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LETTER TO THE EDITOR

Hepatic consequences of a severe dietary restriction in anorexia nervosa: A case report

Consecuencias hepáticas de una restricción dietética severa en la anorexia nerviosa: presentación de un caso clínico

Anorexia nervosa is a serious disorder characterised by restricted dietary intake, weight loss, fear of weight gain and distorted body image[1]. Patients with this disease (mostly women) can present a series of organic complications such as osteoporosis, amenorrhoea, electrolyte disorders, cardiovascular diseases, etc. Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have been detected in up to 50% of cases during a period of inanation[2], although hypertransaminasaemia can also be detected due to hepatic steatosis in anorexia nervosa, due to excessive refeeding. The onset of the disease at an early age (<15 years) is a risk factor[2,3].

Severe acute liver diseases with elevated levels of transaminases and a decrease in coagulation factors have only occurred in a small percentage of patients with anorexia[4,5]. Although the exact mechanisms by which this liver damage occurs are unknown, it has been attributed to a complex process of cell death that originates in response to inanition known as autophagy[4,6], defined as a lysosomal catabolic pathway for long-lived proteins and damaged organelles. This is considered crucial for cell homeostasis and survival in stressful conditions[7]. However, excessive activation of this pathway leads to hepatocyte cell death, which causes liver failure[7]. The prognosis is usually good if patients are cared for with adequate refeeding treatment.

We present the case of a woman who was diagnosed with anorexia nervosa when she was 22 years old. Her poor clinical progress over the years and poor response to prescribed treatments led to multiple hospital admissions, with prolonged periods of hospitalisation in the Eating Disorders Unit. Four episodes of severe hypertransaminasaemia were detected during follow-up and resolved in a short period (less than two months) after refeeding with specific diets had been initiated. Severe hypertransaminasaemia was considered when its values were greater than 10 times the upper limit of normal, and a return to normal was deemed to be when they fell below twice that limit.

The first episode was detected five years after diagnosis, coinciding with a BMI of 13.6 kg/m^2. The patient underwent an exhaustive clinical history and a series of complementary examinations to establish a correct differential diagnosis of hypertransaminasaemia, which reached maximum values of 1.233 IU/l for AST. Among these tests was a liver biopsy that did not detect histological alterations, although technical problems prevented a cytostructural analysis. Serology for hepatotropic viruses and an autoimmunity study were negative. A liver ultrasound found only a slight hepatomegaly and a 15-mm hyperechoic space-occupying lesion (SOL) compatible with a hemangiomahepatomegaly. Regarding the analytical data, the patient did not present alterations in coagulation factors or a complete blood count. The values of serum concentrations of transaminases and bilirubin, which defined the liver disease, are shown in Table 1. Blood glucose was 46 mg/dl. The consumption of hepatotoxic drugs[8] was also ruled out. The episode subsided after one month and 21 days, after establishing dietary treatment.

Two years later, the second episode occurred in which the highest hypertransaminasaemia figures were reached, with 1.690 IU/l for AST and 1.872 IU/l for ALT. On this occasion, a slight thrombocytopenia of 123 $\times$ $10^3/\mu l$ was observed. Apart from the biopsy, the same tests were repeated, which obtained the same results, except for the ultrasound, in which another additional 10-mm haemangioma was observed. In addition, tumour markers were analysed, which were negative. In this case, the transaminases normalised after one month and 26 days.

The last two episodes occurred when the patient was 33 years old, with a BMI of 13.41 and 12.76 kg/m^2, respectively. In the third episode, the patient presented leukocytopenia of 1.7 $\times$ $10^3/\mu l$ and thrombocytopenia of 107 $\times$ $10^3/\mu l$, and a blood glucose of 60 mg/dl. Meanwhile, in the last episode there was a prolonged prothrombin time of 13.8 s, leukocytopenia of 3.1 $\times$ $10^3/\mu l$, anaemia with a complete blood count of 11.6 g/dl and hypoglycaemia of 18 mg/dl. The patient took ibuprofen 400 mg/day occasionally. She was initially treated with a 750 kcal/day diet, with liver function returning to normal after one month and two days.

This case illustrates the possible consequences on liver function of severe dietary restriction. Mild liver damage has been detected in up to 60% of patients with anorexia nervosa. However, highly elevated levels of transaminases are very rare[4]. It is exceptional for repetitive episodes to be described in the same patient, such as in this case, with up to four episodes in six years. ALT, as in non-alcoholic liver

Table 1 Values of biochemical markers of liver function and BMI in the four episodes of hypertransaminasaemia.

Episode	Maximum AST level (IU/l)	Maximum ALT level (IU/l)	Maximum GGT level (IU/l)	Maximum AP level (IU/l)	Maximum bilirubin level (mg/dl)	BMI at time of episode (kg/m^2)
1	1.233	1.187	124	138	1.4	13.6
2	1.690	1.872	122	239	1.1	
3	1.078	942	122	239	1.1	12.76
4	1.400	892			0.7	13.41

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; BMI: body mass index.

disease, tends to be higher than AST in anorexia nervosa[2], unlike what was observed in most of the episodes in this patient (Table 1). Where the data obtained in this case do coincide with other similar cases[9], is in that these episodes occurred with a clearly low BMI, around 13 kg/m^2.

The pathogenic mechanism that can explain the data presented here is not clear, although it is very likely that autophagy plays a key role in this event[7]. In this case, the liver damage could not be explained as secondary to a toxic agent, drug, autoimmune disease or an infectious agent since these were ruled out during the study and although there was no evidence of cytostructural alterations described in autophagy, restitutio ad integrum after a progressive period of refeeding leads towards this diagnosis.

It can be concluded that it is necessary to propose an agile and efficient diagnostic and therapeutic protocol, as well as a close multidisciplinary follow-up, in more complex cases (with BMI less than 13 kg/m^2), taking into account that this stress situation can be reversed with careful refeeding[4,10].

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