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 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

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, and progressive increase in transaminases (AST 513 IU/L, ALT 559 IU/L). 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.
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 syndrome14-16 (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.

| 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 HBe        | neg    |
| Anti HCV        | neg    |

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

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

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

| Volume | Formulation A | Formulation B |
|--------|---------------|---------------|
| 1000   | 1000          |               |
| 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 | 1 FL          | 1 FL          |

*1 mL of trace elements contained: chromic chloride 6 H2O 5.33 µg, copper chloride 2 H2O 0.34 mg, ferric chloride 6 H2O 0.54 mg, manganese chloride 4 H2O 99.0 µg, potassium iodide 16.6 µg, sodium fluoride 0.21 mg, sodium molybdate 2 H2O 4.85 µg, sodium selenite anhydrous 6.90 µg, zinc chloride 1.36 mg; "1 vial of multivitamin preparation contained: retinol palmiatate 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, desipanthenol 16.15 mg corresponding to pantothentic acid (vitamin B5) 17.25 mg, pyridoxine hydrochloride 5.5 mg corresponding to pyridoxine (vitamin B6) 4.55 mg, riboflavin sodium phosphate 5.67 mg corresponding to riboflavin (vitamin B2) 4.14 mg, cobalamin tetrahydroacetylated 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.
Case Report

ALP, alkaline phosphatase.

Clear; some authors have suggested that hepatic biopsies from 12 patients with acute hepatic injury due to anorexia nervosa have questioned this hypothesis by examining liver function tests, due to decreased amino acid availability; in most cases, it resolves with nutritional improvements. 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 hypertransaminasemia (ischemic hepatitis) could be the main pathogenetic mechanism involved in acute liver injury in AN. 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. 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; in this case, AST and ALT increased dramatically. The authors speculated that this finding could be related to the autophagic process that occurs in response to prolonged starvation and that autophagy may play a role in the pathogenesis of liver injury in AN.

Table 3. Biochemical findings and trends.

| Parameter          | 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     | 122     | 136     |
| K mmol/L           | 4.3       | 3.9     | 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     | 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, chloride; P, phosphorus; Mg, magnesium; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase.

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