Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Resolution of hypophosphatemia is associated with recovery of hepatic function in children with fulminant hepatic failure

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Keywords
liver transplantation, liver synthetic function, liver regeneration.

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Received: 16 March 2005
Revision requested: 16 April 2005
Accepted: 14 May 2005

doi:10.1111/j.1432-2277.2005.00171.x

Summary

Fulminant hepatic failure (FHF) is a rare but often fatal disease in children. Clinical and laboratory predictors of liver regeneration and recovery, however, have not been well established. We hypothesized that hypophosphatemia may indicate recovery of liver synthetic function in children with FHF. We retrospectively reviewed the medical records of children with FHF who were admitted to UCLA and recovered hepatic function either spontaneously or by liver transplantation (LTx). Serum phosphate (Ph) and prothrombin time or international normalized ratio (INR) were compared over the patient's clinical course. Records of 39 children who spontaneously recovered experienced profound hypophosphatemia that resolved as liver synthetic function improved. Similar patterns were seen in the 84 children who recovered after LTx. We found that hypophosphatemia precedes the recovery of liver synthetic function in children with FHF who recovered with or without transplantation, and that Ph levels return to normal as liver synthetic function improves. These data suggest that hypophosphatemia may be a useful laboratory indicator of recovering liver function in children with FHF.

Introduction

Fulminant hepatic failure (FHF) is a rare but often fatal disorder that occurs in children that were previously healthy. Prior to the availability of liver transplantation (LTx), survival rates were approximately 20% and management of the disorder was limited to supportive measures. With the introduction of LTx, survival rates have improved to 65% in children [1–3].

Clinicians who manage patients with FHF in transplant centers must promptly determine rather the patient is an appropriate candidate for an LTx. The spontaneous recovery of liver synthetic function infrequently occurs (approximately 25%), while other patients may become poor operative candidates if the decision to perform an LTx is delayed [1–4]. Determining which patients with FHF are best suited to undergo LTx is particularly important because of the current scarcity of available organs [5].

Clinical and laboratory predictors of recovery of liver synthetic function in children with FHF are limited. Metabolic acidosis, hyperlactatemia and increasing serum levels of bilirubin and ammonia, and lower levels of clotting factors II, V and VII have all been associated with lower survival rates [6]. Increases in serum levels of α-fetoprotein have also been suggested to be a useful indicator of an improved clinical outcome [7]. More recently, phosphate (Ph) level has been reported as a predictor of

outcome in adult patients with acetaminophen-induced [8] or nonacetaminophen induced FHF [9]. The identification of other clinical and laboratory variables that would augment the clinician's ability to identify recovering liver function in a patient with FHF would be very useful.

Severe hypophosphatemia is a common metabolic abnormality that is seen in the immediate postoperative period in donors undergoing right hepatic lobectomy for of living-related transplants, and is believed to be the consequence of the rapid liver regeneration that is associated with partial hepatectomy [10].

Hypophosphatemia has also been described in adult patients with FHF. This phenomenon was previously specifically attributed to only Amanita phalloides and acetaminophen poisonings [11–14]. In these reports, investigators speculated that the decline in serum Ph levels was the consequence of renal tubular dysfunction, while others have suggested that liver failure was the result of hypophosphatemia [12]. In a recent study hypophosphatemia has been analyzed as a potential marker of prognosis in adults with FHF [8]. Currently, no study has examined the occurrence of hypophosphatemia in children with FHF, or has documented its potential role as a marker of liver regeneration in FHF in these patients.

The objective of this study was to examine the hypothesis that hypophosphatemia occur in children with poor liver synthetic function secondary to FHF, and that this electrolyte abnormality resolves once liver function improves either spontaneously or via LTx. To perform this analysis we compared serum Ph levels and international normalized ratio (INR) during the clinical course of children who presented with FHF at a large pediatric liver transplant program.

Methods

Study population

We reviewed the charts of all children admitted to UCLA Medical Center with FHF from January 1989 to April 2002. Given that hepatic encephalopathy may or may not be present in children, we followed the Acute Liver Failure Study Group (ALFSG) definition of FHF in children (December 1999): (i) Absence of unknown chronic liver disease; (ii) Evidence of hepatic injury; (iii) prothrombin time (PT) >15 s/INR >1.5 with encephalopathy or PT >20 s/INR >2.0 with or without encephalopathy.

We identified those patients who recovered either after an LTx or spontaneously improved liver synthetic function (without an LTx). Charts were reviewed from these two groups, and records that did not contain at least three serum Ph levels prior to the recovery of liver function were excluded from the analysis. The vast majority of children with low serum Ph levels received parenteral supplementation.

We obtained both the INR and serum Ph levels of those patients who met entry criteria, and compared these results to either the day of transplant (defined as day 0), or the day at which the INR levels declined below 1.3 in those patients that recovered spontaneously (defined as day 0). In those patients who had multiple INR levels drawn on a specific day, only the highest level was used in the analysis.

Since the normal range for serum Ph levels is age dependent, we defined hypophosphatemia as Ph level at least 2 SD below the mean for the age of the child. At our institution, 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, 12 to <16 years: 3.8 ± 0.6 mg/dl, and 16 to <20 years: 3.5 ± 0.6 mg/dl. Since normal Ph levels in serum are a function of age, we estimated the Z-scores for Ph levels. The following formula was used to calculate the Z-score for Ph levels (ZPh) = (serum Ph − mean serum Ph for age)/SD of serum Ph for age. A Z-score or standardized value indicates the number of SD units above (positive) or below (negative) the mean or 50th percentile for normal control subjects.

Statistical analysis

We used chi-square test methods and two-sample *t*-test for univariate statistical analysis of the variables. For the statistical analysis of INR versus ZPh in survivors with or without LTx, we used Spearman (nonparametric rank based) correlations. For each included subject the corresponding slope was estimated. The slope is the average rate of change in INR per SD unit change in phosphate (ZPh). A negative correlation and corresponding negative slope implies that INR decreases as ZPh increases. These correlations and slopes were computed as weighted averages across persons, and were estimated using a mixed effects regression model (SAS Procedure MIXED, SAS Inc, Cary NC, USA) where each person is allowed to have his or her own correlation and slope. A $P < 0.05$ was considered statistically significant.

Results

We identified 149 children with FHF and hypophosphatemia who survived. Forty-seven of these children recovered without LTx. Of these patients, only 39 had records of three or more serum Ph levels and were included in the analysis. One hundred two children with FHF required LTx. Of these patients, only 84 had records of three or more serum Ph levels and were included in this study.

The underlying cause of FHF in these children were due to a wide variety of causes, with the most frequent basis being idiopathic as described in previous studies [1–3]. The children listed in this study were all transferred to UCLA for hepatic failure and were in various stages of the listing process when they either died or recovered with or without transplantation.

Hypophosphatemia precedes the spontaneous improvement in liver synthetic function in 39 children with FHF who recovered without transplantation

To determine the role of hypophosphatemia in the natural course of liver failure, we investigated children who recovered from a bout of liver failure without an LTx ($n = 39$). Figure 1 shows the trend of serum Ph (Z-Ph) and INR in those who survived without transplant with day 0 set to the time when the patients INR levels declined below 1.3. The data demonstrates that more than 2 weeks prior to the recovery of liver synthetic function, the Z-Ph continued to decline and reached a low of −4.4 at 14 days prior to recovery, while INR levels continued to increase. Thereafter, both INR levels and Z-Ph continued to slowly approach the normal range. On the day prior to the full recovery of synthetic function (INR < 1.3), Z-Ph levels improved for the first time to within 2 SD of the mean. After the recovery of full liver function, serum Ph levels continued to improve towards normal.

To determine if the INR levels were inversely related to the Z-Ph, a Spearman correlation was performed. The average Spearman correlation across all persons between INR versus Z-Ph was −0.501 with a 95% confidence interval of (−0.644, −0.323) and $P < 0.001$. The model based average slope is −0.12 ± 0.03 in INR units per Z-Ph ($P < 0.001$). That is, in the average child who spontaneously recovered from a bout of FHF, INR levels decreased on average by 0.12 INR units for every increase in phosphorus by 1 SD. The 95% confidence interval for the true underlying slope is (−1.81, −0.650). These observations confirmed our initial hypothesis that severe hypophosphatemia (mean nadir ZPh −4.4 ± 1.7) precedes the improvement in liver synthetic function in children that recover without transplantation, and that serum Ph levels improved to the normal range immediately after the full recovery of function.

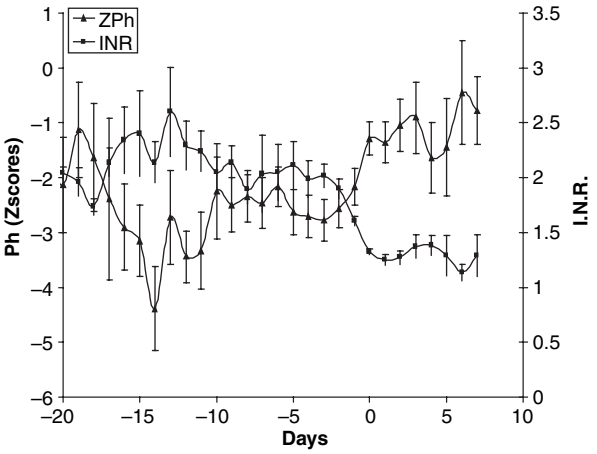

Figure 1 Trend of hypophosphatemia and international normalized ratio (INR) in 39 children with fulminant hepatic failure who survived without liver transplantation. Days before and after full recovery of hepatic synthetic function defined as INR < 1.3 (day 0) are on the *x*-axis. The Ph levels represented as mean Z-scores (ZPh) are on the *y*-axis. Spearman correlation analysis confirmed that serum Ph levels improved to normal limits immediately after full recovery of hepatic synthetic function. Information is presented with SE bars.

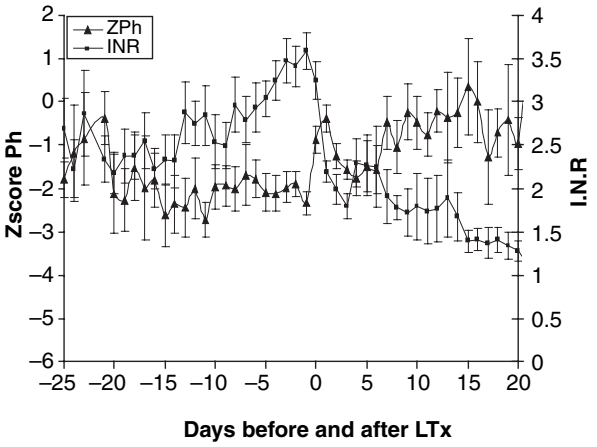

Figure 2 Trend of hypophosphatemia and international normalized ratio in 84 children with FHF who received liver transplantation (LTx). Days before and after LTx (day 0) are on the *x*-axis while Ph levels plotted as mean Z-scores (ZPh) are on the *y*-axis. Spearman correlation analysis confirmed that serum Ph levels improved to normal limits immediately after LTx when good hepatic synthetic function is reestablished. Information is presented with SE bars.

Hypophosphatemia precedes the improvement in liver synthetic function in 84 children with FHF who recovered after LTx

The trend of hypophosphatemia was examined in those children with FHF who survived with the assistance of an LTx ($n = 84$). The Ph levels are represented in mean Z-score versus days before and after the time of LTx. Figure 2 shows the trend of serum Ph (Z-Ph) and INR in those who survived with transplant with day 0 set to the time of LTx. The data demonstrates that from around 20 days before LTx the ZPh remained consistently below

−2 (mean nadir ZPh −2.6 ± 2.4). During that same time interval, mean INR levels continued to increase. Immediately after LTx, the ZPh reached normal limits (within 2 SD) remaining above a Z-score of −1. During this post-transplant period, INR levels slowly approach the normal range (IR < 1.3).

To find out if the INR levels were inversely related to the Z-Ph, a Spearman correlation was performed. The average Spearman correlation across all persons between INR versus Z-Ph was −0.18 with a 95% confidence interval of (−0.29, −0.05) and $P < 0.01$. The model based average slope is −0.11 ± 0.04 in INR units per Z-Ph ($P < 0.01$). That is, in the average child who underwent LTx secondary to FHF, the INR levels decreased on average by 0.11 INR units for every 1 SD increase in phosphorus. The 95% confidence interval for the true underlying slope is (−1.89, −0.32).

Discussion

The results of this study suggest that severe hypophosphatemia is a very common electrolyte disturbance in children with FHF. Since the patients in the study experienced liver failure from a wide variety of causes, hypophosphatemia is not limited to those children with only acetaminophen poisonings as has previously been studied.

The cause of hypophosphatemia develops in patients with FHF is currently unclear. Hypophosphatemia has been reported in adult humans after major hepatic resections or FHF, and suggests that hypophosphatemia may be the consequence of liver regeneration [8–10,15]. For a patient with FHF to recover synthetic function without undergoing a transplant, the residual liver must regenerate to establish a sufficient functional hepatic mass to synthesize adequate clotting factors to improve INR levels. In patients who acquire an LTx of sufficient size and quality, improvements in the levels of clotting factors and INR are generally seen in the first several days after surgery [16]. In our study, we determined that serum Ph levels improved towards normal in patients who recovered synthetic function either with or without transplantation. This simultaneous improvement in our patients is consistent with the hypothesis that hypophosphatemia corresponds to a period of hepatocyte proliferation and recovery. The recovery of normal INR levels would only occur at the time when the functional hepatic mass was of sufficient size to sustain normal metabolic demands, and thereby attenuate the drive for ongoing hepatocyte proliferation. If hypophosphatemia is a laboratory marker of liver regeneration, its occurrence prior to transplantation suggests that the failing livers of these patients were also attempting to regenerate.

The severe 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 [17]. The actual requirement of the regenerative liver for such an influx of Ph is currently not know. 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 that play critical roles in the regeneration process [18–23]. Hepatic Ph levels may also be required as substrate for the formation of ATP that may be excessively consumed in rapidly dividing hepatocytes [18–23]. In fact, liver regeneration after hepatectomy or ischemia has been associated with derangement in energy metabolism, as measured by decrease in the ratio of ATP to its hydrolysis product inorganic Ph [18,19]. The depleted energy status was mirrored in biochemical indices of liver function, and restitution paralleled the course of restoration of hepatic mass [18]. Significant uptake of Ph by the regenerating liver may explain the hypophosphatemia that we identified in patients with FHF.

Severe hypophosphatemia may result in impaired oxygen transport and tissue hypoxia, abnormal leukocyte function, depressed number of platelets and their function, generalized muscle weakness, and disorders of the central nervous system [24]. The clinical consequences of hypophosphatemia may be further amplified in patients with hepatocellular failure where other detrimental neurotoxic substances such as ammonia and neuroactive agents such as 1, 4-benzodiazepines frequently accumulate [25]. Finally, if serum Ph is providing the rapidly dividing hepatocytes with an essential substrate, insufficient replenishment of serum Ph may have deleterious effects in liver ability to regenerate. Timely and aggressive Ph supplementation in these patients with FHF is probably more vital than what has been thought in the past.

If hypophosphatemia is a marker of liver regeneration in patients with FHF, under what clinical circumstances might it not occur in such patients? 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. Finally, renal failure is a common event in patients with FHF, and clearly poor renal function may have a 'guarding effect' against hypophosphatemia by impaired Ph excretion [8].

What would be the clinical efficacy of following frequent serum Ph levels in patients with FHF? 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. Since the life-threatening complications of liver failure are

common and included hemorrhage, infection and cerebral edema, it is certainly possible that many of these complications may still occur in a patient whose liver is undergoing liver regeneration. Therefore, as it has been suggested by two previous studies, the absence of hypophosphatemia in a patient with early evidence of some of the life-threatening complications of liver failure may imply that the liver is unlikely to recover in the immediate future and other options like transplantation need to be considered [8,9].

This study has several limitations that would be addressable in a large multi-center study. Unfortunately, not all patients in our study had daily serum Ph levels, and urinary Ph was not consistently available for analysis. Further evaluation of the role of either endocrine or renal dysfunction in inducing changes in serum Ph levels needs to be addressed. The requirement for aggressively replenishing serum Ph needs to be evaluated, since failure to do so may result in insufficient substrate to support the cellular requirements of liver regeneration [18–23].

In summary, this study identified that severe hypophosphatemia is a frequent occurrence in children with FHF and that serum Ph levels begin to approach normal in those individuals that improve their liver function either surgically or spontaneously. Hypophosphatemia in children with FHF may be related to metabolic and synthetic demands of hepatic regeneration and the consumption of ATP by the rapidly dividing hepatocytes. The previous observation of hypophosphatemia in other clinical states of liver regeneration suggests that low serum Ph levels may be a useful laboratory maker 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.

References

1. Rivera-Penera T, Moreno J, Skaff C, McDiarmid S, Vargas J, Ament ME. Delayed encephalopathy in fulminant hepatic failure in the pediatric population and the role of liver transplantation. *J Pediatr Gastroenterol Nutr* 1997; **24**: 128.
2. Psacharopoulos HT, Mowat AP, Davies M, Portmann B, Silk DB, Williams R. Fulminant hepatic failure in childhood: An analysis of 31 cases. *Arch Dis Child* 1980; **55**: 252.
3. Devictor D, Desplanques L, Debray D, *et al.* Emergency liver transplantation for fulminant liver failure in infants and children. *Hepatology* 1992; **16**: 1156.
4. Devlin J, Roger W. Transplantation for fulminant hepatic failure. *Transplantation* 1996; **62**: 1251.
5. Sussman NL, Lake JR. Treatment of hepatic failure – 1996: current concepts and progress toward liver dialysis. *Am J Kidney Dis* 1996; **27**: 605.
6. O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439.
7. Murray-Lyon IM, Orr AH, Gazzard B, Kohn J, Williams R. Prognostic value of serum alpha-fetoprotein in fulminant hepatic failure including patients treated by charcoal haemoperfusion. *Gut* 1976; **17**: 576.
8. Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. *Hepatology* 2002; **36**: 659.
9. Chung PY, Sitrin MD, Te HS. Serum phosphorus levels predict clinical outcome in fulminant hepatic failure. *Liver Transpl* 2003; **9**: 248.
10. Pomposelli JJ, Pomfret EA, Burns DL, *et al.* Life-threatening hypophosphatemia after right hepatic lobectomy for live donor adult liver transplantation. *Liver Transpl* 2001; **7**: 637.
11. Dawson DJ, Babbs C, Warnes TW, Neary RH. Hypophosphatemia in acute liver failure. *Br Med J* 1987; **295**: 1312.
12. Nanji AA, Anderson FH. Acute liver failure: a possible consequence of severe hypophosphatemia. *J Clin Gastroenterol* 1985; **7**: 338.
13. Jones AF, Harvey JM, Vale JA. Hypophosphataemia and phosphaturia in paracetamol poisoning. *Lancet* 1989; **2**: 608.
14. Florkowski CM, Jones AF, Guy JM, Husband DJ, Stevens J. Retinol binding proteinuria and phosphaturia: markers of paracetamol-induced nephrotoxicity. *Ann Clin Biochem* 1994; **31**: 331.
15. George R, Shiu MH. Hypophosphatemia after major hepatic resection. *Surgery* 1992; **111**: 281.
16. Farmer DG, Yersiz H, Ghobrial RM, *et al.* Early graft function after pediatric liver transplantation: comparison between in situ split liver grafts and living-related liver grafts. *Transplantation* 2001; **72**: 1795.
17. Fisher B, Szuch P, Fisher ER. Evaluation of a humoral factor in liver regeneration utilizing liver transplants. *Cancer Res* 1971; **31**: 322.
18. Mann DV, Lam WW, Hjelm NM, *et al.* Human liver regeneration: hepatic energy economy is less efficient when the organ is diseased. *Hepatology* 2001; **34**: 557.
19. Yang M, Shimada H, Kobayashi T, Niimoto S, Nakagawara G. Predicting the viability of grafted livers in rats through a rapid and sensitive metabolic indicator assessed by 31P-NMR spectroscopy. *Surg Today* 1995; **25**: 711.
20. Morikawa S, Inubushi T, Takahashi K, Terada Y, Iwata S, Ozawa K. Glucose and energy metabolism in rat liver after ischemic damage assessed by 13 C and 31 P NMR spectroscopy. *J Surg Res* 1996; **63**: 393.
21. Morikawa S, Inubushi T, Kitoh K, Kido C, Nozaki M. Chemical assessment of phospholipid and phosphoenergetic metabolites in regenerating rat liver measured by in vivo and in vitro 31P-NMR. *Biochim Biophys Acta* 1992; **1117**: 251.

22. Lee RG, Lanir A, Clouse ME. Liver adenine nucleotide metabolism during ischemia and reperfusion of mice livers studied by phosphorous-31 nuclear magnetic resonance. *Invest Radiol* 1987; **22**: 479.
23. Ellermann J, Gewiese B, David H, *et al.* Electron microscopic and 31-P NMR studies of ischemic injured rat livers during preservation and reflow. *Exp Toxicol Pathol* 1992; **44**: 245.
24. Knochel JP. The clinical status of hypophosphatemia: an update. *N Engl J Med* 1985; **313**: 447.
25. Lee WM. Acute liver failure. *N Engl J Med* 1993; **329**: 1862.