Case report

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Marked elevation of transaminases and pancreatic enzymes in severe malnourished male with eating disorder

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Abstract

We report a case of a 45 year old Caucasian malnourished male with an history of eating disorder who developed severe liver and pancreatic damage and multiorgan disfunction. At admission to our department, his body mass index (BMI) was 11.1. Biochemical evaluation showed elevated serum levels of transaminases (AST= 2291 U/L, ALT= 1792 U/L), amylase (3620 U/L), lipase (4102 U/L), CPK= 1370 U/L, LDH= 2082 U/L. No other cause of acute liver and pancreatic damage was evidenced. Haematological disorders (anemia, thrombocytopenia, leukopenia) found on admission seem related to bone marrow hypoplasia and to gelatinous marrow transformation described in severe state of malnutrition. Although a moderate increase in liver and pancreatic enzymes are a common finding in malnourished patients, only a small number of reports describes severe liver injury and multiorgan dysfunction. After a few days of treatment (hydration and nutritional support) a marked decrease of serum transaminases, lipase, amylase, CPK, LDH occurred, despite a transient increase in these levels secondary to refeeding syndrome. The association of chronic malnutrition and a decrease in systemic perfusion may be responsible for multiorgan dysfunction. In our patient the high levels of transaminases and pancreatic enzymes were the most important biochemical abnormalities normalized after refeeding. ***Clin Ter 2013; 164(5):e387-391.*** **doi: 10.7417/CT.2013.1619**

Key words: *eating disorders, liver injury, malnutrition, multiorgan dysfunction, pancreatic enzymes, refeeding syndrome*

Introduction

Chronic malnutrition is often complicated by endocrine dysregulation, fluid and electrolyte imbalances, cardiovascular and hemodynamic abnormalities, haematological disorders, osteopenia and osteoporosis, increased serum levels of transaminases, amylase and lipase that return within the normal range after an adequate nutritional and volaemic support. We report a case of a 45 year old Caucasian malnourished male with an history of eating disorder who developed severe and unusual liver and pancreatic damage. Although a moderate increase in liver and pancreatic enzymes are a common finding in malnourished patients, only a small number of reports describes severe liver and multiorgan injury.

Case report

On November 2011, a 45 year old caucasian man with an history of eating disorder was admitted to the emergency department because of collapse. The biochemical analyses showed hypoglycemia associated with a marked increase in pancreatic and liver enzymes. He was transferred to our medical unit with the provisional diagnosis of "collapse and pancreatitis in an anorexic subject." When the patient was 35 years old he weighed 70 kg and his body mass index (BMI) was 24.2 Kg/m^2. At that time he underwent plastic surgery for pseudo-gynecomastia. Subsequently, he manifested sexual identity disorder associated with drastic changes in his dietary habits with an obsessive-phobic component, reduction of food intake and marked weight loss. For these reasons the patient had undertaken a discontinued diagnostic-therapeutic approach in a psychiatric clinic.

On January 2011, he was hospitalized in an internal medicine department for "severe malnutrition syndrome complicated by caloric-protein deficiency, myopathy and osteoporosis" and was discharged with a note to contact a specialized center in eating disorders, but the patient refused to continue the diagnostic therapeutic process. When the patient was admitted to our department his weight was 31 kg and his height 167 cm (BMI = 11,1 Kg/m^2). Physical examination revealed poor trophic-nutritional state, body temperature of 35°C, blood pressure of 90/60 mmHg, heart rate of 54 beats/min, SpO_2 100%, dry skin and mucous membranes, anicteric sclerae, carotin icterus, scarse body hair, edema on the back of the foot, absence of subcutaneous fat, severe muscle hypotonia-hypotrophy with difficult ambulation, testicular hypotrophy. Cardiovascular, pulmonary and neurologic exams were normal. His chest showed severe kyphoscoliosis. His abdomen was scaphoid, with bowel sounds and without hepatosplenomegaly. Initial laboratory values showed a leukocyte count of 3.04 x 10^3/

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μl (n.v. 4-11) (neutrophils 87.8% -n.v, 40-74, lymphocytes 8.9% - n.v. 20-48, monocytes 3.3% - n.v. 3-11), hemoglobin of 10,3 g/dL (n.v. 12-18) and a hematocrit of 30.4% (n.v. 37-52); MCV was 93.8 fl (n.v. 80-99) and RDW 14.4% (n.v. 11-15); platelets count was of 39 x 10^3/μl (n.v. 150-450). Serum electrolytes showed a natremia of 132 mEq/L (n.v 132-146) and potassium of 3.7 mEq/L (n.v. 3.7-5.4). Transaminases were elevated (AST 2291 U/L-n.v.< 37, ALT 1792 U/L-n.v.< 41) associated with a marked increase in α-amylase (3620 U/L- n.v. 28-100), lipase (4102 U/L - n.v. 13-60), lactate dehydrogenase (LDH 2082 U/L-n.v. 240-480) and creatine-phosphokinase (CPK 1370 U/L - n.v. <308). Serum alkaline phosphatase was 257 U/L (n.v. 40-129) and γ-glutamiltranspeptidase was of 171 U/L (n.v. 8-61). Total and conjugated bilirubin were 1.4 (n.v. <1.2) and 0.02 mg/dl (n.v.<0.3) respectively, pseudocholinesterase was 2019 U/L (n.v. 5320-12920) and albumin was of 3.4 g/dl (n.v. 3.4-4.8). INR was 1.31 (n.v. 0.8-1.2); fasting plasma glucose was 33 mg/dl (n.v. 70-100) in absence of clinical symptoms. The ammonia value was 13 umol/L (n.v. 11-35), cyanocobalamin 2001 pg/ml (n.v. 180-900), folates 20 ng/ml (n.v. 3-18), total vitamin D 11 ng/ml (n.v.15-80), ferritin 1045 ng/ml (n.v. 30-400) and serum iron 54 mcg/dl (n.v. 58-158). Fecal haemoccult was negative. The hormonal parameters showed mild hypercortisolism (cortisol at 8:00 am was 26 g/dl n.v. 6.2-19.4 and cortisol at 06:00 pm was 13 mg/dl n.v. 2.3 - 11.9), GH was at the upper limit (5.23 ng/ml - n.v. 0-6) and the values of thyroid hormones (TSH 2.35 μUI/ml -n.v. 0,27-4,2; FT4: 1.59 ng/dl -n.v. 0,9-1,7; FT3: 2.9 pg/ml -n.v. 2-4.4) were normal. Testosterone value was 0.39 ng/ml (n.v. 2.4-8.3); FSH: 3.92 mIU/ml (n.v. 1.5-12.4); LH: 2.49 mIU/ml (n.v. 1.7-8.6). Parathormone value was 196 pg/ml (n.v. 11-54). Urine analysis was normal. Creatinine clearance was 107 ml/min. The electrocardiogram showed sinus bradycardia (55 beats/minute).

Radiographic test revealed severe osteopenia and multiple vertebral and sacral fractures. The densitometry values showed a T-score of -3.3 SD and a Z score of -3.1 SD in lumbar vertebrae. At proximal portion of the left femur T-score was -3.1 SD and Z-score -2.9 SD. Psychiatric examination revealed: "a normo-oriented subject, emotionally labile, irritable, suspicious, sometimes hostile, manipulative; evidence of schizotypical traits of personality with obsessive ideation and erroneous beliefs about the somatic self and unadequate reality testing".

The common causes of liver and pancreatic injury were excluded; there was no history of alcohol abuse, use of drugs or toxic substances. Serologic tests for the major hepatotropic viruses (hepatitis viruses A, B and C, Cytomegalovirus, Epstein-Barr virus), for HIV and parvovirus were negative. Imaging studies (ultrasound, computed tomography and nuclear magnetic resonance) failed to demonstrate any abnormalities in liver, pancreas, gallbladder and biliary tract morphology.

Clinical course

The initial medical treatment included intavenous infusion of 10% glucose solution (1500 cc/day). Starting on the third hospital day parenteral nutrition was initiated later associated with oral nutrition. During the first week of treatment infusion of sodium phosphate, magnesium sulfate and thiamine was necessary. After a few days of treatment a marked decrease in levels of transaminases, lipase, amylase, CPK and LDH occurred, despite an initial and further increase in these levels. At the second week of hospitalization an increase in edema of the lower extremities in association with a decrease in the levels of hemoglobin (6.2 g/dl), hematocrit (18%) and albumin (1.7 g/dl) occurred, probably consequent to the refeeding syndrome. Therefore, we reduced his caloric and water intake, infused albumin and low doses of furosemide; subsequently the edema disappeared. After transfusion with red blood cells and erythropoietin therapy (12000 IU/week) hemoglobin levels increased to around 10 g/dl. From the third hospital week, a rapid increase in the platelet count occurred and it gradually returned to normal. At discharge, after a 26-day hospitalization, the patient had a body weight of 32 kg (BMI = 11.5), the clinical and laboratory parameter had improved (AST 38 U/L, ALT 27 U/L, total bilirubin 0.9 mg/dl, alkaline phosphatase 221 U/L, γ-GT 36 U/L, LDH 504 U/L, CPK 39 U/L, α-amylase 262 U/L, lipase 256 U/L, hemoglobin 10.1 g/dl, WBC 4.02 x 10^3/ul, platelets 220 x 10^3/ul (Fig. 1). After physiotherapy, the patient had largely regained his ability to walk independently. On the basis of the psychiatric consultation olanzapine 5 mg/die had been started and the patient was referred to a specialized center for eating disorders.

Discussion

On admission the patient showed an eating disorder which was secondary to a schizotypical personality with erroneous beliefs about the somatic self, obsessive ideas, sitophobia and absence of DSM-IV criteria for the anorexia nervosa diagnosis. The latter can not however be excluded because of the absence of anamnestic data about the onset of the psychiatric disorders. However, for the state of severe malnutrition and the organ complications, our patient is similar to subjects with anorexia nervosa. Chronic malnutrition and anorexia nervosa are often complicated by endocrine dysregulation (hypogonadism, hypercortisolism, GH-resistance, altered regulators of hunger), fluid and electrolyte imbalances, cardiovascular and hemodynamic abnormalities (bradycardia and arrhythmia, hypotension, heart failure), haematological disorders, osteopenia and osteoporosis, increased serum levels of transaminases, amylase and lipase that return within the normal range after an adequate nutritional and volaemic support. Anorexia nervosa is associated with a mortality rate of 5.6% per decade (1-3). High serum levels of amylase and lipase are often found in the absence of clinical and instrumental evidence of pancreatic damage (4-6). However, in patients with chronic malnutrition have also been found cases of idiopathic acute recurrent pancreatitis (7). After a review of the literature, we found a small number of reports describing severe liver injury and multiorgan dysfunction in anorexia nervosa. In 12.2% of patients with anorexia nervosa, a moderate increase in transaminase levels was observed; other reports showed transaminase elevation in 50% of the cases. Incidence and severity of hypertransaminasemia were greater in the patients with low BMI, especially in young men. Transaminase levels

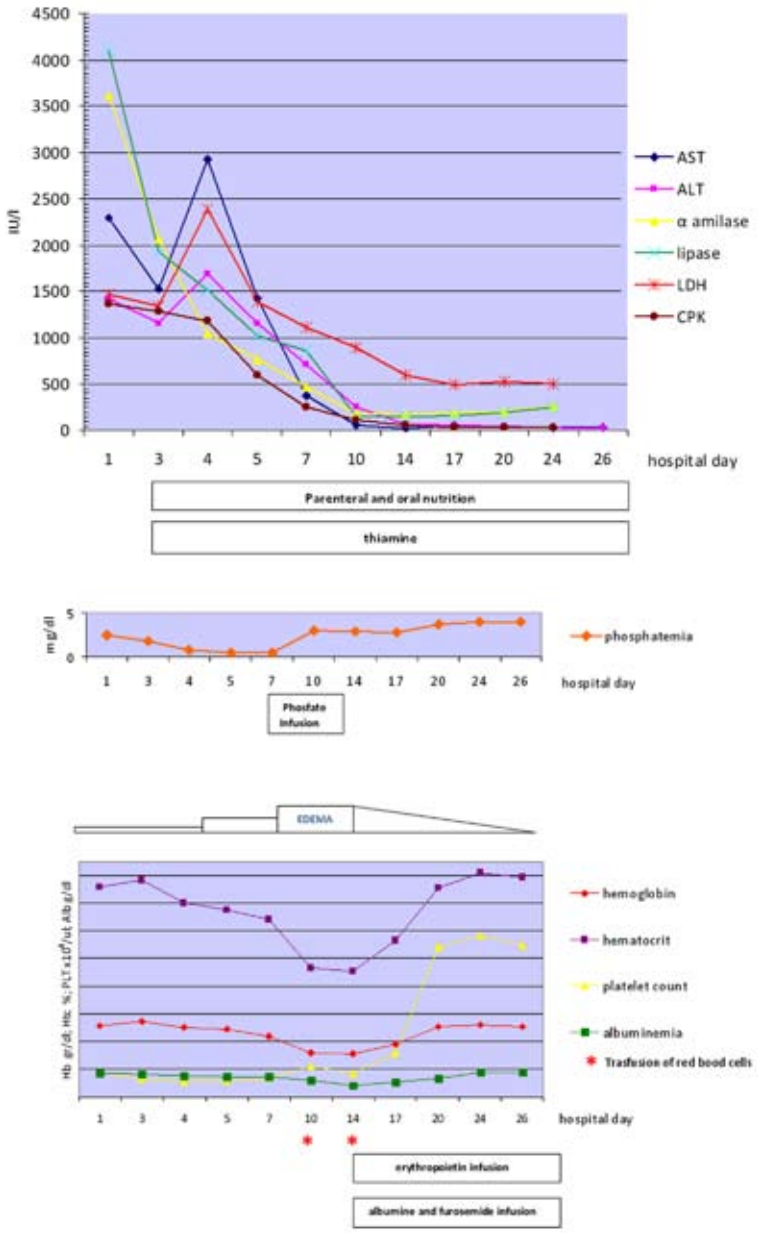

Fig. 1. Evolution of biological parameters during hospitalization.

>200 U/L were observed in 76% of patients with anorexia nervosa and a BMI <12 Kg/m^2; however rare cases of severe hepatic impairment was reported (8-9). Despite a probable multiorgan injury, in our patient the high levels of transaminases and pancreatic enzymes were the most important biochemical abnormalities found which normalized after refeeding. The mechanism of hypertransaminasemia is unclear. According to several studies, it is probably caused by ischaemic hepatitis secondary to liver hypoperfusion. Chronic malnutrition is in fact associated with dehydration, hypovolemia, decreasing in cardiac output, marked hypotension and arrhythmias secondary to electrolyte imbalance which may be exacerbated during refeeding. Our patient showed no signs of cardiac dysfunction, but severe dehydration and hypotension may have been responsible for the reduction in the liver perfusion. Other hypothesis which might lead to liver injury involves changes in hepatocyte lipid metabolism (increased production of triglycerides associated to decreased beta-oxidation of fatty acids), the selenium deficiency followed by the reduction of glutathione-peroxidase activity and increased oxidative stress and iron accumulation in hepatic cells. In some cases, imaging and histologic studies have detected a fatty liver. The largest series of liver biopsy have showed glycogen depletion, trabecular atrophy, sinusoidal fibrosis, autophagosomes or the presence of aggregates of Kupffer cells. It has been reported that steatohepatitis similar to NASH can occur in patients during total parenteral nutrition (9-14).

However the cause of hypertransaminasemia is not only due to liver injury but to a multiorgan injury, as suggested

by the elevated CK and LDH levels found in this patient and in several other cases described in literature in which increased levels of non-hepatic isoforms of LDH have also been shown (15). A transient increase in transaminases also occurs after refeeding. An inadequate nutritional treatment may cause the refeeding syndrome. This syndrome is defined by a severe and potentially fatal fluid and electrolyte imbalance, associated with metabolic abnormalities occurring in malnourished patients undergoing refeeding, whether orally, enterally, or parenterally (16). It is characterized by neurological symptoms (delirium, lethargy, coma), nausea, respiratory and heart failure, hypotension, arrhythmias, hematologic disorders (anemia, thrombocytopenia, abnormal leukocyte function). Hypophosphatemia is the most frequently observed abnormality in association with hypomagnesemia, hypokalaemia, vitamin deficiencies (thiamine) and hypoalbuminemia. Once the subjects at risk of refeeding syndrome are detected, it is advisable to start with a caloric intake of 5-10 kcal/kg per day and to increase slowly. Vitamin supplements (thiamine and vitamin B complex) should be started straight away and fluid balance carefully controlled. In order to prevent the hypophosphatemia a glucose intake of 4-7 mg/Kg/min and a phosphate supplement (31-62 mg/100 kcal) is recommended (17, 18). Mild asymptomatic hypoglycemia is commonly found in anorexia; cases of hypoglycemic coma, often associated with hepatic impairment, are rare. Hypoglycemia is an unfavorable prognostic factor in these patients. The correct pathogenesis of hypoglycemia has not been elucidated but several mechanisms including depletion of liver glycogen, glucagon secretion deficiency and decreased gluconeogenesis have been proposed (19). In our patient haematogical test showed thrombocytopenia, leukopenia (with lymphocytopenia), anemia and increased levels of ferritin and vitamin B12. Anemia and leukopenia are found in approximately one-third of the anorexic subjects while thrombocytopenia in 11.5%. The reticulocyte count is usually normal or reduced. Iron deficiency is an uncommon finding in these patients, especially in males. The ferritin levels, elevated in 30% of cases, are reduced to the normal range after refeeding. Vitamin B12, folate and erythropoietin levels are usually normal; the latter increase significantly during the refeeding with weight gain. Leukopenia was observed in 29-36% of the cases. Granulocytopenia, lymphocytopenia and normal lymphocytes T/B ratio are frequent (20), although the exact pathogenic mechanisms of these features remain unclear. In the 50% of patients with anorexia nervosa and hematological changes in the peripheral blood count, signs of bone marrow hypoplasia and less frequently a complete atrophic transformation with deposition of amorphous material were observed. This alteration has been described as "gelatinous degeneration". It would be secondary to a chronic deficit of carbohydrates and it regresses rapidly after an adequate refeeding to which the use of hematopoietic growth factors have been associated (21, 22). Altered levels of inflammatory cytokines (1L-1, IL-6, TNF-α) and leptin may also contribute to the genesis of hematopoietic disorders (23). In our case the haematological disorders found on admission seem to be the result of the severe state of malnutrition. Anemia, treated with red blood cell transfusion and erythropoietin, could depend on the refeeding syndrome. After the nutritional treatment, a normalization of the blood platelet count associated with a slightly increase of the leukocyte has been observed. Osteopenia and osteoporosis are further complications of chronic malnutrition. In a group of adult women with anorexia the prevalence of osteopenia would reach 92%. A reduction in bone mineral density (BMD) was observed in 41% of female adolescents and in 35% of anorexic young males. Possible causes involve the hypoestrogenism and the hypoandrogenism, the hypercortisolism, the reduction of IGF-1 associated with GH-resistance, the high levels of appetite regulators such as ghrelin and peptide YY (24). Our patient showed severe osteoporosis, low levels of vitamin D3 and testosterone, increased levels of PTH and cortisol.

Conclusions

In this case the association of chronic malnutrition and the decrease in systemic perfusion, secondary to dehydration and hypotension, may be responsible for multiorgan injury. In our patient the high levels of transaminases and pancreatic enzymes were the most important biochemical abnormalities normalized after refeeding.

A treatment strategy aimed at the nutritional support and at the correction of the electrolyte imbalance associated with the supplement of thiamine and erythropoietin was helpful in achieving a favorable outcome.

References

1. Smink FR, Van Hoeken D. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Curr Psychiatry Rep 2012; 14:406-4
2. McLean AEM. Hepatic failure in malnutrition. Lancet 1962; 2:1292-4
3. Bola OA, Bolodeoku JO. Serum aspartate and alanine aminotransferase activities in protein energy malnutrition. Enzyme 1982; 28:300-4
4. Hempen I, Lehnert P, Fichter M, et al. Hyperamylasemia in anorexia nervosa and bulimia nervosa. Indication of a pancreatic disease? Dtsch Med Wochenschn 1989; 114:1913-6
5. Park JH, Lee TH, Cheon SL, et al. Severe acute liver and pancreas damage in anorexia nervosa. Korean J Gastroenterol 2009; 54:257-60
6. Nordgren L, Von Scheele C. Hepatic and pancreatic dysfunction in anorexia nervosa: a report of two cases. Biol Psychiatry 1977; 12:681-6
7. Morris LG, Stephenson KE, Herring S, et al. Recurrent acute pancreatitis in anorexia and bulimia. JOP. J Pancreas 2004; 5:231-4
8. Furuta S, Ozawa Y, Maejima K, et al. Anorexia nervosa with severe liver dysfunction and subsequent critical complications. Intern Med 1999; 38:575-9
9. Di Pascoli L, Lion A, Milazzo D, et al. Acute liver damage in anorexia nervosa. Int J Eat Disord 2004; 36:114-7
10. Fong HF, Di Vasta AD, Di Fabio D, et al. Prevalence and predictors of abnormal liver enzumes in young women with anorexia nervosa. J Pediatr 2008; 153:247-53
11. Tsukamoto M, Tanaka A, Arai M, et al. Hepatocellular injuries observed in patients with an eating disorder prior to nutritional treatment. Intern Med 2008; 47:1447-50

12. Dowman J, Arulraj R, Chesner I. Recurrent acute hepatic dysfunction in severe anorexia nervosa. Int J Eat Disord 2010; 43:770-2
13. Hanachi M, Melchior JC, Crenn P. Hypertransaminasemia in severely malnourished adult anorexia nervosa patients: risk factors and evolution under enteral nutrition. Clin Nutr 2012; xxx:1-5
14. Nieves JR, Kozaiwa K, Parrish R, et al. Marked transaminase elevation in anorexia nervosa. Dig Dis Sci 2000; 45:1959-63
15. Ozawa Y, Shimizu T, Shishiba Y. Elevation of serum aminotransferasis as a sign of multiorgan-disorders in severely emaciated anorexia nervosa. Intern Med 1998; 37:32-9
16. Crook MA, Hally V, Panteli V. The importance of the refeeding syndrome. Nutrition 2001; 17:632-7
17. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ 2008; 336: 1495-98
18. Viana L, Burgos M, Silva R. Refeeding syndrome: clinical and nutritional relevance. ABCD Arq Bras Cir Dig 2012; 25:56-9
19. Chin CS, Ito N, Taguchi M, et al. Hypoglicemic coma in a patient with acute exacerbation of liver injury induced by oral intake of nutrients. Intern Med 2010; 49:1553-6
20. Hutter G, Ganepola S, Hofmann WK. The hematology of anorexia nervosa. Int J Eat Disord 2009; 42:293-300
21. Orlandi E, Boselli P, Covezzi R, et al. Reversal of bone marrow hypoplasia in anorexia nervosa: case report. Int J Eat Disord 2000; 27:480-2
22. Charania RS, Kern WF, Charkrabarty S, et al. Successful management of gelatinus trasformtion of the bone marrow in anorexia nervosa with hematopoietic growth factors. Int J Eat Disord 2011; 44:469-72
23. Vaisman N, Hahn T, Karov Y, et al. Changes in cytokine production and impaired hematopoiesis in patients with anorexia nervosa: the effect of refeeding. Cytokine 2004; 26:255-61
24. Misra M, Klibanski A. Anorexia nervosa and osteoporosis. Rev Endocr Metab Disord 2006; 7:91-9