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The Role of Etiology in the Hyperamylasemia of Acute Liver Failure

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Abstract

OBJECTIVES—Hyperamylasemia (HA) is often reported in patients with acute liver failure (ALF). Direct toxic effects of acetaminophen on the pancreas have been postulated, but the occurrence of HA in other etiologies raises the question of whether multiorgan failure is part of the pathogenesis of HA in this setting. Our main aim was to describe and analyze the incidence, clinical characteristics, and outcomes of HA in ALF of different etiologies.

METHODS—Patients enrolled in the Acute Liver Failure Study Group registry with an admission amylase value available were included. For the purpose of this analysis, HA was defined as $3\times$ upper limits of normal. Patients were classified as having acetaminophen (APAP)- or non-APAP-induced ALF, and by amylase group: normal (< 115), mildly elevated (115–345), or HA (> 345). Significant variables identified by univariate analysis were added to a multiple linear regression model. The primary outcome was overall survival.

RESULTS—In total, 622 eligible patients were identified in the database, including 287 (46%) with APAP-induced ALF; 76 (12%) patients met the criteria for HA. Among patients with HA, 7 (9%) had documented clinical pancreatitis. The incidence of HA was similar among APAP (13%) and non-APAP (12%) patients. Although HA was associated with renal failure and greater Model for End-stage Liver Disease scores for both groups, HA was not an independent predictor of mortality in multivariate analysis.

CONCLUSIONS—Although not an independent predictor of mortality, HA in ALF was present in all etiologies and was associated with diminished overall survival. HA appeared to be related to renal dysfunction in both groups and multiorgan failure in non-APAP ALF.

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CONFLICT OF INTEREST

Guarantor of the article: Andres Blei, MD.

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INTRODUCTION

Acute pancreatitis has been reported in 6–41% of cases of acute liver failure (ALF), a complication whose pathophysiology has not been well elucidated (1–5). Proposed mechanisms include pancreatic damage from hypoperfusion or hemorrhage from coagulopathy, as well as direct injury from an etiologic agent, such as hepatitis B or drug/toxins, specifically acetaminophen (5). Although hyperamylasemia (HA) is commonly associated with acute pancreatitis, elevation in serum amylase levels may also be seen in acute or chronic renal failure in the absence of clinical pancreatitis (6–8). Collen *et al.* (7) reported serum amylase levels as high as 503 U/l among patients whose creatinine clearance was less than 50 ml/min. There are numerous nonpancreatic etiologies for an elevated amylase, including bowel perforation and ischemia, ketoacidosis, pneumonia, as well as macroamylasemia (9). HA from nonpancreatic amylase fractions has been reported in critically ill patients, including those with ALF (3,5,10). There are limited data associating HA with a poor prognosis in ALF, particularly related to acetaminophen (3,5).

In the largest reported series of 148 subjects with ALF due to acetaminophen (APAP), an elevated serum amylase, defined as >100 U/l, was noted in 80 % of subjects (5). This high prevalence, together with APAP-induced HA/pancreatitis in patients with APAP hepatotoxicity without changes in mental state, led the authors to postulate a possible direct effect of the drug on the development of pancreatic injury. Although reports of HA/pancreatitis in non-APAP-induced ALF have been published (1–4), the series are small and cannot ascertain whether etiology is an important factor in the evaluation of HA in ALF.

The large database of over 1,000 patients accumulated by the Acute Liver Failure Study Group provides an opportunity to address this question. Hypothermia has been suggested as treatment for cerebral edema in ALF. Accidental hypothermia has been reported to be complicated by acute pancreatitis (11–15) and HA has been reported in up to 65% of cases of therapeutic hypothermia (16). A diagnosis of acute pancreatitis in patients with ALF treated with hypothermia is difficult to establish, as pancreatitis may reflect the impact of ALF itself. In anticipation of a trial examining the impact of hypothermia in APAP-induced ALF (17), our objective in this study was to examine the incidence, clinical characteristics, and outcomes of patients with ALF and HA, comparing APAP-induced ALF with non-APAP etiologies.

METHODS

This was a retrospective, cohort analysis using the ALF study group database. The details of patient recruitment and data collection for this database are provided elsewhere (18). Briefly, the Acute Liver Failure Study Group is a consortium of 23 tertiary care liver centers established in 1997 to study the clinical epidemiology of ALF in the United States, provide insight into its pathophysiology, and perform clinical trials to assess the role of new therapies (18). After informed consent, patients are enrolled into the registry if entry criteria are met: prothrombin time >15 s or international normalized ratio >1.5 with any symptoms of hepatic encephalopathy, features that developed within 26 weeks of symptom onset with no preexisting liver disease (19).

All patients with available amylase levels within the database at the time of hospital admission between 1 January 1998 and 31 August 2007 were included in this analysis. Analysis was based on etiology of ALF, divided in two major groups: APAP and non-acetaminophen (non-APAP). This division reflects the hyperacute nature of APAP-related injury with its distinctive clinical features (20). Normal values for amylase were defined as 115 U/l, a reference value shared across the laboratories of the different centers. Patients

were classified as “elevated” for values between 116 and 345 U/l, whereas HA was defined as $>3 \times$ upper limit of normal, or 345 U/l, a cutoff that increases the sensitivity of HA for the diagnosis of acute pancreatitis (9).

The following clinical data were recorded for each case: age, sex, admission hepatic encephalopathy grade, prior alcohol use, and clinical pancreatitis. Prior alcohol use was defined as a possible risk factor based on the history provided at the time of admission. A clinical diagnosis of pancreatitis was made with an elevation of serum amylase level in conjunction with documented clinical features of pancreatitis within the ALF database. Admission laboratories including serum amylase, creatinine, total bilirubin, international normalized ratio, alanine aminotransferase/aspartate aminotransferase levels, as well as arterial lactate and pH were recorded. In addition, several ALF prognostic systems were calculated for all patients, including King’s College Criteria (21), Model for End-stage Liver Disease (MELD) (22), and Sequential Organ Failure Assessment (SOFA) scores (23 – 25). SOFA scores, based on six clinical parameters (including the Glasgow Coma Scale), were estimated based on five readily available parameters together with the admission coma grade. Registry data use a scale of hepatic encephalopathy from I to IV, adapted from the West Haven Criteria (26). Values of coma grade were converted to mean Glasgow coma scores from a recent comparison of both scales in a controlled trial of albumin dialysis in acute-on-chronic liver failure (27): I: 15 points, II: 14 points, III: 9 points, and IV: 4 points.

Primary and secondary outcomes

The primary outcome measure was the relation between HA and overall survival rate in both APAP and non-APAP-induced ALF, defined as survival to discharge from hospital or 3 weeks after admission. We also analyzed spontaneous survival rates, classified as those patients who met overall survival criteria in the absence of an emergency liver transplantation. Secondary analyses focused on measuring relevant clinical characteristics of our study population including admission creatinine, coma grade, total bilirubin, and arterial lactate levels. Finally, we compared various prognostic scores across all groups, including the proportion of patients meeting King’s criteria, mean MELD score, and mean SOFA score.

Statistical analysis

Statistical analysis was performed using Stata version 10.0 (StataCorp LP, College Station, TX). Dichotomous variables were compared using χ^2 -tests and continuous variables using one-way analysis of variance. Significant factors defined in univariate analysis were then added into a multivariate linear regression model using amylase as a continuous variable.

RESULTS

Among 1,033 patients enrolled in the ALF registry, we identified 622 patients with a recorded serum amylase on hospital admission. Of these, 287 (46 %) patients developed ALF due to APAP, whereas 335 (54 %) were due to non-APAP etiologies. Clinical characteristics are shown in Table 1. There were no significant differences in age, sex, or prior alcohol use within the two main etiologic categories, though alcohol use was significantly higher in the APAP group (53%) compared to the non-APAP group (53% vs. 23%, Fisher’s exact test, $P < 0.0001$). Among ALF patients because of APAP, 37 (12.9%) met criteria for HA compared to 39 (11.6%) patients with non-APAP ALF ($P = \text{NS}$, χ^2 -test). Among all 76 patients with HA, 7 (9%) had documented clinical pancreatitis within the database.

The etiologies of non-APAP patients across all three amylase groups are summarized in Table 2. A small number of non-APAP ALF patients presented as a result of hepatic ischemia (9%). HA was more frequently identified among indeterminate (18%) and ischemia (13%) patients compared to a viral cause (9%), drug (9%), and other (9%) etiologies, although this did not reach statistical significance. Other etiologies of non-APAP ALF included autoimmune hepatitis (28), Wilson's disease (9), Budd–Chiari (7), fatty liver of pregnancy (6), other viruses (4), and *Amanita phalloides* toxicity (4), among others.

Overall and spontaneous survival rates are summarized in Figure 1a and b. Among patients with HA, survival rates were consistently lower in both APAP and non-APAP groups. The spontaneous survival rate in APAP patients was significantly lower among HA patients (46 %) compared to elevated amylase (values between 116 and 345 U/l) (70 %) and normal amylase (67 %) patients ($P < 0.03$). Overall survival rates were also lower, although this did not reach statistical significance ($P = 0.08$). Overall survival differences were most pronounced among non-APAP ALF patients, where the rate increased from 44 % among patients with HA to 66% among patients with a normal amylase ($P = 0.03$).

A comparison of clinical predictors and prognostic models across amylase groups are shown in Tables 3a and b. Among APAP patients, serum creatinine was significantly higher among patients with high amylase and HA compared to those with normal values. HA patients were significantly more likely to meet King's College criteria (30 %) and have higher mean MELD (19.0) and estimated SOFA (10.9) scores compared to patients with normal amylases.

Similarly, non-APAP patients with HA were found to have a higher admission creatinine and mean MELD (19.4) and estimated SOFA (12.7) scores. However, non-APAP patients were less likely to meet King's criteria (18%) at the time of admission compared to high amylase (45%) and normal amylase (41 %) patients. (χ^2 -test, $P = 0.011$). This discrepancy reflected lower bilirubin values in this group. Admission bilirubin was lower among HA patients (mean 12.9 mg/dl) compared to elevated amylase (18.2) and normal amylase (18.8) patients in the non-APAP group. The interval from symptom onset to development of coma was significantly shorter in the HA group (7.1 ± 8.5 days) compared to the elevated amylase (18.4 ± 23.0) and normal amylase (21.3 ± 23.6) groups ($P < 0.002$, analysis of variance). Similarly, the period from noticed icterus to coma was significantly shorter among HA patients (4.6 ± 11.0 days) compared to elevated amylase (13.1 ± 17.2) and normal amylase (11.7 ± 15.1) patients ($P < 0.02$, analysis of variance). Patients with HA in the non-APAP group thus presented with features of hyperacute ALF (19).

Non-APAP HA patients presented with higher coma grade and higher arterial lactate levels compared to elevated amylase and normal amylase patients (Table 3b). However, there were no significant differences in need for pressor support, mechanical ventilation, or positive blood culture rates across all groups.

In both APAP and non-APAP groups, multivariate analysis using amylase as a continuous variable did not demonstrate a significant difference in survival when the values of amylase were controlled for age, sex, MELD, SOFA, lactate, creatinine, bilirubin, and coma grade.

DISCUSSION

This large series examined the relation of etiology of ALF with the presence of elevated amylase levels. The prevalence of elevated amylase values was high, with 47% of subjects with APAP (136 of 287 cases) and 41% of non-APAP etiologies (139 of 335 cases) exhibiting abnormal values. When using the more rigorous criterion of threefold elevation of amylase levels, HA was again comparable among APAP and non-APAP etiologies, with

slightly over 10 % of all cases of ALF demonstrating this abnormality. No significant differences were noted among the different etiologies included within the non-APAP group.

When CT scans were used to confirm the diagnosis of acute pancreatitis in a general population, the sensitivity of a threefold rise in serum amylase was greater than 80%, although the specificity was highly variable (9). Among patients with HA in our cohort, only 9% were found to have clinical pancreatitis within the registry. This is comparable to Schmidt and Dalhoff (5) who identified 8 cases of acute pancreatitis among 246 patients with HA in the setting of acetaminophen toxicity. It is likely that the specificity of serum amylase is particularly low among ALF patients, particularly in view of reports of elevations of nonpancreatic amylase in this disease (3). It should be noted that our findings are limited by the retrospective nature of the analysis and may be susceptible to underreporting within the registry.

Nonetheless, our study provides insight into the pathogenesis of this abnormality, whose mechanism has not been fully elucidated. In spite of the similarities in the prevalence of elevated amylase or HA between APAP and non-APAP etiologies, our data suggest a different pathogenic explanation for each group. Among ALF patients due to APAP, the most striking difference across all three subgroups was an elevated serum creatinine, whose mean values rose with increasing amylase levels. HA has been reported among patients with renal failure in several series (7,8,10). Abnormal renal function contributed to the higher MELD and SOFA scores as well as the greater proportion of patients with HA who met King's criteria (Table 3b). Other clinical predictors such as coma stage, international normalized ratio, and arterial lactate did not discriminate between the subgroups. Bilirubin was characteristically low across all subgroups, a typical feature of the hyperacute course seen in APAP-induced ALF (19,20). We cannot exclude a direct toxic effect of APAP on the pancreas, as postulated by Schmidt and Dalhoff (5); nonetheless, our results highlight the importance of renal failure in the interpretation of amylase values in this group.

The mechanism responsible for the rise of amylase levels in non-APAP ALF patients may be different. First, no singular cause of non-APAP ALF had a greater likelihood of presenting with elevated amylase or HA, suggesting that etiology is not a major factor in the pathogenesis of this abnormality. Second, although elevated amylase and HA patients presented with greater renal dysfunction, as shown by a stepwise increase in serum creatinine (Table 3a), they also exhibited a higher admission coma grade and arterial lactate levels. This reflects more severe multiorgan failure among patients with HA. The combination of higher coma grade along with creatinine and lactate levels accounts for the elevated MELD and SOFA scores seen in the HA group. Of note, HA patients had a significantly lower serum bilirubin value when compared to the elevated amylase and normal amylase groups. Although this initially seems contradictory, this may be a reflection of disease acuity. The interval from symptom onset and icterus to coma was significantly shorter among HA patients, a feature of rapid clinical deterioration.

The presence of HA (not simply an elevated amylase value) was associated with a poorer prognosis. On univariate analysis, spontaneous survival was significantly reduced in the HA groups of both APAP and non-APAP etiologies (Figure 1a and b); on multivariate analysis, HA did not exert an independent effect when other clinical factors and scoring systems were analyzed. The association between renal failure/multiorgan failure and HA highlights the overall poor outcome of subjects in whom a 3-fold elevation in serum amylase is detected.

Finally, these data provide guidance to the interpretation of elevated amylase/HA during the application of therapeutic hypothermia in ALF (28). With a very high prevalence of abnormalities of amylase levels in ALF as well as with hypothermia, it may be difficult to

separate the effects of cooling from those of liver failure itself. In an individual with ALF treated by cooling, lower degrees of renal/multiorgan failure would make hypothermia a likelier explanation for the presence of elevated amylase/HA levels. Such clinical criteria should facilitate the management of complications during the performance of a randomized controlled trial of moderate hypothermia in ALF (17).

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Hyperamylasemia has been reported in acetaminophen-induced (APAP) acute liver failure (ALF) and to a lesser extent, in non-APAP ALF.
- Hyperamylasemia may be due to multiple causes.

WHAT IS NEW HERE

- The incidence of hyperamylasemia is comparable among APAP and non-APAP ALF patients.
- In APAP ALF, HA appears to be related to renal failure.
- In non-APAP ALF, HA is related to multiorgan failure.
- Hyperamylasemia is not an independent predictor of mortality in ALF.

Figure 1.

(a) Acetaminophen-induced (APAP) acute liver failure (ALF): overall and spontaneous survival rates. (b) Non-APAP ALF: overall and spontaneous survival rates. * P value for overall survival, χ^2 -test. Among APAP ALF patients (a), spontaneous (blue) and overall (red) survival rates were lower among patients with hyperamylasemia (HA). Among non-APAP ALF patients (b), overall survival rates were significantly lower in the HA group, whereas spontaneous survival rates were similar.

Table 1

Patient demographics

	APAP ALF (n=287)		Non-APAP ALF (n=335)		
	Normal amylase (n=151)	Elevated amylase (n=99)	HA (n=37)	Normal amylase (n=196)	Elevated amylase (n=100)
Mean age (s.d.)	37 ±12	36 ±13	40 ±13	42 ±16	41 ±14
% Female	77	67	62	59	66
% EtOH use	52	56	49	28	10
Amylase (s.d.)	63 ±28	194 ±62	838 ±557 *	60 ±26	185 ± 71
					798 ±489 *

ALF, acute liver failure; APAP, acetaminophen; HA, hyperamylasemia; EtOH, ethanol.

* $P < 0.001$ (analysis of variance).

Table 2

Etiology of non-APAP ALF patients

Etiology	Normal amylase (n=196)	Elevated amylase (n=100)	HA (n=39)	Total (%)
Viral hepatitis (<i>n</i>)	47	17	6	70 (21)
Indeterminate (<i>n</i>)	42	30	16	88 (26)
Ischemic (<i>n</i>)	15	11	4	30 (9)
Drug (<i>n</i>)	41	11	5	57 (17)
Other (<i>n</i>)	51	31	8	90 (27)
Total (<i>n</i>)	196	100	39	335 (100)

ALF, acute liver failure; APAP, acetaminophen; HA, hyperamylasemia.

No statistical differences were seen across these groups.

Table 3a

Association of HA with known clinical predictors in ALF

	APAP ALF (n=287)			Non-APAP ALF (n=335)				
	HA (n=37)	Elevated amylase (n=99)	Normal amylase (n=151)	P value	HA (n=39)	Elevated amylase (n=100)	Normal amylase (n=196)	P value
Creatinine, mg/dl (s.d.)	3.4 ±1.9	2.9 ±1.9	2.0 ±1.8	<0.05	3.4 ±1.9	2.5 ±1.6	1.8 ±1.5	<0.05
Coma grade (s.d.)	2.8 ±1.2	2.5 ±1.3	2.4 ±1.2	NS	3.3 ±0.9	2.8 ±1.1	2.3 ±1.1	<0.0001
Total bilirubin, mg/dl (s.d.)	5.2 ±4.2	6.0 ±5.6	5.2 ±3.2	NS	12.9 ±11.3	18.2 ±12.1	18.8 ±11.8	<0.02
INR (s.d.)	3.8 ±2.1	3.9 ±3.0	3.7 ±3.2	NS	3.3 ±2.2	3.5 ±2.8	3.6 ±3.0	NS
Arterial lactate, mmol/l (s.d.)	8.1 ±4.1	8.8 ±9.8	9.0 ±14.3	NS	15.0 ±19.0	7.3 ±7.8	7.1 ±9.0	0.0001

ALF, acute liver failure; APAP, acetaminophen; HA, hyperamylasemia; INR, international normalized ratio; NS, not significant.

Analysis of variance, vs. all other groups.

Although serum creatinine was the sole difference among APAP patients, four of five variables were significant among non-APAP patients.

Table 3b

Association of HA with ALF prognostic models

	APAP ALF (n=287)				Non-APAP ALF (n=335)			
	HA (n=37)	Elevated amylase (n=99)	Normal amylase (n=151)	P value	HA (n=39)	Elevated amylase (n=100)	Normal amylase (n=196)	P value
% met King's criteria	30	18	9	0.004	21	45	47	0.009
Mean MELD (s.d.)	19.0 ±3.8	18.1 ±4.8	15.9 ±4.5 ^a	<0.05	19.4 ±4.0	18.9 ±4.1	17.3 ±4.3 ^a	<0.05
Mean estimated SOFA (s.d.)	10.9 ±3.6	9.8 ±3.6	8.8 ±3.7 ^b	<0.05	12.7 ±2.5	12.3 ±3.5	9.4 ±3.4 ^b	<0.05

ALF, acute liver failure; APAP, acetaminophen; HA, hyperamylasemia; MELD, Model for End-stage Liver Disease; SOFA, Sequential Organ Failure Assessment.

All prognostic models were different across all groups.

^a Analysis of variance, vs. all other groups.

^b Analysis of variance, vs. HA group.