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Case report

Transaminases and celiac disease: a relationship to be reassessed

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Summary. Celiac Disease is a permanent intolerance to ingested gluten. The occurrence of liver impairment in CD is well described and can be regarded as one of the mainfold extra intestinal presentations of gluten-sensitive enteropathy. This increase is always mild or moderate, up to 5 times the upper limit of normal and transaminases decrease to normal range in most of patients on Gluten-free diet in maximum 12 months. We describe the case of a 16 months male addressed to our Operative Unit because of chronic diarrhea and poor weight growth with a severe increase of transaminases without a possible explanation. The case of our patient has highlighted the possibility of very high aminotransferase levels (up to 17 times the upper level normal of ALT) with a very slow decrease on a Gluten-free diet. It is necessary to study liver function in children at CD diagnosis and to seek celiac disease also in cases of severe hypertransaminasemia of unknown cause.

Key words: Celiac Disease, transaminases, liver biopsy, hypertransaminasemia, gluten-free diet

Introduction

Celiac Disease (CD) is a permanent intolerance to ingested gluten, the storage protein components of wheat, barley and rye. The intolerance to gluten results in immune-mediated damage of small intestinal mucosa, which resolves with the exclusion of gluten from the diet.

The occurrence of liver impairment in CD is well described and can be regarded as one of the mainfold extraintestinal presentations of gluten-sensitive enteropathy (1). In this context, different patterns of liver injury can be observed in CD patients, including a close association with autoimmune liver disorders such as primary biliary cirrhosis, autoimmune hepatitis and primary sclerosing cholangitis (2).

Case report

A 16 months male was addressed to our Operative Unit because of chronic diarrhea and poor weight growth (Weight: 9.450 kg, 5° percentile; Lenght: 77.5 cm, 10°-25° percentile; Head Circumference: 47 cm, 25°-50° percentile; Weight for Lenght: 10°-25° percentile).

Laboratory exams showed the presence of specific antibodies for CD: IgA anti-transglutaminase 75 UA/L (n.v. <16 UA/L), IgA deamidated gliadin peptides autoantibodies 28 UA/L (n.v. <20 UA/L) and IgG deamidated gliadin peptides autoantibodies 32 UA/L (n.v. <10 UA/L). Duodenal biopsy demonstrated the presence of 3c type lesions according to Marsh modified by Oberhuber classification. Thus, the child was serologically and bioptically diagnosed with CD and began gluten-free diet (GFD).

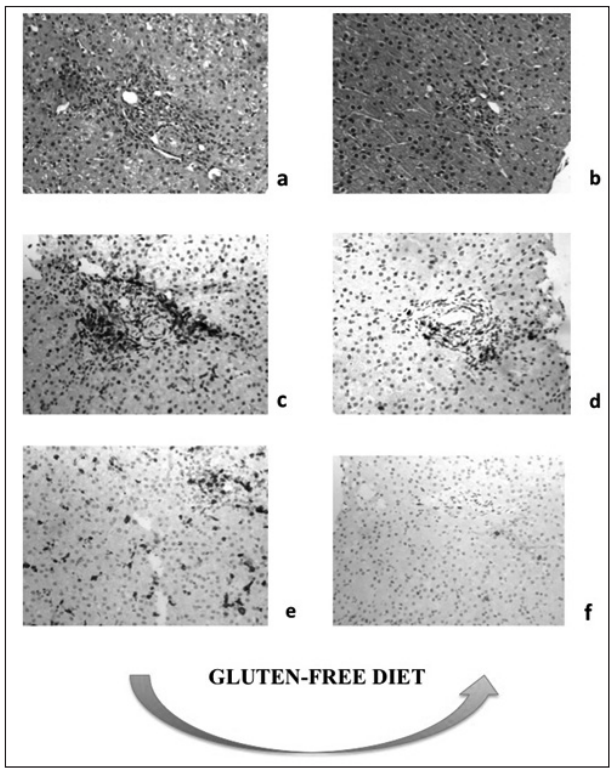

Figure 1. a: Portal space affected by chronic inflammation with lymphocytes and rare eosinophils. Extension to the surrounding hepatic parenchyma with mild activity interface. Bile canaliculi are not attacked by inflammation. (Original magnification: 20x; hematoxylin and eosin stain); b: Mild inflammatory infiltrate confined within the portal space (Original magnification: 20x; hematoxylin and eosin stain); c: on immunohistochemistry, the inflammatory infiltrate is made up mainly by T lymphocytes. (Original magnification: 20x ; immunohistochemical staining for CD3+); d: mild portal inflammation made up by T lymphocytes. (Original magnification: 20x; immunohistochemical staining for CD3+); e: The T lymphocytes within the portal infiltrate and within the lobules are mostly CD8+. (Original Magnification: 20x; immunohistochemical staining for CD8+); f: Scarce CD8+ lymphocytes are observed within the portal space. (Original magnification: 20x; Immunohistochemical staining for CD8+).

At time of diagnosis, laboratory studies revealed also the presence of elevated aminotransferase levels (AST 222 U/L, ALT 200 U/L, GGT 149 U/L, LDH 431 U/L, alkaline phosphatase 547 U/L); creatine phosphokinase and thyroid function were in the normal range. After about 2 months of strict GFD the exams revealed an important transaminases arousing: AST 876 U/L, ALT 601 U/L.

Therefore, an extensive diagnostic work-up including viral serology (HAV, HBV, HCV, CMV, EBV), autoimmune markers (ANA, ASMA, LKM1, LC1), metabolic exams (urinary organic acids, plasma aminoacids, ammonium, lactate) was performed and resulted negative. Ultrasound evaluation showed no liver morphological alterations.

After further 4 months from CD diagnosis, the child had an improvement in body weight (10.650 kg, 5°-10° percentile) and a decrease of specific antibodies for CD: IgA anti-transglutaminase 18 UA/L (n.v. <16 UA/L), IgA deamidated gliadin peptides autoantibodies 88 (n.v. <20 UA/L) and IgG deamidated gliadin peptides autoantibodies 9 (n.v. <10 UA/L).

Nevertheless, because of minimal reduction of liver enzymes levels (AST 720 U/L, ALT 485 U/L) liver biopsy was performed and showed the presence of chronic inflammatory infiltrate, mainly T lymphocytes (CD3 +, CD8 +) (Figures 1a, 1c, 1e) and B lymphocytes (CD20+), associated with mild interface activity. Liver parenchyma was also characterized by mild microvacular steatosis (Grade I) without preferential distribution pattern. This finding (Hepatitis interface activity = 2; lobular activity = 2; Stage 1 to Scheuer) appeared therefore compatible with the framework of chronic mild hepatitis associated with CD (3).

The child was then discharged with the prescription of hypolipidic GFD and therapy with ursodeoxycholic acid at a dose of 10 mg/kg/day. After a total of 14 months of GFD, liver tests were decreasing (AST 96 U/L, ALT 85 U/L, GGT 50 U/L); and second liver biopsy, suggested by pathologists, showed a complete recovery of liver parenchyma with only minimal residual inflammation (Figures 1b, 1d, 1f).

Discussion

In literature, the increase of transaminases in adults and in children with CD was described with a prevalence of 15-35% and 59%, respectively (1,4). This hypertransaminasemia involves mainly the AST and can be the only manifestation of the CD disease. This increase is always mild or moderate, up to 5 times the upper limit of normal (2) and transaminases decrease to normal range in most of patients on GFD in

maximum 12 months. Liver histology is also altered in about 66% of celiac patients with elevated aminotransferase levels and alterations appear mild and unspecific (2). The case of our patient has highlighted, instead, the possibility of very high aminotransferase levels (up to 17 times the upper level normal of ALT) with a slow decrease on a GFD.

Severe liver injury was previously described in the context of celiac disease by Kaukinen K et al. and by Casswall TH et al.

Kaukinen et al. described 4 patients with severe liver disease and celiac disease: among them 1 had congenital liver fibrosis, 1 had massive hepatic steatosis, and 2 had progressive hepatitis without apparent origin.

Although rare, severe hepatic damage or failure can develop in association with celiac disease. The etiology is varying and multifactorial. Indeed the liver enzymes improve/normalize within one year of gluten-free diet, but recovery is delayed if patients do not completely follow the diet (possible dietary indiscretion even in the presence of declining levels of antibodies such as in your patient).

It is difficult to explain the exact mechanism which provokes liver injury.

It is possible that tissue transglutaminase can modify external or self-antigens and generate different neoantigens. The increased permeability in enteropathy may further facilitate external antigens such as food proteins, bacterial products, and endotoxins to reach portal circulation, and liver (7).

This case report suggests therefore to study liver function in children at CD diagnosis and to seek celiac disease also in cases of severe hypertransaminasemia of unknown cause.

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