Acute liver injury and anorexia nervosa: a case report

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ABSTRACT

Anorexia nervosa is an eating disorder characterized by restriction of energy intake leading to a significant decrease in body weight. While it is primarily a psychiatric disorder, numerous medical complications can occur. In this article we describe a case of a 25-year-old woman with a 12-year history of severe restrictive anorexia nervosa that was referred to the Emergency Service of our Hospital, transferred from a psychiatric institute, for severe weight loss, dehydration, and progressive increase in transaminases. During the hospital stay she developed an acute liver injury with an increase in transaminase level up to 40× the ULN. Infective and immunological causes of acute hepatitis were excluded. In the suspect of severe starvation acute liver injury, we performed a nutritional assessment and started parenteral nutrition. After 15 days of parenteral nutrition, she gained 2.5 kg of body weight and liver tests were drastically reduced and nearly normal.

Introduction

Anorexia nervosa (AN) is an eating disorder characterized by restriction of energy intake leading to a significant decrease in body weight, intense fear of gaining weight or getting fat, disturbance in the way body weight or shape is experienced.[1] Although it is primarily considered a psychiatric disorder, several medical complications can occur, including electrolyte disorders, cardiovascular problems, endocrine disorders, osteoporosis, and gastrointestinal manifestations.[2] Achalasia, gastroesophageal reflux, alteration of gastric motility, liver abnormalities, impaired coagulation, pancreatic injury, superior mesenteric artery syndrome and rectal prolapse are the most common gastrointestinal complications.[3] Alteration of liver enzymes is quite commonly observed in this setting, and a number of case reports have described transaminase elevation in patients with AN.[4-11] Nagata *et al.* reported in anorexic patients aged 10-22 years old (n=356) a 37.0% prevalence of aspartate transaminase (ALT) >40 IU/L on admission, while the prevalence of ALT>80 IU/L was 6.2%.[12] Rosen *et al.* reported in older patients (22-36 yo, n=181) a 35.4% prevalence of alanine transaminase (AST) >120 IU/L or ALT>135 IU/L.[13]

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Case Report

DL, a 25-year-old woman with a 12-year history of severe restrictive AN, was referred to the Emergency Service of our Hospital, transferred from a psychiatric institute, for severe weight loss, dehydration, progressive increase in transaminases (AST 513 IU/L, ALT 559 IU/L) and hyponatremia (128 mEq/L). Upon admission, body weight was 22.5 kg [height 1.51 m, body mass index (BMI) 9.9]. Blood pressure (BP) was 55/40 mmHg and she presented with severe bradycardia (heart rate 35/min). The patient complained of abdominal discomfort and confusion. General examination showed severe cachexia, dehydration, acrocyanosis; thoracic, abdominal and neurological examinations were normal. Blood tests showed: white blood cells count 4640/mmc, hemoglobin 14.3 g/dL, platelets 174,000/mmc, international normalized ratio (INR) 1.26, glucose 39 mg/dL, sodium 122 mmol/L, potassium 4.3 mmol/L, albumin 5.2 g/dL, AST 735/35 IU/L, ALT 857/35 IU/L, creatine phosphokinase 443/170 IU/L, C-reactive protein 0.02 mg/dL.

The patient was admitted to our Internal Medicine Unit, where we immediately started rehydration therapy to correct severe dehydration and electrolyte imbalance. During the first days, the patient was extremely non-compliant with the therapeutic proposals (she refused i.v. liquids and the minimum caloric intake). Psychiatric therapy was implemented with olanzapine 5 mg p.o./die, sertraline 25 mg p.o./die and clonazepam 1 mg p.o./tid. On 4th day of hospitalization, after the development of progressive blurred speech and loss of consciousness, severe hypoglycemia (13 mg/dL) was documented and successfully treated with 10% glucose i.v. solution. However, liver enzymes continued to increase and on day 6 AST and ALT rose to 3658 IU/L and 3553 IU/L, respectively; INR was 1.57; infective and immunological causes of acute hepatitis were excluded (Table 1). In the suspect of severe starvation acute liver injury, we performed a nutritional assessment (BMI 9.21 - weight 21 kg - basal energy expenditure 804 Kcal/day, total energy expenditure 964 Kcal/day) and proposed parenteral nutrition; after discussion with the patient, her family, her psychiatrist and psychologist, she finally accepted. On day 7, parenteral nutrition was started, with an overall intake of 400 daily Kcalories to avoid refeeding syndrome[14-16] (see formulation A - Table 2) distributed during 12 h of continuous infusion and administered *via* a central venous catheter. On day 14 the caloric intake was raised to 600 Kcal/die (see Formulation B - Table 2). Liver function tests immediately began to improve, and serial controls showed normalization of INR and sodium levels (Table 3 and Figure 1).

After some days of acceptable compliance and adherence to the nutritional treatment, the patient became agitated, showing anxiety and suspicious behavior towards her parents and the Hospital staff.

On day 22, she developed fever (up to 39.5°C); blood cultures were taken, empirical antibiotic therapy (ceftriaxone i.v. 1 g/die) was started and, in the suspect of a central venous device infection, parenteral nutrition was discontinued. Blood cultures resulted positive for *Candida albicans*, therefore antifungal therapy (caspofungin 50 mg i.v./die) was initiated. After excluding thrombosis of the jugular vein, the central device was removed.

Antimycotic therapy was rapidly effective and in 48 h the patient was afebrile; we repeated blood cultures, which resulted negative. The patient refused any additional proposal of nutrition and asked to be discharged. After 26 days of hospitalization and 14 of parenteral nutrition, she gained 2.5 kg of body weight (BMI 11.0), liver tests were drastically reduced and nearly normal (AST 78 IU/L, ALT 150 IU/L), electrolytes were normal (sodium 136 mmol/l, potassium 3.8 mmol/L), BP was 85/55 mmHg, heart rate 70/min.

In agreement with the Psychiatrist, the patient was discharged and subsequently followed up by the psychiatric territorial service.

Table 1. Tests performed in order to rule out other causes of acute liver injury in the patient.

Test performed	Result
ANA	neg
IgA anti-transglutaminase	neg
IgG anti deaminated gliadin peptides	neg
Liver Immunoblot	neg
Ceruloplasmin	21 mg/dL
Anti CMV IgG	pos
Anti CMV IgM	neg
Anti EBV IgG	pos
Anti EBV IgM	neg
Anti HAV IgM	neg
HBsAg	neg
Anti HBc	neg
Anti HCV	neg

ANA, anti-nuclear antibody; IgA, IgG, IgM, immunoglobulin A, G, and M; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, HCV, hepatitis A and C viruses.

Table 2. The two different formulations administered to the patient, provided by a nutrition consultant.

	Formulation A	Formulation B
Volume	1000	1000
Total kilocalories	400	600
g glucose	30	28
g lipids (as fish oil)	20	35
g amino acids	20	26
Sodium (mEq)	30	40
Calcium (mEq)	5	5
Potassium (mEq)	20	20
Magnesium (mEq)	6	7
Chlorine (mEq)	30	40
Phosphate (mEq)	20	20
Mixture of trace elements (mL)*	5	5
Multivitamin preparation (vial)°	1 fL	1 fL

*1 mL of trace elements contained: chromic chloride 6 H_2O 5.33 µg, copper chloride 2 H_2O 0.34 mg ferric chloride 6 H_2O 0.54 mg, manganese chloride 4 H_2O 99.0 µg, potassium iodide 16.6 µg sodium fluoride 0.21 mg, sodium molybdate 2 H_2O 4.85 µg, sodium selenite anhydrous 6.90 µg zinc chloride 1.36 mg; °1 vial of multivitamin preparation contained: retinol palmitate corresponding to retinol (vitamin A) 3500 IU, cholecalciferol (vitamin D3) 200 IU, DL α-tocopherol 10.2 mg corresponding to α-tocopherol (vitamin E) 11.2 IU, ascorbic acid (vitamin C) 125 mg, nicotinamide (vitamin B3) 46 mg, dexpanthenol 16.15 mg corresponding to pantothenic acid (vitamin B5) 17.25 mg, pyridoxine hydrochloride 5.5 mg corresponding to pyridoxine (vitamin B6) 4.53 mg, riboflavin sodium phosphate 5.67 mg corresponding to riboflavin (vitamin B2) 4.14 mg, cocarboxylase tetrahydrate 5.8 mg corresponding to thiamine (vitamin B1) 3.51 mg, folic acid 414 mcg, D-biotin 60 mcg, cyanocobalamin (vitamin B12) 5.5 mcg.

Discussion and Conclusions

AN is a well-known psychiatric disorder associated with a variety of medical complications, including electrolyte disorders, cardiovascular problems, endocrine disorders, osteoporosis and gastrointestinal manifestations.[2]

Mild to moderate hypertransaminasemia in AN has been reported[4-9] and appeared to be associated with hepatic steatosis induced by an imbalance between hepatic triglyceride synthesis and decrease in lipoprotein synthesis, due to decreased amino acid availability; in most cases, it resolves with nutritional improvements:[17] marked elevation of transaminase levels, jaundice and coagulopathy, as seen in our case, are a much rarer presentation of acute liver injury associated with AN.

The pathological mechanisms involved remain unclear; some authors have suggested that hepatic hypoperfusion (ischemic hepatitis) could be the main pathogenetic mechanism involved in acute liver injury in AN.[18,19] On the other hand, Ratou and his colleagues have questioned this hypothesis by examining liver biopsies from 12 patients with acute hepatic injury due to anorexia nervosa.[17] None of the biopsies showed hallmarks of ischemic injury, and the Authors supposed starvation-induced hepatocyte autophagy to be the main pathogenetic mechanism. In a recent case report, Massoud and Crowe described the case of a 24-year-old man with markedly elevated transaminases, jaundice and coagulopathy;[20] in this case, AST and

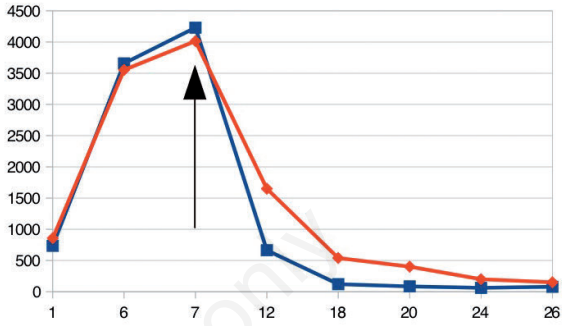

Figure 1. Transaminase trend. The arrow points start of intravenous nutrition.

Table 3. Biochemical findings and trends.

	Admission	Day 6	Day 7	Day 12	Day 18	Day 20	Day 24	Discharge
WBC 10^9/L	4.64	3.17	3.68	2.06	1.67	1.7	4.79	
N% - L%	51-44	45-50		50-41	47-37	63-25	57-32	
Hb (MCV) g/dL (fL)	14.3 (87)	13.20 (85)	13.9 (87)	10.1 (89)	8.6 (89)	9 (89)	8.9 (88)	
Hct %	39.7	35.4	38.7	28.4	24.8	25	30.9	
PLT 10^9/L	174	73	55	39	86	115	176	
INR-aPTT	1.27-1.32	1.57	1.42	1.03				
Glucose mg/dL	39			141		81	69	
Creatinine mg/dL	0.52	0.5	0.54	0.36	0.3		0.34	0.26
Na mmol/L	122	127	124	132	136	134	122	136
K mmol/L	4.3	3.9	4.3	4,3	3.6	3.8	4	3.8
Cl mmol/L			92	95	101		88	103
Ca mg/dL	9.6		8.2	8.6	8.1	8.4	8.1	7.1
P mg/dL			2.1	3.6	1.8	3.7	3	4.5
Mg mg/dL	2.3		1.8	1.7		1.9	1.6	1.5
Albumin g/dL	5.2		4.2		3.18	3.5		
Bilirubin tot./direct mg/dL	1.90/0.46		1.48/0.35	0.53/0.13	0.44/0.1			
AST IU/L	735	3658	4231	663	120	84	61	78
ALT IU/L	857	3553	4015	1650	539	401	199	150
GGT IU/L				163	125	119	114	95
ALP IU/L				279	177	180	146	147

WBC, white blood cells count; Hb, hemoglobin; MCV, mean corpuscular volume; Hct, hematocrit; PLT, platelets; INR, international normalized ratio; aPTT, activated partial thromboplastin time; Na, sodium; K, potassium; Cl, chlorum; P, phosphorus; Mg, magnesium; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.

ALT values reached a peak of 2033 IU/mL and 1410 IU/mL respectively (up to 40× the ULN), and completely returned to normal levels after proper nutrition; they managed to get a liver biopsy that excluded ischemic hepatitis; surprisingly, the histological changes they found were minimal in contrast with the marked elevation of transaminases.

We could not perform a liver biopsy because of the poor compliance of our patient; however, we still believe that our case is peculiar, as it is the only case described with such a marked elevation of transaminases (up to 120× the ULN); moreover, hypertransaminasemia almost normalized after only 14 days of proper nutrition.

This case report demonstrates that AN can cause acute life-threatening medical conditions, such as the acute liver injury we described, for which pathogenesis is still largely unclear. What is clear is that these conditions need a rapid recognition and a multidisciplinary approach (involving Psychiatrist-Nutritionist-Internist) to initiate as soon as possible a proper treatment, in order to improve the otherwise poor prognosis of these fragile patients.

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