Associations of Elevated Liver Enzymes among Hospitalized Adolescents with Anorexia Nervosa

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Objectives To analyze the prevalence, predictors, and evolution of increased liver enzymes in a large sample of adolescents hospitalized with anorexia nervosa (AN).

Study design Electronic medical records of all subjects 10-22 years of age with AN, first admitted to a tertiary children's hospital from January 2007 to December 2012, were reviewed retrospectively. Demographic factors, anthropometric factors, initial prescribed calories, and alanine aminotransferase levels were recorded. Multivariate analysis was performed to assess the effect of sex, degree of malnutrition, and initial calories prescribed on having alanine aminotransferase $\geq$40 IU/L.

Results A total of 356 subjects met eligibility criteria (age 16.1 $\pm$ 2.4; 89.0% female; admission body mass index [BMI] 15.9 $\pm$ 1.9; admission percentage median BMI 78.2 $\pm$ 8.5), with elevated liver enzymes present in 37.0% on admission and in 41.1% at any point during the hospitalization. Lower percentage median BMI (aOR 0.96; 95% CI 0.93-0.98) and male sex (aOR 0.45; 95% CI 0.22-0.94) were significantly associated with odds of elevated liver enzymes on admission. Higher initial prescribed calories were associated with odds of elevated liver enzymes after admission (aOR 1.81; 95% CI 1.04-3.18).

Conclusions In this study of AN and elevated liver enzymes, the degree of malnutrition and male sex predicted elevated liver enzymes on admission but initial prescribed calories also may be associated with elevated liver enzymes after admission in a small proportion of patients. Future research should better characterize the evolution of elevated liver enzymes in patients hospitalized with AN undergoing refeeding. *(J Pediatr 2015;166:439-43)*.

Anorexia nervosa (AN) is characterized by self-induced weight loss, fear of weight gain, and severe body image distortion.[1] Its prevalence ranges between 0.9% and 2.2% of young women[2] and is associated with a mortality rate between 5% and 10% after 10 years of onset.[3] Medical complications associated with AN include electrolyte disorders, bone loss and fractures, and gastrointestinal manifestations such as constipation, gastric dilation, early satiety, and pancreatitis.[4]

Liver enzyme abnormalities among patients with AN remain poorly characterized. The few studies of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in AN are limited to case reports[4-10] and studies with small sample sizes,[11-15] with a wide range in the reported prevalence of elevated ALT/AST, from 0% to 76%.[11] In initial studies researchers found that elevated ALT/AST was associated with lower body mass index (BMI)[11,13] and decreased percentage body fat.[13] In univariate analyses of the largest study to date, elevated aminotransferases were associated with increased age, male sex, and the pure restrictive form (vs binge-eating/purging type); however, these associations did not hold in the multivariate analyses.[11] More recent studies have suggested that elevated aminotransferase in AN may occur secondary to refeeding.[4]

The time course, evolution, and physiopathology of elevated aminotransferase during hospitalization for AN remain unclear. In particular, whether the etiology of elevated aminotransferase stems from degree of malnutrition vs refeeding remains a source of debate. Some reports have found resolution of liver enzyme abnormalities with nutritional support and hydration,[10,11] supporting malnutrition as a potential cause. In contrast, in a few reports authors have found elevations in liver tests during the process of refeeding.[4,7] In the largest study to date (n = 126), 96% of patients had normalizing aminotransferases by 4 weeks of enteral nutrition, whereas only 4% had worsening with refeeding.[11]

Therefore, the objective of this study was to analyze, in a large sample of adolescents with AN hospitalized in a tertiary children's hospital, the prevalence of elevated liver enzymes, predictors of elevated liver enzymes including degree of malnutrition and refeeding, and the evolution of elevated liver enzymes throughout the hospitalization.

%mBMI	Percentage median body mass index
ALT	Alanine aminotransferase
AN	Anorexia nervosa
AST	Aspartate aminotransferase
BMI	Body mass index
mBMI	Median body mass index

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Methods

Criteria for study eligibility included adolescents ages 10-22 years with AN admitted to the inpatient eating disorders unit at Lucile Packard Children's Hospital at Stanford between January 2007 and December 2012 for medical stabilization. Criteria for admission included one or more of the following: severe malnutrition (<75% median BMI [mBMI]), heart rate <50 beats per minute during the day or 45 beats per minute at night, hypotension <90/45 mm Hg, orthostatic changes in pulse and blood pressure, hypothermia <36.3°C, dehydration, electrocardiographic abnormalities, or electrolyte disturbances according to published national guidelines.[16,17] Only the first admission was included if patients subsequently were readmitted during the study period to ensure that the aminotransferase levels analyzed in this study would not reflect previous medical interventions.

Exclusion criteria included patients with bulimia nervosa or eating disorder not otherwise specified, subjects transferred from another facility after nutritional rehabilitation had already been initiated, and those who signed out against medical advice before they were medically stable.

Electronic medical records of eligible subjects with AN were reviewed for this retrospective cohort study. Demographic factors (sex, race, age), anthropometric measures (height and daily weight), and duration of illness were collected. BMI was calculated using weight in kilograms divided by the square of height in meters (kg/m^2). mBMI was defined as the 50th percentile BMI for age using the Centers for Disease Control and Prevention growth curves.[18] Percentage mBMI (%mBMI) on admission was defined as the patient's BMI on admission divided by the mBMI multiplied by 100. Rate of weight loss was defined as weight loss before admission divided by duration of illness (kg/month). Liver function tests were checked in all patients at admission and subsequently repeated approximately 1 week later based on the patient's clinical status or if initially abnormal. ALTs were selected because of their specificity for liver damage[19]; ALT ≥40 IU/L was considered elevated.[15] Serum chemistries, including phosphorus, were drawn on admission then at 6 a.m. every 24-48 hours for the first week, and afterward as clinically indicated; phosphorus >3.0 mg/dL was considered normal. Dietary recall and prescribed caloric intake on the first day of the hospitalization were reviewed and recorded by one investigator, a registered dietician. During admission, patients received a diet composed of approximately 40%-50% carbohydrate, 25%-30% protein, and 25%-30% fat, supplemented by a high-calorie liquid supplement consisting of 60% carbohydrate, 15% protein, and 25% fat. The Stanford University Human Subjects Research Committee approved the protocol.

Statistical Analyses

Quantitative statistical analyses were conducted with SPSS 12.0 for Windows (SPSS Inc, Chicago, Illinois). The primary outcome variable was elevation of aminotransferase (ALT ≥40 IU/L).[15] Bivariate and multivariate logistic regression was performed with presence of elevated aminotransferase as the binary dependent variable, and age, %mBMI on admission, duration of illness, initial prescribed calories, and rate of weight loss as continuous independent variables and sex as a binary independent variable. For initial prescribed calories, we chose increments of 200 kcal because for adolescents with eating disorders, calorie prescription is usually increased by increments of 200-300 kcal every 48-72 hours.[20] A scatter plot and best fit line were constructed with ALT (IU/L) as the y-axis and time (weeks) as the x-axis for patients presenting with elevated aminotransferase on admission.

Results

Overall, 356 subjects met eligibility criteria between 2007 and 2012 and were included in the study (Table I). They were predominantly female (89.0%) and non-Hispanic white (72.2%), but included a sizeable percentage of Hispanic (12.6%) and Asian (11.5%) subjects. Mean age was 16.1 ± 2.4 years. Average duration of illness was 1.1 years and average rate of weight loss was 1.7 kg per month before admission. They were moderately malnourished (BMI 15.9 ± 1.9) and were restricting their calories to <1000 kcal/d. Elevated liver enzymes (ALT ≥40) were present in 37.0% of patients on admission and 41.1% of patients at any point during the hospitalization. Only 6.2% had elevated liver enzymes 2 times the upper limit of normal (ALT ≥80) on admission, and only one patient

Table I. Demographic and clinical characteristics of sample upon first hospital admission for AN

	n	%/mean	SD	Range
Demographics				
Sex, %	356			
Female	317	89.0%		
Male	39	11.0%		
Race, %	356			
White (non-Hispanic)	257	72.2%		
Hispanic	45	12.6%		
Asian	41	11.5%		
Black	3	0.8%		
Native American	2	0.6%		
Other	8	2.2%		
Age, y	356	16.1	2.4	10.3-22.0
Clinical characteristics				
Duration of illness, y	356	1.1	1.1	0.1-6.5
BMI on admission, kg/m^2	356	15.9	1.9	9.1-20.7
Percentage median body weight on admission, %	356	78.2	8.5	41.9-102.3
Dietary recall, kcal	316	945.1	592.0	0-4200
Initial prescribed calories, kcal	355	1452.4	290.0	720-2800
Length of stay, d	356	14.1	9.9	2-91
ALT on admission	338	45.4	35.5	12-360
ALT ≥40 IU/L on admission	125	37.0%		
ALT ≥80 IU/L on admission	21	6.2%		
ALT ≥40 IU/L at any point during hospitalization	139	41.1%		
ALT ≥80 IU/L at any point during hospitalization	1	0.3%		