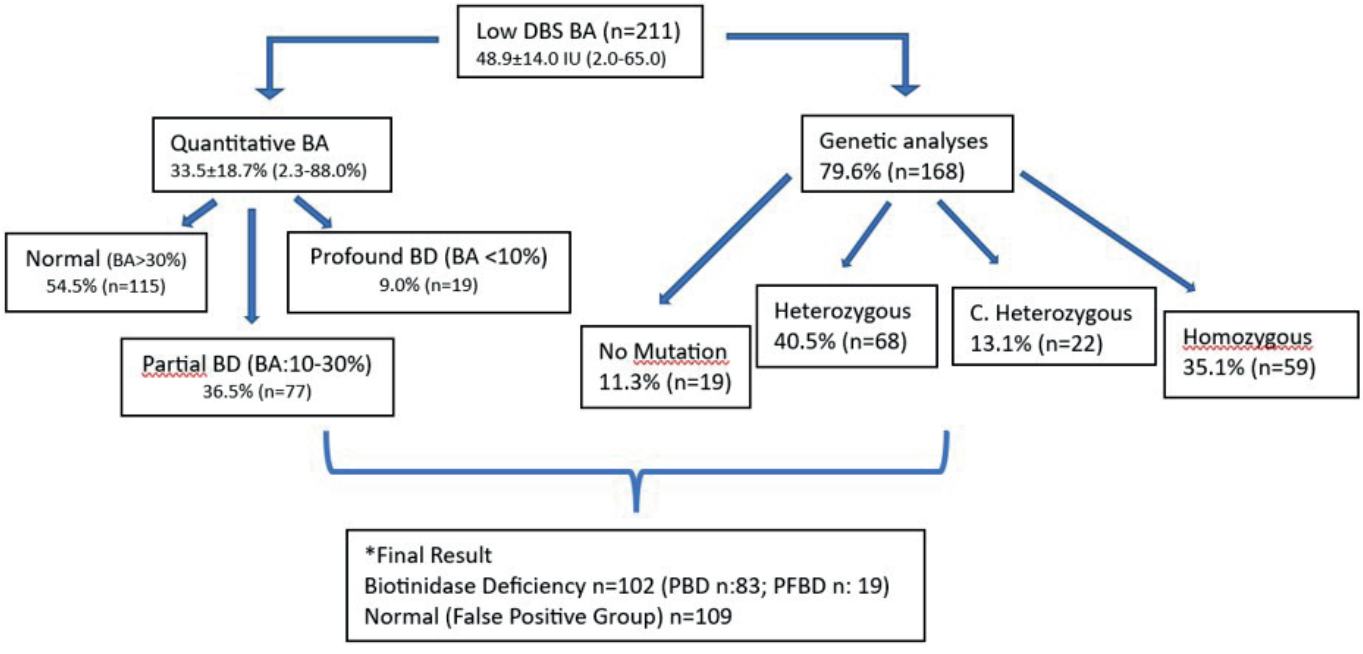

Figure 1. Evaluation scheme of patients referred from newborn screening

*The result determined after evaluating both genetic analysis and biotinidase activity of the patients

Table 2. Classification by biotinidase activity					
Quantitative BA	**Normal**	**PBD**	**PFBD**	***Combined BD**	**p**
Genetik					
N	14 (%15.1)	5 (%8.5)	0 (%0.0)	5 (%6.7)	<0.001[1]
Heterozygous	54 (%58.1)	14 (%23.7)	0 (%0.0)	14 (%18.7)	
Compound Heterozygous	5 (%5.4)	13 (%22.0)	4 (%25.0)	17 (%22.7)	
Homozygous	20 (%21.5)	27 (%45.8)	12 (%75.0)	39 (%52.0)	
**Total	93	59	16	75	
DBS Mean	55.0 (40.0-65.0)	49.0 (6.0-65.0)	14.0 (2.0-55.5)	46.8 (2.0-65.0)	<0.001[2]

*Combined BD= PBD+PFBD
**Total= The total number of quantitative BA in the genetically analyzed patients.
[1]The heterozygous mutation was more frequent in normal quantitative BA group and the homozygous mutation was more frequent in PFBD group.
[2]Normal vs PBD, Normal vs PFBD, PBD vs PFBD were significant (p<0.001)

Table 3. Classification by consanguinity				
Consanguinity	**Exist**	**No**	**Total**	**p**
Genetic				
No mutation	8 (42.1%)	11 (57.9%)	19	<0.001[1]
Heterozygous	26 (38.2%)	42 (61.8%)	68	
Compound Heterozygous	11 (50%)	11 (50%)	22	
Homozygous	44 (74.6%)	15 (25.4%)	59	
Total	89	79	168	
Quantitative type				
PBD	40 (51.9%)	37 (48.1%)		0.344
PFBD	12 (63.2%)	7 (36.8%)		
Normal	53 (46.1%)	62 (53.9%)		
Total	62 (100%)	44 (100%)		

[1]Consanguinity was detected more frequently in patients with homozygous mutations detected by genetic analysis.

early initiation of biotin therapy. Therefore, the age of admission becomes vital. In the studies conducted at Dokuz Eylül University[18] and Ege University[19] Hospitals (both located in the western region of Türkiye), the median age at presentation of patients with biotinidase deficiency who were referred from the NBS program was 15 days (5-46), 1.20 months (0.4–5), respectively. The median age of admission in this study was 22 days (10-240). Another metabolic center in the same region as our study also found the mean age of admission to be 96.30 (min-max, 2-828) days.[17] The reason for the late age at first presentation in these two studies conducted in the same period and region may be the lack of awareness about NBS, poor socioeconomic conditions, and inadequate care at the time of referral to the hospital. The patients in this study were asymptomatic, whereas the study by Kazanasmaz et al.[17], in which the age at first presentation was higher, reported the presence of symptomatic patients in the PFBD group. This highlights the importance of early diagnosis.

There was no statistically significant difference between males and females in this study. In other studies carried out in Türkiye, it has been observed that the ratio of females to males is similar.[17-21] As this is an autosomal recessive disease, there are no significant differences between the genders, as would be expected. The rate of consanguineous marriage is as high as 24% in Türkiye. The consanguinity rate was found to be 49.8% in all patients included in this study. It was 60.8% in the BD group and 39.4% in the false-positive group and was found to be statistically significant (p=0.002). It is known that the consanguinity rate in the southeastern region of Türkiye is higher than the average in Türkiye, which is 43%. In similar studies conducted in the same

region, Şanlıurfa study group detected consanguinity rate as 38.5% in BD group while 13.5% in false negative group (p=0.002), Adana group detected consanguinity rate in all enrolled patients as 61.5%. All these consanguinity rates are significantly higher than the Turkish average.[17,21,22] This situation can be explained by the autosomal recessive inheritance of the disease, as well as the higher consanguineous marriage rate in the region.

DBS BA mean is 48.9(2-65), and quantitative BA 33.5% (2.3-88%). There were 77(36.5%) patients in the PBD group and 19(9%) in the PFBD group (Figure 1). Consistent with the literature, partial and profound BD patients' rates are similar to this study.[17,19,21]

In the consanguineous marriage group, molecular analysis revealed 29.1% (n=26) heterozygous and 12.3% (n=11) compound heterozygous mutations (p<0.001). Furthermore, heterozygous mutations were detected in 40% (n=68) and compound heterozygous mutations in 13% (n=22) of the patients in this cohort. In a study conducted in the same region, compound heterozygous mutations were detected in 43% (n=89) of patients.[21] These results indicate the high carrier frequency in the BTD gene.

When the patients were evaluated with both activity and molecular analyses, it was demonstrated that 109 patients (51.7%) – false-positive group – were normal, and 102 patients (48.3%) were diagnosed with BD. In patients recalled with suspicion of BD, In Italy 17% (n=49/287) of patients[15] and 3.9% (n=18/461) of patients[14], and in the Netherlands 42% (n=111/261) of patients[9] were diagnosed as BD. In Türkiye, Kazanasmaz et al. demonstrate 57.3% false-positive results.[17] These results suggest that the laboratory measurement method is controversial and not sufficient. In Türkiye, DBS BA is analyzed by fluoroscopic immune assay and generally spectrophotometric method is used for the measurement of quantitative biotinidase activity in recalled suspicion of BD patients. However, in a study, conducted in Türkiye in 2016, spectrophotometric and fluorometric methods were compared in the evaluation of biotinidase deficiency. It was reported that the fluorometric method is more sensitive.[23] In this study, this conclusion could be reached as the samples were studied in the same center, which will increase the quality of the sample. It raises the question of whether sample quality is degraded during the transfer of DBS cards to public health laboratories.

In this study, molecular analysis confirmed BD in all PFBD. In cases of partial deficiency with molecular analysis (n=59), any mutation was detected in 8.5% (n=5) of patients, and heterozygous mutations were detected in 23.7% (n=14) of patients. In addition, the genetic result was compatible with BD in %26.8 (n=25) of the patients with normal quantitative BA levels whose molecular analysis was performed (n=93). Of these patients, 20% (n=5/25) have compound heterozygous mutations and 80% (n=20/25) have homozygous mutations. In the study conducted in the Netherlands, 54% (n=50) of the 92 patients, who were referred with suspicion of BD, were diagnosed. 66% (n=61) of 92 the patients have molecular analysis. Of these, 7 of 21 patients with normal quantitative BA were heterozygous, and the other 7 had compound heterozygous mutations.[9]

CONCLUSIONS

Regarding all these results, it may be considered that there is residual enzyme activity in patients with compound heterozygous mutation and biotinidase activity may be borderline low in carriers. These results demonstrate us that the diagnosis of BD should be confirmed via molecular analysis. Since BA may be affected by technical reasons and the sensitivity and specificity of measurement methods are still controversial and inconsistent, this study predicts that confirming results by molecular analysis will reduce the risk of misdiagnosis.

Therefore, all patients referred for suspected BD within the scope of the newborn screening program should have access to molecular analysis by healthcare providers.

Limitations of this study

Because the laboratory where the genetic analysis was performed was in a different area from the center where the patients were enrolled, the molecular analysis could not be carried out in all patients. MLPA analysis could not be performed in heterozygous patients due to technical incompetence.

Ethical approval

This study has been approved by the Gaziantep University Clinical Research Ethics Committee (approval date 04.11.2020, number 2020/367). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: EG; Concept: EG; Design: EG; Data Collection or Processing: EG; Analysis or Interpretation: EG; Literature Search: EG; Writing: EG. All authors reviewed the results and approved the final version of the article.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Non-perforated cardiac tamponade associated with a central venous catheter in a premature infant with extremely low birth weight

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ABSTRACT

Central venous catheterization is almost routinely used in neonatal intensive care, especially in premature and extremely low-birth-weight infants. One of the rare but life-threatening complications is pericardial effusion and cardiac tamponade. In addition to perforation, tamponade may develop with osmotic damage of the fluid administered. This article presents a case of cardiac tamponade due to central venous catheterization in an extremely low birth weight newborn.

Keywords: Cardiac tamponade, central venous catheter, premature, pericardiocentesis

INTRODUCTION

Central venous catheters are used to provide safe access to intravenous fluid and antibiotic therapy, total parenteral nutrition, and blood collection in low birth weight and sick newborns. They are often placed as the first step in the management of infants hospitalized in the neonatal intensive care unit. During and after central catheter placement, several complications have been observed, including catheter fracture, migration, and dislodgement that may result in occlusion, catheter-related infection, thrombosis, and also vessel wall perforation.[1,2]

Pericardial effusion following umbilical venous catheterization is a rare complication.[1] It may occur with the perforation of the atrial wall by the catheter or by osmotic effect without mechanical damage.[2,3] Cardiac tamponade is a life-threatening condition associated with massive pericardial effusion that can cause hemodynamic instability, low cardiac output, severe hypotension, and mortality in the newborn. Early diagnosis and pericardiocentesis are lifesaving.[3]

We aimed to present the management of central venous catheter-associated cardiac tamponade in a premature infant.

CASE

A 750 g female baby born from a 36-year-old healthy mother at 28+4 weeks of gestation by cesarean section was admitted to the neonatal intensive care unit for respiratory distress. After she had been intubated, respiratory distress syndrome developed, and then she was operated for necrotizing enterocolitis.

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A 28-gauge peripheral central venous catheter (PICC) was placed through the left basilic vein on postnatal day 19. After placement, the position of the catheter was confirmed by chest radiography, and the catheter tip was found at the junction of the superior vena cava and right atrium. Circulatory disturbance and hypotension (36/12/22 mmHg) developed on postnatal day 23, 4 days after catheter placement. Dopamine infusion was started at a dose of 5 mcg/kg/min. Ventilator parameters (frequency and FiO_2) were increased to maintain oxygen saturation above 92%. When echocardiography was performed on the patient, who was found to have cardiomegaly on chest radiography, subcostal examination revealed 10 mm of fluid accumulation in the pericardial space and collapse of the right ventricle in diastole and the right atrium in systole was observed (Figure 1, 2).

The patient was evaluated as cardiac tamponade and 25 ml of clear fluid was drained during pericardiocentesis with echocardiography. 2-3 leukocytes/mm^3 and rare erythrocytes were observed in the fluid cell count. There was no microbiological growth in the fluid sample taken. The pericardial fluid was biochemically similar to the total parenteral nutrition she was receiving (glucose 708 mg/dl, LDH 17 U/L, albumin 0.1 g/dl).

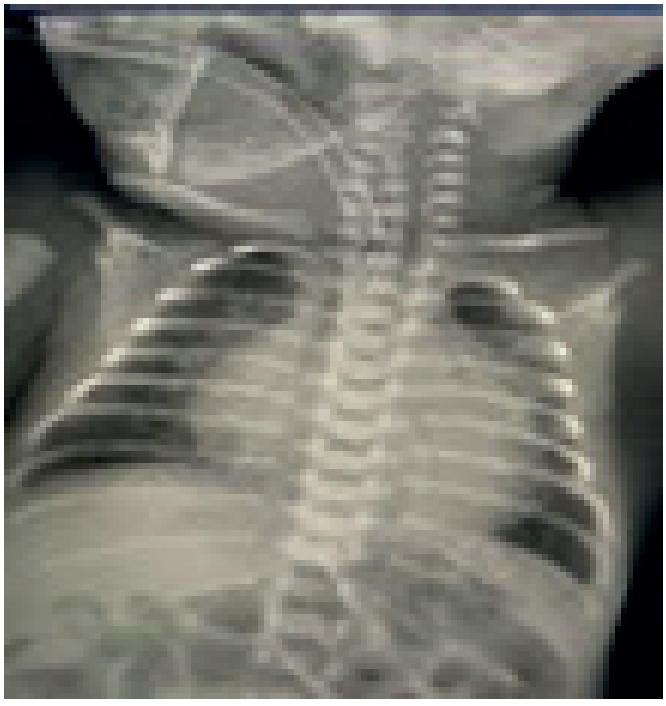

Figure 1. Chest x-ray showing increase of the cardiac area

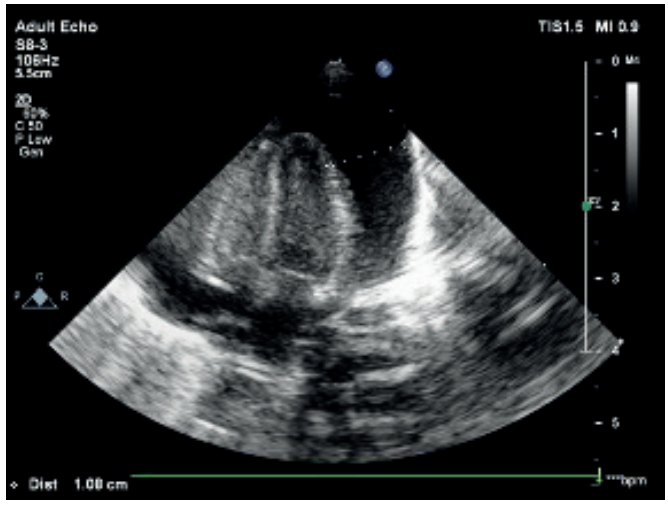

Figure 2. Four chamber echocardiography view showing a significant pericardial effusion

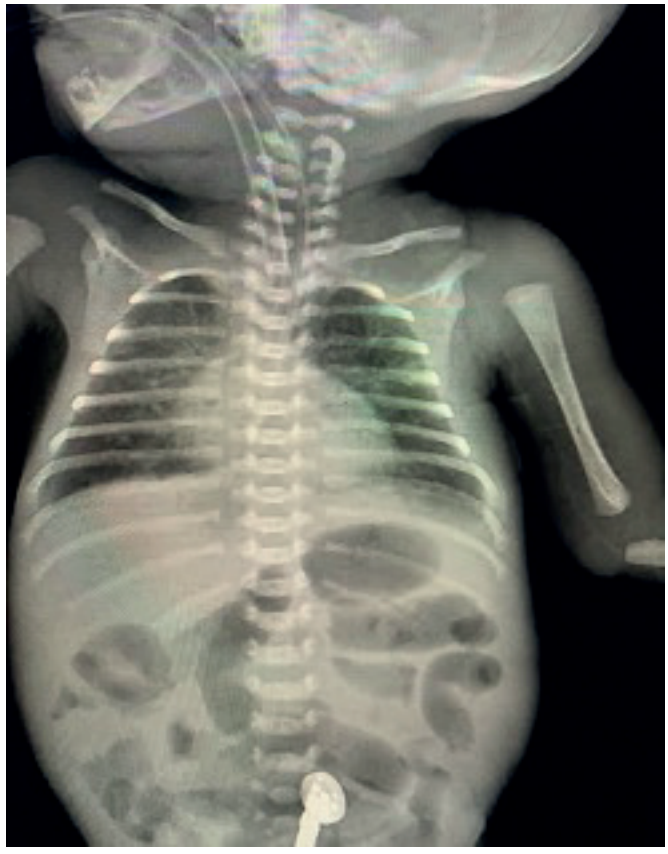

Figure 3. Chest X-ray after pericardiocentesis

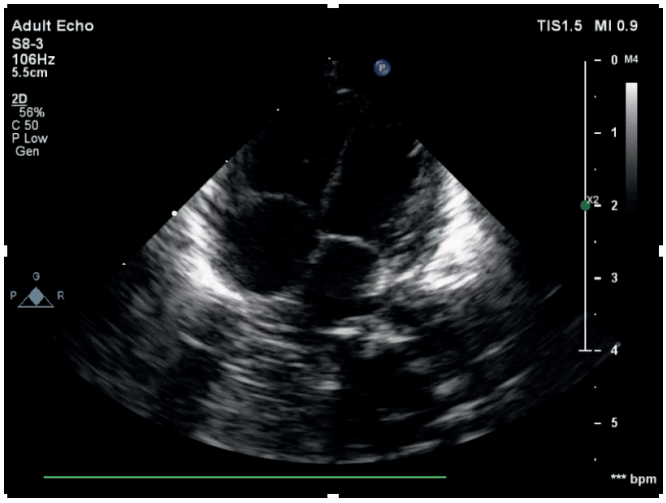

Figure 4. Four chamber echocardiography view after pericardiocentesis

After pericardiocentesis, the catheter was withdrawn 1 cm. Saline contrast echocardiography was performed and the catheter was left in place to be used when no transition between the pericardial leaves was observed. The catheter tip was checked with a chest radiograph (Figure 3). No pericardial effusion was observed on follow-up echocardiography (Figure 4).

DISCUSSION

Central venous catheters are widely used in neonatal intensive care units to provide total parenteral nutrition, especially in premature newborns.[4] In addition to the convenience it provides, it may lead to complications such as catheter-related infection, cardiac arrhythmia, intracardiac thrombosis, embolism, endocarditis, myocardial perforation, pleural effusion, and pericardial effusion.[5]

Pericardial effusion and cardiac tamponade, which are life-threatening complications, occur with catheter misplacement or dislodgement and are frequently observed on the 3rd day after insertion.[6] To prevent this, the recommended position for the catheter tip is at the junction of the inferior vena cava and the right atrium. The position of the catheter tip is determined by radiography both during insertion and at follow-up.[3] The 2001 Manchester Report recommended that all central venous catheters placed in newborns, especially for total parenteral nutrition, should be left outside the borders of the heart on chest radiography.[7] In addition, when autopsy reports were examined, it was thought that hyperosmolar fluid may cause osmotic damage to the endothelium and lead to effusion formation without mechanical damage to the catheter. The presence of non-hemorrhagic pericardial fluid samples with biochemical characteristics similar to TPN supports this hypothesis.[6]

In our case, cardiac tamponade developed on the 4th day after catheter placement. The catheter tip was seen in the right atrium on echocardiography, although it was seen in the appropriate position on the chest radiograph taken on the day of insertion. After pericardiocentesis, the catheter tip was withdrawn and checked by saline contrast echocardiography and no passage was observed. The catheter was continued to be used and the effusion did not reoccur in the follow-up.

In conclusion, central venous catheters may be dislodged from their proper position in premature patients with weight loss and decreased abdominal circumference. It should be kept in mind that the central catheter may cause cardiac tamponade without perforation. The tip should be followed up with chest radiographs during use, and echocardiography should be performed in case of unexplained clinical deterioration, considering pericardial effusion and cardiac tamponade. In the presence of tamponade, it should be remembered that pericardiocentesis is a life-saving procedure.

Ethical approval

A written informed consent was obtained from the patient's family.

Author contribution

Surgical and Medical Practices: SÖ, RÖ; Concept: SÖ, KY, CK; Design: SÖ, RÖ, CK; Data Collection or Processing: SÖ, SB, NN; Analysis or Interpretation: SÖ, RA, KY; Literature Search: SÖ, RÖ, RA, NN; Writing: SÖ, RÖ, KY, NN. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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