Case Report ISSN 2639-9334

Gastroenterology, Hepatology & Digestive Disorders

Severe Transaminitis and Iron Deposition Induced by Anorexia Nervosa

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Received: 05 August 2020; **Accepted:** 31 August 2020

Citation: Wilson Lee, Raymond E. Kim. Severe Transaminitis and Iron Deposition Induced by Anorexia Nervosa. Gastroint Hepatol Dig Dis. 2020; 3(2): 1-3.

ABSTRACT

Introduction: *Anorexia nervosa is associated with a vast amount of general medical complications caused by severe weight loss and malnutrition. Common complications from affected organ systems lead to many physiologic disturbances and multi-organ complications, but rarely severe transaminitis or iron deposition. We discuss a case report of severe transaminitis and iron deposition in a patient with anorexia nervosa.*

Case: *31 year old male presents to the ED with a history of altered mental status and found to have severe transaminitis. Introduction of nutrition lead to a quick downtrend in liver transaminases with eventual normalization. Additionally, iron deposition as seen in the liver of our patient.*

Discussion: *Severely elevated transaminitis has been a rare complication of anorexia nervosa. Starvation induced autophagy has been a proposed mechanism. There has been one case report of hepatic iron deposition in a patient with anorexia nervosa. Iron deposition has been seen in starved mice livers with gluconeogenesis and alteration in iron homeostasis possibly playing a role.*

Keywords

Anorexia nervosa, Malnutrition, Transaminitis, Acute liver injury.

Introduction

Anorexia nervosa is associated with many medical complications caused by severe weight loss and malnutrition. All major organ systems are affected and result in complications such as amenorrhea, hypoglycemia, hypotension, bradycardia, arrhythmias but rarely transaminitis [1]. Multiple case reports have emerged showing an association with severe malnutrition in anorexia nervosa patients and transaminitis. Of all reported cases of starvation induced severe transaminitis, male patients were rarely seen [2]. Additionally, there has only been one case report in which iron deposition was seen in the liver of a patient with anorexia nervosa [5]. We discuss a case report of a young male patient found to have severe transaminitis and iron deposition in his liver associated with anorexia nervosa.

Case

A 31-year-old male with a past medical history of autosomal recessive polycystic kidney disease (ARPKD) presented to the ED with a history of altered mental status. According to his parents, he had progressively worsening confusion with slow mentation within the two days prior to presentation. His parents have noted that he has been losing weight with an associated decrease in appetite over the past couple of months. Upon presentation, his vital signs were pertinent for bradycardia (42bpm). His weight was noted to be 39.5kg corresponding with a BMI of 13.23 kg/m^2. On physical examination the patient was found to be cachexic with temporal wasting. He was lethargic with slow speech; occasionally staring off and taking long pauses with difficulty keeping his eyes open. There was no scleral icterus or skin changes. Abdominal exam did not reveal any organomegaly or tenderness to palpation.

Laboratory data on admission were as follows Na+ 130 mmol/L (N: 136–144), K+ 3.8 mmol/L (N: 3.6–4.6), Cl- 90 mmol/L (N: 98-107), creatinine 1.81 mg/dl, Mg2+ 1.80 mmol/L (N: 1.6–2.3), P2- 4.4 mmol/L (N: 2.5-4.5), Ca2+ 8.8mmol/L (N: 8.5-10.1). Platelets 127 K/L (N: 150–350), hemoglobin was 10.3 gm/dl and Leucocytes 2.8 k/UL. Additionally, liver function tests (LFTs) were severely abnormal with ALT 710 u/L (N: 9–42), AST 1,515 u/L (N: 11–42), total bilirubin 1.4 mg/dl (N: 7–25), direct bilirubin

0.2 (N: 0.0-0.3), alkaline phosphatase 216 u/L (N: 45-117), PTT 14.6 sec, INR 1.1, and albumin was 4.1 gm/DL.

Prior to this hospitalization, his liver function tests (LFTs) were within normal limits and he had no prior history of liver disease. The patient was started on IV hydration and multivitamins. On Day 2, there was acute worsening of LFTs with AST rising to 1,920 u/L, ALT 2,230 u/L, alkaline phosphatase 226 u/L, and total bilirubin of 1.7 mg/dl. Viral hepatitis serology, serum Tylenol and alcohol levels were negative. Abdominal ultrasound revealed a coarsened liver echotexture and possible subtle nodular contour suggestive of underlying parenchymal liver disease. An MRI was performed which showed iron deposition within the liver and spleen consistent with secondary hemosiderosis. Genetic testing for hemochromatosis (H63D, C282Y, S65C) was negative. Additional workup included ceruloplasmin, alpha1-antitrypsin, ANA, AMA, smooth muscle antibody, HIV, and transglutaminase Ab IgA which were all negative. Iron studies showed ferritin 4,697 ng/ml (N: 12-300), Iron 179g (13/5-17.4g), transferrin 131, TIBC 187, Iron Sat 96% (N: 25-35%). Liver biopsy was recommended, however the patient's family refused.

Nutrition was slowly introduced via a regular diet with Ensure supplementation. The patient developed refeeding syndrome and required transfer to the medical ICU for electrolyte repletion and monitoring. The patient was diagnosed with anorexia nervosa by Psychiatry using DSM-V criteria. On Day 3, the patient's liver enzymes began to downtrend to AST 1,316 u/L, ALT 1,826 u/L falling down to AST 53 u/L and ALT 276 u/L on Day 15. There was normalization of liver enzymes at four week follow up with AST, ALT, alkaline phosphatase, and total bilirubin reaching 26 u/L , 64 u/L, 97 u/L and 0.3 mg/dl, respectively.

Discussion

Various case reports have shown the association of severe malnutrition in anorexia nervosa and transaminitis. Liver enzymes have been seen to normalize after feeding in such cases. While mild increases in serum transaminases (<200 IU/L) have been observed in up to 75% of anorexia nervosa patients, marked increase (>200 IU/L) are rare. Independent groups have shown that serum transaminases inversely correlate with body mass index thereby indicating the role of nutritional status in liver changes in starved patients [10].

The proposed mechanism involves starvation-induced autophagy. Autophagy is a catabolic pathway in cells that is crucial for homeostasis and survival under stressful conditions. The process involves lysosomal degradation of excess or aberrant cytosolic organelles or proteins through the formation of the autophagosome and eventually to the autolysosome. This process allows for the recycling of macromolecules, specifically in situations of stress conditions such as with starvation [7]. Although a liver biopsy was not performed in our patient, a case series of liver biopsies performed in patients with liver failure and anorexia showed that malnourishment induces autophagy [6]. Rautou et al. was able to show through histology that the mechanism in which patients developed transaminitis from starvation was not via apoptosis, hypoxic hepatitis, or necrosis. They found that starvation induced the formation of autophagosomes compared to controls. It was also suggested that the autophagy induced by starvation causes the hepatocyte plasma membrane to become more permeable leading to release of aminotransferases into the blood without any cell death, thereby explaining the elevation in serum transaminases. Additionally, it has been proposed that the role of autophagy helps to delay apoptosis during nutrient deprivation in mammalian cells [8]. It is thought that this response is initially hepatoprotective to allow cells to cope with a nutritional depletion, however, when starvation is critically prolonged or when BMI reaches 13 kg/m2 or lower, excessive autophagy will occur leading to cell death and acute liver insufficiency [6].

Iron deposition was also seen in our patient's liver and spleen. Upon literature review, there was one report of a patient with hepatic injury with histology showing fat deposition, peroxidized lipid products and iron deposition in hepatocytes [9]. There has not been a defined mechanism, however a study examining iron homeostasis during starvation in mice showed that starvation led to increased transcription of the gene phosphoenolpyruvate carboxykinase in mice livers. Phosphoenolpyruvate carboxykinase is a gene seen in gluconeogenesis, which occurs mainly in the liver to generate glucose and other substrates for use throughout the body to maintain glucose levels. This process would be active in periods of starvation [10]. Glucose metabolism requires cellular iron availability as well. Hepatic iron also plays a part in influencing insulin signaling and sensitivity [11]. In mice models, hepcidin has been shown to be regulated by gluconeogenic signals leading to increased levels of hepcidin during starvation. In addition, in starved mice there was seen to be a degradation of ferroportin compared to non starved mice. Ferroportin is a transmembrane protein that helps transport iron from inside of a cell to the outside while hepcidin is a protein that helps to sequester iron in cells [10]. As a result, in the starved mice, it was seen that the pathway of gluconeogenesis leads to regulation of iron homeostasis such that there was increase iron deposition in the starved mice hepatocytes due to increased hepcidin and decreased ferroportin. This could explain the hepatic iron deposition seen in our patient as a complication of his severe malnutrition. This case highlights the importance of recognizing severe transaminitis and possibly hepatic iron deposition as a complication of patients with severe malnutrition or those who suffer from anorexia nervosa.

Conclusion

We describe a case with an adult man with anorexia nervosa who presented with severe transaminitis and iron deposition in his liver. Starvation induced autophagy has been proposed as the possible mechanism. Severe levels of transaminitis can be reached from anorexia; however normalization can occur with slow refeeding. Iron deposition has been seen on one case report in a patient with anorexia and no mechanism has been explained. Although starved mice models have shown that iron homeostasis is affected by gluconeogenesis.

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