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Fulminant hepatic failure and serum phosphorus levels in children from the western part of Turkey

Türkiye'nin batısında çocuklarda fulminan karaciğer yetmezliği ve serum fosfor düzeyleri

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Background/aims: *Clinical and laboratory predictors of recovery in children with fulminant hepatic failure are limited. Recently, hypophosphatemia has been reported as a laboratory indicator of recovering liver function in children with fulminant hepatic failure . We aimed to determine the incidence of hypophosphatemia and its association with clinical outcome in children in our center with fulminant hepatic failure.* ***Methods:*** *We analyzed 21 children who had been diagnosed with fulminant hepatic failure. Laboratory findings were recorded from admission date until the patient spontaneously recovered, underwent orthotopic liver transplantation or died.* ***Results:*** *Eight patients (38%) died, 6 (28.6%) underwent orthotopic liver transplantation, and 7 (33.3%) recovered without orthotopic liver transplantation. We identified hypophosphatemia in 57.1% of children with fulminant hepatic failure. Serum phosphorus levels were significantly lower in patients who recovered than in the orthotopic liver transplantation+death group. The presence of encephalopathy was determined at a much lower rate in the recovery group than in the orthotopic liver transplantation+death group. Serum phosphorus concentration ≥2.9 mg/dl and presence of encephalopathy were identified as independent risk factors for mortality.* ***Conclusions:*** *Hypophosphatemia can be identified as a marker of recovery in children with fulminant hepatic failure. Presence of encephalopathy and a serum phosphorus level ≥2.9 mg/dl appear to indicate a poor prognosis in children with fulminant hepatic failure.*

Key words: Hepatic failure, liver, children, phosphorus, transplantation

Amaç: *Çocukluk çağı fulminan karaciğer yetmezliğinde iyileşmeyi gösteren klinik ve laboratuvar belirteçleri oldukça sınırlıdır. Son zamanlarda, fulminan karaciğer yetmezliği olan çocuklarda başlangıçta hipofosfatemi varlığının karaciğer fonksiyonlarında düzelmenin göstergesi olduğu bildirilmektedir. Merkezimizde fulminan karaciğer yetmezliği olan çocuklarda hipofosfatemi sıklığını ve klinik sonuç ile ilişkisini araştırmayı amaçladık.* ***Yöntem:*** *Fulminan karaciğer yetmezliği tanısı almış 21 çocuğun dosyaları incelendi. Klinik ve laboratuvar bulguları hastanın geliş tarihinden itibaren spontan düzelme, ölüm ya da transplantasyon yapılana dek kaydedildi.* ***Bulgular:*** *Sekiz vaka (38%) ölmüştü, 6'sı (28.6%) transplantasyon'a ihtiyaç göstermişti ve 7'si (33.3%) spontan düzelmişti. Fulminan karaciğer yetmezliği olan çocuklarda hipofosfatemi sıklığını %57.1 olarak bulduk. Serum fosfor düzeyleri spontan düzelenlerde, transplantasyon+ölen gruba göre belirgin düşük bulundu. Ensefalopati varlığı spontan düzelen grupta, transplantasyon+ölen grubuna göre düşük bulundu. Serum fosfor düzeyinin ≥2.9 mg/dL olması ve ensefalopati varlığı mortalite için bağımsız risk faktörleri olarak belirlendi.* ***Sonuç:*** *Fulminan karaciğer yetmezliği olan çocuklarda başlangıçta hipofosfatemi varlığı, iyileşmenin göstergesi olarak tanımlanabilir. Ensefalopati varlığı ve serum fosfor düzeyinin ≥2.9 mg/dL olması ise kötü prognoz işaretidir.*

Anahtar kelimeler: Karaciğer yetmezliği, karaciğer, çocuk, fosfor, transplantasyon

INTRODUCTION

Fulminant hepatic failure (FHF) is a rare but often fatal disorder in children who were previously healthy. Despite the advent of orthotopic liver transplantation (OLT), the mortality rate attributable to FHF remains high, at 20% to 68% (1-3). Clinical and laboratory recovery predictors for children with FHF are limited. Encephalopathy, metabolic acidosis, hyperlactatemia, increasing

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serum levels of bilirubin and ammonia, and lower levels of clotting factors II, V and VII have all been associated with lower survival rates (4, 5). Recently, serum phosphorus (Ph) levels have been reported as a predictor of the outcome in adult and pediatric patients with FHF (5-7). Severe hypophosphatemia is a common metabolic abnormality that is seen in the immediate postoperative period in donors undergoing right hepatic lobectomy for living-related transplants and is believed to be the consequence of the rapid liver regeneration that is associated with partial hepatectomy (8, 9). The relationship between liver regeneration and hypophosphatemia postulates in patients with FHF was reported. Low serum levels of Ph represent increased consumption by the rapid synthesis of liver adenosine triphosphate (ATP) as a consequence of the high rate of liver regeneration (5). Thus, hypophosphatemia may be a laboratory indicator of recovering liver function in children with FHF. We aimed to determine the incidence of hypophosphatemia in children in our center with FHF and its association with clinical outcomes of FHF.

MATERIALS AND METHODS

We retrospectively analyzed 21 children referred to the Pediatric Gastroenterology, Hepatology and Nutrition Department at Dokuz Eylül University between November 2000 and December 2007who had a diagnosis of FHF. The inclusion criteria were the following: (1) Diagnosis of FHF made according to the criteria of the Acute Liver Failure Study Group (ALFSG) definition of FHF in children (December 1999) (7): (i) absence of unknown chronic liver disease; (ii) evidence of hepatic injury; (iii) prothrombin time (PT) >15 sec/international normalized ratio (INR) >1.5 with encephalopathy or PT >15 sec/INR >2.0 with or without encephalopathy; (2) Complete medical records; and (3) Length of hospitalization more than 24 hours before a terminating event (OLT, recovery, death). Of 29 FHF patients treated, 21 patients fulfilled the inclusion criteria.

We reviewed the charts of children with FHF. Age, gender, etiology of liver disease, and presence of encephalopathy were analyzed. Serum bilirubin, albumin, creatinine, ammonium, alkaline phosphatase, magnesium, calcium, HCO_3, PT, INR, and serum Ph levels were recorded from the admission date until the patient spontaneously recovered, underwent OLT or died.

Serum inorganic Ph levels were measured according to the phosphate ammonium molybdate absorbance method (Beckman Synchron LX-20; Beckman Instruments, Fullerton, CA).

Since the normal range for serum Ph levels is age-dependent, we defined hypophosphatemia at a Ph level that is at least 2 SD below the mean for the age of the child. The mean Ph±SD is: 0 to <2 years: 5.6±0.7 mg/dl; 2 to <5 years: 5.2±0.8 mg/dl; 5 to <12 years: 4.6±0.8 mg/dl; and 12 to <16 years: 3.8±0.6 mg/dl.

Data analyses were performed with SPSS for Windows (version 11.0) and NCSS and PASS (2004). Univariate analyses was performed using the odds ratio (OR), likelihood ratio (LR) and the chi-square or Fisher's exact test to evaluate the association between binary clinical findings and terminating event or outcome. Mann-Whitney U test was used to assess the relationship between laboratory variables and terminating event. The power of the study to detect risk factors for predicting death in children at the $p<0.05$ significance level was greater than 90%.

In order to evaluate the accuracy of significant predictive variables, we used the area under the receiver operating characteristic curve (ROC area). The statistically significant ($p<0.05$) risk factors were then dichotomized (high risk 1, low risk 0).

RESULTS

The median age of patients was 8 years (range: <1-14.7 years), and 33.3% of the patients were female. Nine patients (42.8%) had infections, 5 (23.8%) had Wilson's disease and the rest had autoimmune hepatitis (2), cryptogenic liver disease (2), mushroom poisoning (2), or Budd-Chiari disease (1). The median follow-up until terminating event was six days.

Eight patients (38%) died, 6 patients (28.6%) underwent OLT, and 7 patients (33.3%) recovered without OLT (Table 1). We identified hypophosphatemia in 57.1% of children with FHF.

There were no differences between the recovery group versus the OLT+death group in age, gender and serum bilirubin, albumin, creatinine, ammonium, alkaline phosphatase, magnesium, calcium, HCO_3, PT, and INR (Table 2).

Hypophosphatemia was found in all of the children who recovered without OLT and in 35.7% of the OLT+death group. Serum Ph levels were significantly lower in patients that recovered versus

Table 1. Age, gender, diagnosis and outcome of 21 patients with fulminant hepatic failure

Age (year)	7.1±3.8
Gender	
Female	7 (33.3%)
Male	14 (66.7%)
Diagnosis	
Infection	9 (42.8%)
Wilson's disease	5 (23.8%)
Mushroom poisoning	2 (9.5%)
Autoimmune hepatitis	2 (9.5%)
Budd-Chiari syndrome	1 (4.8%)
Cryptogenic	2 (9.5%)
Outcome	
Spontaneous recovery	7 (33.3%)
OLT	6 (28.6%)
Death	8 (38.0%)

OLT: Orthotopic liver transplantation.

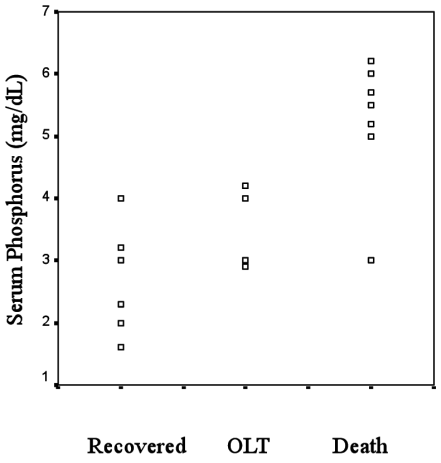

Figure 1. Serum phosphorus and clinical outcome. Serum phosphorus levels were significantly lower in patients that recovered versus those that died or underwent OLT (2.7±0.9 versus 4.8±1.3 mg/dl; p<0.05).

those in the OLT+death group (p>0.05) (Table 2). Presence of encephalopathy was determined at a much lower rate in the recovery group than in the OLT+death group (p<0.05) (Table 2).

By logistic regression analysis, Ph concentration ≥2.9 mg/dl (OR 15.0, 95% CI 1.6-122.1) and presence of encephalopathy (OR 9.2, 95% CI 1.3-65.5) were identified as independent risk factors for mortality. Association between serum Ph and clinical outcome is seen in Figure 1.

DISCUSSION

Nanji and Anderson (10) first reported hypophosphatemia in a case of FHF in 1985. Thereafter, various studies reported hypophosphatemia in adult and pediatric patients with FHF and hepatic resection (5-9, 11). The latter studies suggest that hypophosphatemia may be the consequence of liver regeneration.

The hypophosphatemia that develops in patients with FHF suggests that a massive influx of Ph may be occurring in the residual liver that is attempting to regenerate (12). Hepatic Ph may serve to meet the metabolic or synthetic demands of hepatic regeneration and may be used as substrate for various kinase enzymes that phosphorylate proteins, which play critical roles in the regeneration process (13-18). Hepatic Ph levels may also be

Table 2. The comparison of clinical and laboratory parameters as a prognostic factor between the spontaneous recovery group versus the OLT+Death group (mean±SD)

Parameter	**Recovery (n=7)[2]**	**OLT+Death (n=14)[a]**		
		OLT (n=6)	**Death (n=8)**	**p value[b]**
Presence of encephalopathy	2 (28.6%)	4 (66.7%)	7 (87.5%)	**<0.05**
INR	2.8±1.2	3.2±1.7	3.4±1.3	>0.05
PT (s)	32.0±19.4	32.1±9.4	32.1±9.4	>0.05
Serum total bilirubin (mg/dl)	20.7±7.6	17.8±2.4	22.4±4.0	>0.05
Serum creatinine (mg/dl)	0.7±0.3	0.8±0.5	0.9±0.6	>0.05
Serum albumin (g/dl)	3.1±0.7	3.1±1.3	2.8±0.5	>0.05
Serum ammonium (Ìg/dl)	138.1±37.2	177.5±96.6	189.2±47.2	>0.05
Serum alkaline phosphatase (U/L)	155.7±41.3	171.6±52.0	143.2±40.1	>0.05
Serum magnesium (mg/dl)	1.9±0.3	1.8±0.3	1.9±0.3	>0.05
Serum calcium (mg/dl)	9.3±0.9	8.9±0.9	8.9±0.9	>0.05
Serum HCO3 (mmol/L)	19.1±3.2	19.0±2.6	18.5±2.0	>0.05
Serum phosphorus (mg/dl)	2.7±0.9	3.3±0.6	5.3±1.0	**<0.05**

[a]*Analyses include patients on supportive care.*

[b]*Analyses show the difference between recovery versus OLT+Death group.*

INR: International normalized ratio. OLT: Orthotopic liver transplantation. PT: Prothrombin time.

required as substrate for the formation of ATP that may be excessively consumed in rapidly dividing hepatocytes (13-18). In fact, liver regeneration after hepatectomy or ischemia has been associated with derangement in energy metabolism, as measured by the decrease in the ratio of ATP to its inorganic Ph hydrolysis product (13, 14). The depletion energy status was mirrored in biochemical indices of liver function and restitution paralleled the course of restoration of hepatic mass (13). In the liver, Ph depletion may stimulate lactic acid production by reducing hepatic ATP stores (Pasteur effect) and producing intracellular alkalosis. ATP depletion may also limit the hepatic uptake of lactate. These effects may complicate the clinical course of FHF. Baquerizo et al. (5) also hypothesized that the maximal rate of ATP synthesis in the liver may be impaired in patients with low serum Ph and that administration of supplemental Ph may prevent the decrease in ATP synthesis, facilitating the regeneration of the liver and improving the outcome of patients with FHF.

Quirós-Tejeira et al (7) hypothesized that, if the relative mass of the regenerating liver is small, the decline in serum Ph may not be clinically evident. Alternatively, if the derangement in liver synthetic function is mild, the actual size of the regenerating liver may be insufficient to induce the decline in serum Ph levels. The absence of hypophosphatemia in a patient with normal renal function may be an indication of a liver whose regenerative mass is of insufficient size to induce changes in serum Ph. These opinions are supported by the data in our study in which hypophosphatemia was found in many FHF patients (57%).

The ability to assess prognosis accurately in FHF generates greater confidence in selecting patients for transplantation. Many prognostic markers have been extensively analyzed to identify patients who will require OLT (4, 19-24). Although not standardized, most centers have adapted the King's College (4) and the Clichy criteria (21). In our study, the univariate analysis of the other factors further reinforced previous observations (1, 4, 21, 25, 26) that encephalopathy was a statistically significant factor that differentiated between patients who recovered spontaneously and those who died or required OLT.

The results of this study demonstrate that serum Ph level is an important predictive factor in children with FHF. A statistically significant better prognosis has been observed in patients with hypophosphatemia. It may be hypothesized that this is related to the metabolic and synthetic demands of a liver with the capacity to regenerate. In contrast, serum Ph greater than 2.9 mg/dl in children with FHF was the main predictive factor for spontaneous recovery failure and would suggest massive hepatocyte necrosis and lack of liver regeneration.

The limitations of this study are two-fold: the small number of cases and its retrospective design. The previous observation of hypophosphatemia in other clinical states of liver regeneration suggests that low serum Ph level may be a useful laboratory marker of a recovering liver in pediatric patients with acute liver dysfunction. However, the actual role of Ph and etiology of hypophosphatemia in pediatric patients with FHF will need to be assessed in a prospective, multi-center study. Additional studies are required to further investigate serum Ph as a potential prognostic parameter in FHF.

In conclusion, hypophosphatemia is a frequent occurrence in the setting of FHF. Lower serum Ph levels are noted in children who have recovered as compared with those who have either died or had OLT. Presence of encephalopathy and a serum Ph level of ≥2.9 mg/dl appear to indicate a poor prognosis in Turkish children with FHF.

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