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Acute liver failure in children: 20-year experience

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Background/aims: *We aimed to determine the causes, demographic findings, clinical status, outcomes, and prognostic risk factors of patients with acute liver failure admitted to Hacettepe University Children's Hospital between October 1987 - October 2006.* ***Methods:*** *This retrospective case study included 74 patients with acute liver failure according to the Pediatric Acute Liver Failure Study Group definition.* ***Results:*** *The etiology of acute liver failure was metabolic in 26 (35.1%) and infectious in 21 (28.4%) patients. Sixteen (21.6%) patients had indeterminate causes. Wilson's disease (16/26 patients, 61.5%) was the most frequent metabolic disease, while hepatitis A (14/21 patients, 66.7%) was the most frequent infectious agent. Neurologic functions were normal in 21 (28.4%) patients. Forty-nine (66.2%) patients died and 24 (32.4%) recovered. Two patients underwent liver transplantation. The mortality rate was 82.9% for patients who were not transplanted but fulfilled King's College Hospital criteria and 45.4% for patients who were not suitable for transplantation. This difference was statistically significant (p=0.001). Total bilirubin >5.35 mg/dl, international normalized ratio (INR) >3.66 and prothrombin time >23.5 seconds were shown to be the risk factors to predict death.* ***Conclusions:*** *Metabolic and infectious etiologies were responsible for most of the acute liver failure cases. Clinical encephalopathy may not be present in children.*

Key words: Acute liver failure, Wilson's disease, pediatric

Çocuklarda akut karaciğer yetmezliği: 20 yıllık deneyim

Amaç: *Hacettepe Üniversitesi İhsan Doğramacı Çocuk Hastanesi'ne Ekim 1987- Ekim 2006 yılları arasında akut karaciğer yetmezliği ile başvuran hastalarda nedenlerin, demografik özelliklerin, klinik durumun, sonuçların ve prognostik risk faktörlerinin değerlendirilmesi.* ***Yöntem ve Gereç:*** *Pediatrik Akut Karaciğer Yetmezliği Çalışma Grubu tanımlamasına göre akut karaciğer yetmezliği tanısı almış 74 hasta retrospektif olarak değerlendirilmiştir.* ***Bulgular:*** *Akut karaciğer yetmezliği etiolojisini hastaların 26'sında (% 35,1) metabolik, 21'inde (%28,4) enfeksiyöz nedenler oluşturmaktadır. Onaltı (%21,6) hastada neden belirlenememiştir. En sık metabolik hastalık Wilson hastalığı (16/26 hasta, %61,5) iken, hepatit A (14/21 hasta, %66,7) en sık enfeksiyöz ajan olarak belirlenmiştir. Nörolojik fonksiyonlar 21 hastada (%28,4) normal olarak değerlendirilmiştir. Hastaların 49'u (%66,2) ölmüş, 24'ü (%32,4) iyileşmiştir. İki hastaya karaciğer nakli yapılmıştır. King's College nakil kriterlerini karşılayıp nakil yapılamayan hastalarda ölüm oranı %82,9 iken, kriterleri karşılamayan hastalarda bu oran %45,4 olarak bulunmuştur. Bu farklılık istatistiksel olarak anlamlıdır (p=0,001). Total bilirubin düzeyinin 5,35 mg/dl'nin üzerinde, uluslararası normalleştirilmiş oranın (INR) 3,66'nın ve protrombin zamanının 23,5 saniyenin üzerinde olmasının mortaliteyi belirleyen risk faktörleri olduğu gösterilmiştir.* ***Sonuç:*** *Akut karaciğer yetmezliği vakalarının çoğunda metabolik ve enfeksiyöz nedenler saptanmıştır. Çocuklarda ensefalopatinin klinik bulguları gözlenmeyebilir. Wilson hastalığına bağlı akut karaciğer yetmezliğinin erken tanısının konulmasında tipik klinik ve laboratuvar bulgulardan yararlanılabilinir.*

Anahtar kelimeler: Akut karaciğer yetmezliği, Wilson hastalığı, pediatrik

INTRODUCTION

Acute liver failure (ALF) is a rare but rapidly and frequently mortal condition, characterized by jaundice, coagulopathy, encephalopathy, multiple organ failure, and brain edema in a patient with

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unknown previous liver disease. Different from adults, encephalopathy is a late finding in children. The Pediatric Acute Liver Failure (ALF) Study Group has defined ALF in the case of: 1-having no known evidence of chronic liver disease, 2-biochemical evidence of acute liver injury, and 3-hepatic-based coagulopathy defined as prothrombin time (PT) ≥15 seconds (s) or international normalized ratio (INR) ≥1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or PT ≥20 s or INR ≥2.0 regardless of the presence or absence of clinical hepatic encephalopathy (1).

The etiology includes infectious and metabolic diseases and toxic causes that may differ depending on age and geographical location. Specific diagnosis cannot be made in a majority of patients (2-6). Survival rates have been raised from 15% to 65% with liver transplantation. Thus, it is especially important to decide if the patient is a candidate for liver transplantation. In different studies, etiology, age, neurologic status, prolonged PT, ammonia, bilirubin, and creatinine levels were found to be related to prognosis (3,4,7,8).

The major goal of this study was to identify ALF etiology, clinical and laboratory features, prognosis, and prognostic risk factors in our patients.

MATERIALS AND METHODS

In a 20-year period between October 1987 - October 2006, a total of 74 patients with ALF admitted to Hacettepe University Children's Hospital were included, and their demographic, clinical and laboratory findings were evaluated retrospectively. Patients with 1- no known evidence of chronic liver disease, 2- biochemical evidence of acute liver injury, and 3- hepatic-based coagulopathy defined as PT ≥15 s or INR ≥1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or PT ≥20 s or INR ≥2.0 regardless of the presence or absence of clinical hepatic encephalopathy were considered to have ALF (3).

Patients' age at admission, sex, complaints, and duration of complaints, together with consanguinity between parents, were noted. Ascites, jaundice, hepatomegaly, splenomegaly, edema, and stage of encephalopathy were noted as initial physical findings.

Encephalopathy grade was defined as follows: stage I- mild intellectual loss, sleep reversal; stage II-somnolence, confusion, disturbed orientation, changes in mood, asterixis; stage III- somnolence, no response to verbal stimuli, delirium, hyperreflexia, positive Babinski sign; and stage IV- comatose, decerebrate or decorticate posture, arousable with painful stimuli (IVa), or no response (IVb) (3).

Initial hemoglobin level, white blood cell (WBC) and thrombocyte counts were evaluated. Patients with hemoglobin levels less than reference age normals (9) and with thrombocyte counts <150 x 10^3/μL or scarce platelets in blood smear were considered to be anemic and thrombocytopenic, respectively.

Initial serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, blood urea nitrogen (BUN), creatinine, glucose, blood pH, activated partial thromboplastin time (aPTT), INR, and PT levels were recorded. Blood ammonia levels studied by spectrophotometry (normal: 20-120 μg/dl) at admission were recorded.

After common causes were excluded, non-acetaminophen drug-induced hepatitis was diagnosed if a temporal relationship between exposure to suspected hepatotoxic drug and onset of ALF symptoms was established.

Hepatitis A, B, or C infection was confirmed serologically, and evidence of other viral infections required a positive immunoglobulin M antibody.

Anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), liver-kidney-microsomal antibody (LKM), anti-double stranded DNA (anti-dsDNA), and anti-microsomal antibody (AMA) were checked in clinically suspected patients. The diagnosis of autoimmune hepatitis was established when a patient had >15 points according to the International Autoimmune Hepatitis Group Report scoring system (10).

Metabolic disease investigations consisting of amino acids in blood and urine and reducing substances and organic acids in urine and tandem mass spectrometry were performed in clinically suspected patients. Patients who had three of the following five criteria were diagnosed as Wilson's disease: 24-hour (h) urinary copper level >100 μg/day, positive Kayser-Fleischer ring, serum ceruloplasmin level <20 mg/dl, liver copper content >250 μg/g liver, and a positive family history (11).

Liver tissue samples were analyzed in 44 patients, 3 of which were liver biopsy specimens, while the

others were postmortem necropsy samples. Massive necrosis, fibrosis, central vein necrosis, cholestasis, fat accumulation, hepatitis, and findings related to cirrhosis were evaluated by the same pediatric pathologist.

Patients with positive blood, catheter or urine cultures or pulmonary infiltration during follow-up and patients with positive postmortem cultures were considered to have infection as a complication. Patients with gastrointestinal system bleeding during follow-up were also noted.

Patients with neurologic involvement were classified according to O'Grady classification (12), as hyperacute, acute and subacute when the time between jaundice and emergence of encephalopathy was 7 days, 8-28 days and 29 days-12 weeks, respectively. Days between admission to discharge/death were recorded as the follow-up period. Patients who met the King's College Hospital criteria for liver transplantation at admission (13) and patients who underwent liver transplantation were also noted.

Statistical Methods

Data were analyzed by SPSS for Windows version 11.0. Data are reported as means with standard deviations. Continuous variables were compared with Student's *t* test (or nonparametric Mann-Whitney rank sum test for unpaired data). Categorical variables were compared by chi-squared or Fisher exact test. Statistical significance was established at a p value of <0.05. Receiver operating characteristics (ROC) curves were used for establishing significant cut-off points between groups of risk-determining variants.

RESULTS

Seventy-four patients (39 male, 52.7%) during a 20-year period were included in the study. Median age was 69 months (1 month-17 years). Age distribution was as follows: 7 (9.4%) patients were newborn, 17 (23%) were between 1 month-2 years, 11 (15%) were between 2-5 years, 32 (43.2%) were between 5-12 years, and 7 (9.4%) were >12 years age. Parents of 32 (43.2%) patients were consanguineous.

The most common initial clinical finding was jaundice (61 patients, 82.4%). Hepatomegaly (47 patients, 63.5%), splenomegaly (22 patients, 29.7%), ascites (16 patients, 21.6%), and pretibial edema (16 patients, 21.6%) were the other frequent clinical findings. Neurologic functions of 21 (28.4%) patients were normal, while 8 (10.8%) patients had stage I, 10 (13.5%) had stage II, 10 (13.5%) had stage III, and 25 (33.8%) patients had stage IV encephalopathy. Out of 53 patients who had neurologic dysfunction, 27 (50.9%) patients had hyperacute liver failure, 17 (32.1%) had ALF and 9 (17%) had subacute liver failure according to O'Grady classification.

The initial abnormal laboratory results are listed in Table 1.

Abnormal test results were obtained in blood-urine amino acid tests, reducing substance in urine, tandem mass spectrometer, and organic acid levels in urine at rates of 59%, 72.7%, 77.8%, and 100%, respectively. From these patients, 3 had tyrosinemia and 3 galactosemia.

Metabolic diseases were the most common cause of ALF (26 patients, 35.1%), while infectious causes were identified in 21 (28.4%) patients. The cause of ALF was indeterminate in 16 (21.6%) patients. The etiologies of ALF are listed in Table 2.

The etiology of ALF was investigated according to the first and second 10-year periods, and the incidence of hepatitis A decreased from the rate of 30.2% for the first 10 years to 3.2% for the second 10 years, while incidence of metabolic diseases other than Wilson's disease increased from the rate of 4.6% to 25.9% in the last 10 years.

The etiology of ALF was toxic hepatitis in 4 (5.4%) patients. The hepatotoxic drugs were diphenyl-

Table 1. The initial abnormal laboratory test results of patients

Abnormal laboratory test	Number of patients with abnormal test result/number of tested patients (%)
Anemia	41/74 (55.4)
Thrombocytopenia	16/72 (22.2)
Increased ALT	61/74 (82.4)
Increased AST	71/74 (95.9)
Increased conjugated bilirubin	64/74 (86.5)
Low protein	39/74 (52.7)
Low albumin	61/74 (82.4)
Elevated ammonia levels	28/59 (47.5)
Hypoglycemia	16/65 (24.6)
Acidosis	10/47 (21.3)
Prolonged INR	26/29 (89.7)
Prolonged prothrombin time	55/56 (98.2)
Prolonged aPTT	71/72 (98.6)

ALT: Alanine aminotransferase. aPTT: Activated partial thromboplastin time. AST: Aspartate aminotransferase. INR: International normalized ratio.

Table 2. The etiology of acute liver failure in patients

Etiology	Number of patients n (%)
Indeterminate	16 (21.6)
Wilson's disease	16 (21.6)
Hepatitis A	14 (18.9)
Hepatitis B	4 (5.4)
Toxic hepatitis	4 (5.4)
Mushroom intoxication	3 (4.0)
Tyrosinemia	3 (4.0)
Galactosemia	3 (4.0)
Autoimmune hepatitis	2 (2.7)
Hypoxic hepatitis	2 (2.7)
Hepatitis A and B co-infection	1 (1.4)
Epstein-Barr virus hepatitis	1 (1.4)
Herpes virus hepatitis	1 (1.4)
Niemann Pick-B disease	1 (1.4)
Neonatal hemochromatosis	1 (1.4)
Wolman disease	1 (1.4)
Alpers disease	1 (1.3)
Total	74 (100.0)

hydantoin (n: 1), indomethacin and leflunomide (n: 1), meropenem, isoniazid, rifampin and pyrazinamide (n: 1), and aspirin (n: 1). Three patients (4%) had ALF due to mushroom intoxication.

Thirteen of the 16 patients with Wilson's disease were aged 5-12 years, while the other metabolic diseases were mostly seen in the newborn period. The most common etiology was infectious diseases in patients <5 years old.

The diagnostic test results of patients with Wilson's disease are given in Table 3.

Liver biopsy specimens were evaluated in 44 patients, and results are given in Table 4. Sixteen patients had liver fibrosis, and 10 of these had Wilson's disease. Five of the 16 patients were diagnosed as hepatitis B, tyrosinemia, galactosemia, mushroom intoxication, and Alpers disease, and one had indeterminate cause.

Table 3. The diagnostic test results of patients with Wilson's disease

Diagnostic test (normal values)	Patients with abnormal test results / patients tested (%)
Low ceruloplasmin (25-63 mg/dl)	28/43 (65.1%)
High urine copper levels (<50 µg/24- h urine)	19/23 (82.6%)
High hepatic copper content (<50 µg/g dry weight)	10/16 (62.5%)
Presence of Kayser-Fleischer ring	10/16 (62.5%)

Twenty-eight (37.8%) patients had either pulmonary infiltration or positive blood or urine cultures obtained during follow-up or postmortem. Twenty-two (78.6%) of these patients died during follow-up. Twenty (27%) patients had gastrointestinal bleeding.

Forty-nine (66.2%) patients died, while 24 (32.4%) patients recovered. Sixteen (21.9%) patients succumbed in the first two days of follow-up. Two patients went to liver transplantation. One of them had Wilson's disease and transplantation was successful, while the other had toxic hepatitis and died three months after liver transplantation due to acute rejection. The follow-up period (period until death or discharge) varied from 1 to 38 days.

Thirteen (61.9%) of the 21 patients who had normal neurologic examination on admission died, while 68.6% of patients with grade III or IV encephalopathy died (p>0.05). Five of the 8 patients (62.5%) with grade I and 1 of the 10 patients (10%) with grade II encephalopathy recovered spontaneously.

The mortality rate in the non-Wilson group was 58.6%, while it was 93.7% in the Wilson group (p=0.008). All the Wilson patients except one who had liver transplantation died, while 24 of the 58 non-Wilson patients recovered.

Forty-one (55.4%) patients fulfilled King's College transplantation criteria; 34 (82.9%) of them died before transplantation, and 7 (17.1%) recovered. Only one of them had liver transplantation. The mortality rate of patients who did not fit the criteria was 45.4% (p=0.001).

Laboratory and clinical features of patients who recovered (excluding the transplanted patient in the recovery group) or died are given in Table 5. Total and conjugated bilirubin levels, PT, INR, and blood pH values were significantly different between the two groups.

We evaluated the statistically significant features with ROC curves: total bilirubin level >5.35 mg/dl was a risk factor for death, with 89.7% sensitivity and 68% specificity. Similarly, INR level >3.66 (76.4% sensitivity, 83.3% specificity) and PT >23.5 s (92.3% sensitivity, 65% specificity) were risk factors for death. Patients were divided into three risk groups:

Group I: Total bilirubin level <5.35 mg/dl and INR <3.66 (or PT <23.5 s).

Table 4. Liver biopsy (3 patients)/necropsy findings of patients

Liver biopsy findings	Non-Wilson patient with positive finding/ Non-Wilson patients evaluated (%)	Wilson patient with positive finding/ Wilson patients evaluated (%)	Total patients with positive finding/ Patients evaluated (%)
Massive necrosis	19 / 32 (59.4)	3 / 12 (25)	22 / 44 (50)
Central vein necrosis	4 / 32 (12.5)	0 / 12 (0)	4 / 44 (9.1)
Fibrosis	6 / 32 (18.8)	10 / 12 (83.3)	16 / 44 (21.6)
Cholestasis	4 / 32 (12.5)	11 / 12 (91.7)	15 / 44 (20.3)
Steatosis	2 / 32 (6.3)	0 / 12 (0)	2 / 44 (2.7)
Hepatitis	16 / 32 (50)	1 / 12 (8.3)	17 / 44 (23)
Cirrhosis	1 / 32 (3.1)	11 / 12 (91.7)	12 / 44 (16.2)
Copper accumulation	0 / 1 (0)	8 / 12 (66.7)	8 / 13 (10.8)

Table 5. Laboratory and clinical features of patients who recovered or died

Laboratory or clinical features	Recovery (n=24) Mean ± SD	Death (n=49) Mean ± SD	p value
Age (months)	57.1±54.8	79.7±56.2	>0.05
Duration of the complaints (day)	10.8±9.9	17.0±15.0	>0.05
Hemoglobin (g/dl)	11.0±2.7	10.1±2.7	>0.05
ALT (IU/L)	1516.6±2173.6	906.9±1444.0	>0.05
AST (IU/L)	2144.0±3492.8	1149.6±1614.2	>0.05
Total bilirubin (mg/dl)	7.5±9.7	22.7±16.7	<0.001
Conjugated bilirubin (mg/dl)	4.7±6.5	14.5±11.8	<0.001
PT (sec)	30.1±27,0	49.0±30.4	<0.05
INR	3.0±1.1	6.0±4.4	<0.05
Creatinine (mg/dl)	0.65±0.45	0.76±0.78	>0.05
Ammonia (µg/dl)	143.6±116.9	132.5±105.5	>0.05
pH	7.38±0.08	7.42±0.09	<0.05

ALT: Alanine aminotransferase. aPTT: Activated partial thromboplastin time. AST: Aspartate aminotransferase. INR: International normalized ratio. PT: Prothrombin time.

Group II: Total bilirubin level >5.35 mg/dl or INR >3.66 (or PT>23.5 s).

Group III: Total bilirubin level >5.35 mg/dl and INR >3.66 (or PT >23.5 s).

According to the classification criteria, 14 patients were classified in group I, 20 patients in group II and 38 patients in group III. The death rates for groups I, II and III were as follows: 7.1% (1 of the 14 patients died), 45% (9 of the 20 patients died) and 97.4% (37 of the 38 patients died), respectively.

DISCUSSION

Acute liver failure (ALF), although seen infrequently, is an important situation that may be rapidly fatal. Survival rates have increased with improved intensive care and liver transplantation, but it has no known treatment yet.

Recently, hepatic encephalopathy has not been regarded as a prerequisite for the diagnosis of ALF in children, because features of especially early stages of hepatic encephalopathy may be difficult to ascertain in neonates and infants. According to the Pediatric ALF Study Group data, 20% of patients without encephalopathy either died or needed liver transplant (3). Similarly, 28.4% of our patients did not have any neurologic findings, and 13 of them died. The fact that patients with grade II encephalopathy on admission had a high rate of mortality (90%) shows that the grade of encephalopathy is not correlated well with mortality rates in children.

The consanguinity rate was 43.2% in our study, which was far higher than the consanguinity rate in Turkey (25.1%) (14). This may explain the high rate of hereditary and metabolic diseases as causes of ALF in children.

Albumin levels show the synthesizing functions of the liver. As it has a long half-life of 21 days, low levels show a chronic liver disease. Albumin levels were low in 61 (82.4%) patients, although only 9 (17%) patients applied with subacute liver failure. This may show an underlying chronic defect in the liver. Some studies have shown that albumin levels were lower in patients with ALF compared to the control group, and low albumin level indicated a poor prognosis (15,16).

The etiology of ALF varies in different age groups. According to the Pediatric ALF Study Group data, metabolic diseases were the most common etiology in children <3 years, while acetaminophen intoxication was the leading cause of ALF >3 years of age (3). The most common etiology was metabolic diseases in our study, most of which (except Wilson's disease) were seen in those <2 years of age. Wilson's disease was the most common metabolic cause of ALF in our study. Six of the 7 newborn patients had a metabolic disease, similar with the literature results. Serum amino acids were shown to be increased in acute and chronic liver failure (17). Metabolic tests may reveal nonspecific findings in ALF, and these should not be interpreted as metabolic diseases. Low rate of infectious disease or indeterminate causes of ALF in this age group may be related to the limited number of patients.

Ceruloplasmin level was decreased in 28 patients, while 16 of them had the diagnosis of Wilson's disease. Decreased ceruloplasmin levels may be found in 1% of controls, 10% of heterozygotes, malabsorption, nephrotic syndrome, chronic liver disease, copper deficiency, Menkes disease, and hereditary hypoceruloplasminemia. In addition, 20% of Wilson's disease patients may have normal ceruloplasmin levels (18). The facts that ceruloplasmin may increase as an acute phase reactant in ALF and difficulties in urine collection and liver biopsy complicate the diagnosis. In our study, 19 patients had 24-h urine copper level >100 µgr. Urine copper level may also increase in heterozygotes and other chronic liver diseases (18). Similarly, only 50-60% of ALF patients have Kayser-Fleischer rings. As fulminant Wilson's disease is mostly fatal, more accurate diagnostic measures are needed for life-saving transplantation.

Fibrosis was detected on liver biopsies of 62.5% of Wilson patients. Although Wilson's disease and autoimmune hepatitis patients may apply with fulminant liver failure, there is often an undetectable underlying chronic period. Lower levels of ammonia and albumin in Wilson patients may be related to this underlying chronic period. Also, liver biopsies of patients with mushroom intoxication showed fibrosis, which may be explained by an undetectable chronic liver disease, which has had a fulminant course via the superimposed mushroom intoxication.

The viral etiology of ALF changes according to geographical location. Hepatitis B infection is endemic in Far East Asia, while hepatitis A is the most common cause in Latin America and Pakistan (6,19,20). Infectious causes constituted 28.4% of the ALF etiology in our study, with hepatitis A being the most frequent. Viral work-up is absent in most of our patients due to limited laboratory measures in the past years and the short period of follow-up, and for these reasons, we thought that an infectious etiology would be even more frequent. Sanitation and socioeconomic factors play an important role in hepatitis A infection. Frequency of hepatitis A has significantly reduced in the last 10 years, which may be due to improved sanitation and vaccination in our country.

Infections during follow-up were shown to be the cause of death in 11-20% of ALF patients (21,22). The infection rate was 37.8% in our patients, and 78.6% of them died during follow-up. Evidence of infection may be subtle, such as tachycardia, intestinal bleeding, reduced renal output, or changes in mental status (23). Fever and leukocytosis are absent in 30% of patients (21). Thus, frequent blood and urine cultures should be obtained and broad spectrum antibiotics should be started prophylactically.

Spontaneous recovery without liver transplant was seen in 32.4% of our patients. Spontaneous recovery rates from different centers have ranged between 15%-78.9% (3,4,6,24-26). Differences between centers may be related to differences in ALF diagnostic criteria, etiology or differences in medical support. Centers that include patients without encephalopathy seem to have a higher spontaneous recovery rate (3,26). Although 21 patients did not have encephalopathy, the spontaneous recovery rate was low in our study, which we thought may be due to the high incidence of fulminant Wilson patients, who have a high mortality rate without liver transplantation.

Most of our patients died in the first two days of follow-up (21.6%). The anticipation of the progno-

sis is important because the disease has a rapid progression, and early transplantation can be life-saving. Transplantation recovery rates from different centers ranged between 67.5%-71.4% (3,4,6,24-26). When making a decision of transplantation, the chance of spontaneous recovery, risks of surgery and long-term complications of immunosuppressive treatment should be evaluated. King's College criteria are widely used for the decision of transplantation. The mortality rate was 82.9% in patients who fulfilled the transplantation criteria but could not be transplanted, while it was 45.4% in patients that did not fulfill the criteria. We think that King's College criteria can be used as a good predictor of transplantation necessity.

Several studies have shown PT, grade of encephalopathy, bilirubin level, ALT, and ammonia levels to be the risk factors for mortality (3,4,7,8). We found significant differences between bilirubin, PT, INR, and pH levels of recovered and succumbed patients. The mortality rate of patients with a total bilirubin level >5.35 and INR >3.66 or PT >23.5 was 100%, while the mortality rate of patients with both bilirubin and INR under the cut-off values was 7.1%. The numbers of recovered and exitus patients were similar in patients with either bilirubin or INR value above the cut-off level. Thus, in this patient group, other prognostic indicators are needed.

Recently, hepatic encephalopathy has not been regarded as a prerequisite for the diagnosis of ALF in children because features of especially early stages of hepatic encephalopathy may be difficult to ascertain in neonates and infants. According to the Pediatric ALF Study Group data, 20% of patients without encephalopathy either died or needed liver transplant (3). Similarly, 28.4% of our patients had no neurologic findings, and 13 of them died. The fact that patients with grade II encephalopathy on admission had a high rate of mortality (90%) shows that the grade of encephalopathy is not correlated well with mortality rates in children.

Lastly, organ donation should be encouraged in our country, as liver transplantation is life-saving. Prevention of consanguineous marriages and vaccination programs for hepatitis A and B will help to decrease the prevalence of metabolic and infectious diseases.

REFERENCES

1. Bucuvalas J, Yazigi N, Squires RH. Acute liver failure in children. Clin Liver Dis 2006; 10: 149-68.
2. O'Grady JG, Wendon J. Acute liver failure. In: Weinstein WM, Hawkey CJ, Bosch J, eds. Clinical gastroenterology and hepatology. 1st ed. Philadelphia: Elsevier Inc., 2005; 745-53.
3. Squires RH, Schneider BL, Bucuvalas J. Acute liver failure in children: the first 348 patients in the Pediatric Acute Liver Failure Study Group. J Pediatr 2006; 148: 653-8.
4. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United Kingdom. J Pediatr Gastroenterol Nutr 2005; 40: 575-81.
5. Ciocca M, Moreira-Silva SF, Alegria S. Hepatitis A as an etiologic agent of acute liver failure in Latin America. Pediatr Infect Dis J 2007; 26: 711-5.
6. Escorsell A, Mas A, Mata M. Acute liver failure in Spain: analysis of 267 cases. Liver Transpl 2007; 13: 1389-95.
7. Ciocca M, Ramonet M, Cuarterolo M, et al. Prognostic factors in pediatric acute liver failure. Arch Dis Child 2008; 93: 48-51.
8. Liu E, MacKenzie T, Dobyns EL, et al. Characterization of acute liver failure and development of a continuous risk of death staging system in children. J Hepatol 2006; 44: 134-41.
9. Schwartz E. The anemias. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics. 16th ed. Philadelphia: WB Saunders Company, 2000; 1461-2.
10. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-38.
11. Dhawan A, Taylor RM, Cheeseman P, et al. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl 2005; 11: 441-8.
12. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet 1993; 342: 273-5.
13. O'Grady JG, Alexander GJ, Haylar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97: 439-45.
14. Tunçbilek E. Clinical outcomes of consanguineous marriages in Turkey. Turk J Pediatr 2001; 43: 277-9.
15. Funk GC, Doberer D, Fuhrmann V, et al. The acidifying effect of lactate is neutralized by the alkalinizing effect of hypoalbuminemia in non-paracetamol-induced acute liver failure. J Hepatol 2006; 45: 387-92.
16. Shin SJ, Ahn SH, Kim HM, et al. Clinical features and prognostic factors of fulminant hepatic failure in Koreans. Korean J Hepatol 2004; 10: 298-307.
17. Honda T, Fukuda Y, Nakano I, et al. Effects of liver failure on branched-chain -·keto acid dehydrogenase complex in rat liver and muscle: comparison between acute and chronic liver failure. J Hepatol 2004; 40: 439-45.
18. Medici V, Rossaro L, Sturniolo GC. Wilson disease-a practical approach to diagnosis, treatment and follow-up. Dig Liver Dis 2007; 39: 601-9.
19. Shah U, Habib Z, Kleinman RE. Liver failure attributable to hepatitis A virus infection in a developing country. Pediatrics 2000; 105: 436-8.
20. Chang MH, Lee CY, Chen DS, et al. Fulminant hepatitis in Taiwan: the important role of hepatitis B virus. J Pediatr 1987; 111: 34-9.

21. Rolando N, Harvey F, Brahm J, et al. Prospective study of bacterial infection in acute liver failure: an analysis of 50 patients. Hepatology 1990; 11: 49-53.
22. Wyke RJ, Rajkovic IA, Eddleston AL, Williams R. Defective opsonization and complement deficiency in serum from patients with fulminant hepatic failure. Gut 1980; 21: 643-9.
23. Squires RH. Acute liver failure in children. Semin Liver Dis 2008; 28: 153-66.
24. Aydoğdu S, Özgenç F, Yurtsever S, et al. Our experience with fulminant hepatic failure in Turkish children: etiology and outcome. J Trop Pediatr 2003; 49: 367-70.
25. Areia M, Romãozinho JM, Ferreira M, et al. Fulminant hepatic failure: a Portuguese experience. Eur J Gastroenterol Hepatol 2007; 19: 665-9.
26. Wei G, Bergquist A, Broomé U, et al. Acute liver failure in Sweden: etiology and outcome. J Intern Med 2007; 262: 393-401.