Journal of Pediatric Gastroenterology and Nutrition, Publish Ahead of Print

DOI : 10.1097/MPG.0000000000002209

Changing Epidemiology of Liver Involvement in Children with Celiac Disease

Elisa **Benelli**, MD[1]*, Samuele **Naviglio**, PhD[2]*, Luigina **De Leo**, PhD[2], Giacomo **Stera**, MD[1], Manuela **Giangreco**, PhD[2], Luca **Ronfani**, PhD[2], Vincenzo **Villanacci**, MD[3], Stefano **Martelossi**, MD[2], Alessandro **Ventura**, MD[1,2], Tarcisio **Not**, MD[1,2].

*** Elisa Benelli and Samuele Naviglio contributed equally to this work.**

1. Department of Medicine, Surgery, and Health Sciences, University of Trieste, Trieste, Italy.
2. Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy.
3. Pathology Section, Spedali Civili, Brescia, Italy.

Corresponding author:

Samuele Naviglio, MD

Institute for Maternal and Child Health - IRCCS "Burlo Garofolo"

Via dell'Istria 65/1, 34137, Trieste, Italy.

Phone: +3938785497 Fax: +390403785452

e-mail: samuele.naviglio@gmail.com

Key words: Hypertransaminasemia; Celiac hepatitis; Gluten-free diet; Epidemiology; Pediatrics

Conflicts of Interest and Source of Funding:

This study was supported by the European Union - European Regional Development Fund (Interreg Central Europe “Focus in CD” project N° CE11).

All Authors declare no conflict of interests.

Abstract

Objectives: Available data indicate that liver involvement is present in a significant proportion of children with celiac disease (CD) at the diagnosis (elevated transaminases 15-57%, autoimmune liver disease 1-2%). We sought to evaluate prevalence, clinical course, and risk factors for liver involvement in a large cohort of children with CD.

Methods: Children (age 0–18 years) diagnosed with CD from March 2010 to April 2016 were enrolled. Liver involvement was considered to be present when ALT levels were >40 U/L (hypertransaminasemia, HTS). Patients with HTS were re-evaluated after at least 12 months of a gluten-free diet (GFD).

Results: CD was diagnosed in 806 patients during the study period; of these, ALT levels were available for 700 patients (86.9%), and were elevated in 27 (3.9%, HTS group); median ALT and AST levels in the HTS group were 57 U/L (IQR 49-80 U/L) and 67 U/L (IQR 53-85 U/L), respectively. Younger age, malabsorption symptoms, and low hemoglobin or ferritin were significantly more common in the HTS group at univariate analysis. At multivariate analysis, only age ≤4.27 years correlated with risk of liver involvement (OR 3.73; 95% CI: 1.61 - 8.66). When retested on a GFD, all but three patients normalized ALT levels; of these, one was diagnosed with sclerosing cholangitis.

Conclusions: Liver involvement in celiac children is now less frequent than previously reported, possibly due to changing CD epidemiology. Younger age is the only risk factor. Associated autoimmune liver disease is rare.

Key words: Hypertransaminasemia; Celiac hepatitis; Gluten-free diet; Epidemiology; Pediatrics

What is known

- Liver involvement in children with celiac disease (CD) ranges from asymptomatic hypertransaminasemia to more severe conditions, including autoimmune liver disease and cirrhosis.
- Available studies report a high burden of liver involvement in celiac children at the diagnosis (asymptomatic hypertransaminasemia 15-57%, autoimmune liver disease 1-2%).
- Data on risk factors for liver involvement are discordant.

What is new

- Prevalence of liver involvement (ALT>40 U/L) in children with CD at the diagnosis is low (27/700 patients, 3.9%).
- Younger age is the only risk factor.
- CD-associated autoimmune liver disease is rare (1/700 patients, 0.14%).

Introduction

Celiac disease (CD) is a systemic autoimmune disorder triggered by gluten ingestion in genetically predisposed subjects.[1 2] Beyond enteropathy, CD may be associated with multiple extraintestinal manifestations.[3–5] Among these, liver involvement is one of the most common.[6–8] Hepatic manifestations of CD range from asymptomatic elevation of liver enzymes (also known as "celiac hepatitis") to more severe hepatic disorders, including autoimmune hepatitis, primary biliary cholangitis, and sclerosing cholangitis.[9–13] Data on the prevalence of liver involvement in CD are highly heterogeneous. In adults, hypertransaminasemia (HTS) has been reported in 11-42% of patients,[14–18] with a 2011 meta-analysis estimating its prevalence at 27%.[19] In children, there are few prevalence studies. Available data indicate that an elevation of serum transaminases is present in 15% to 57% of celiac children at the diagnosis (36% according to a 2013 meta-analysis),[20–24] and reported prevalence of autoimmune liver disease in celiac children is 1-2%.[23 25] Data on risk factors for liver involvement are also discordant. We sought to evaluate prevalence, clinical course, and risk factors for liver involvement in a large cohort of children with CD.

Materials and Methods

All children (age 0–18 years) who received a diagnosis of CD from March 2010 to April 2016 at Referral Center for Celiac Disease of the Institute for Maternal and Child Health "Burlo Garofolo", in Trieste, Italy, were prospectively enrolled to be included in our institutional pediatric CD database. Informed consent was obtained from all patients' parents or caregivers. Institutional approval from our Institute's independent bioethics committee was obtained. Baseline data of all patients were collected at the time of diagnosis: sex, age, presenting symptoms, associated autoimmune diseases, familial history of CD and other autoimmune diseases. Serum anti-tissue transglutaminase 2 (anti-TG2) IgA was measured

using an enzyme-linked immune sorbent assay (ELISA) (Eu-tTG, Eurospital, Italy). A cut-off value of 7 U/mL was used. In case of IgA deficiency, anti-TG2 IgG was measured. Serum endomysial antibodies (EMA) positivity was evaluated by immunofluorescence on human umbilical cord sections by an experienced analyst (T.N.). HLA genotyping was performed when necessary to reach a diagnosis. Susceptibility alleles for CD were determined by polymerase chain reaction assay (PCR) with allele-specific primers (Eu-Gene-Risk kit, Eurospital, Italy). Other blood and serum tests were performed according to our laboratory guidelines. We reviewed the following parameters, when available: hemoglobin, aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyltransferase (GGT). Ferritin levels were measured when clinically indicated. HTS was considered to be present if ALT levels were >40 U/L. Isolated elevation of AST was not considered, since this finding may be non-specific or due to hemolysis in the blood sample.[26] In patients with HTS, serum transaminases were retested after at least 12 months of a gluten-free diet (GFD). Further tests for liver disorders were performed as clinically indicated. Duodenal biopsies were obtained during diagnostic esophagogastroduodenoscopy. For each subject, four specimens were taken: two from the duodenal bulb and two from the distal duodenum. The histological description was based on the Marsh classification.[27] Diagnosis of CD was made according to available clinical guidelines.[1 28 29] After 2012, the new ESPGHAN diagnostic guidelines for CD were used; therefore, in patients with clinical symptoms highly suggestive for CD (diarrhea with weight loss, failure to thrive, and/or iron deficiency anemia), plus a permissive HLA haplotype, positivity of EMA, and an anti-TG2 IgA antibody serum concentration over 10 times the upper limit of normal, CD was diagnosed without intestinal biopsy. A diagnosis of potential CD was made in patients with clinical signs and symptoms suggestive of CD plus a positive CD-specific serology and a CD-compatible HLA haplotype who lacked diagnostic mucosal findings (i.e. Marsh 0 or 1) if anti-TG2 IgA antibody deposits were present in the

duodenal mucosa, since these have been shown to represent an early marker of CD-specific immune response that can be detected before evidence of intestinal damage on histology.[1 30–32] Mucosal anti-TG2 IgA deposits were investigated by direct double immunofluorescence according to a method described previously.[30] Briefly, six frozen duodenal sections per patient were incubated with a mouse anti-human TG2 antibody (1:100 dilution; CUB7402, NeoMarkers, USA) followed by an Alexa Fluor 594-conjugated donkey anti-mouse IgG secondary antibody (1:100 dilution; Eugene, USA) and then by a fluorescein rabbit anti-human IgA antibody (1:80 dilution; Dako, Denmark). The multicolor analysis was performed using an Axioplan2 fluorescence microscope (Carl Zeiss, Germany) to localize the anti-TG2 IgA antibody deposits.

Statistical analysis: HTS prevalence was calculated on the population with transaminase levels available. For the risk analysis, subjects with HTS were compared with those with normal ALT levels (control group). Chi-square or Fisher's test and Wilcoxon-Mann Whitney's test were applied, according to the variable distribution, to establish the crude association between HTS and population characteristics. Continuous variables were reported as median and interquartile range (IQR); categorical data as number and percentage. Multivariate logistic regression models were constructed with HTS as outcome and population characteristics as explanatory variables. The variables included in the final model were those with a p-value of 0.10 in the univariate logistic model; to dichotomize continuous variables a cut-off value was fixed using the first quartile. Data on risk analysis were reported as odds ratio (OR) and 95% confidence interval (95% CI).

Results

Between March 2010 and April 2016, 806 patients received a diagnosis of CD (median age 7.39 years, range 0.8-17.9 years). Of these, transaminases levels were available for 700

patients (86.8%), who were therefore included in the prevalence analysis. Fifty-six of 700 patients (8.0%) were diagnosed with potential CD, while 24 patients (3.4%) received a diagnosis without biopsy according to the 2012 ESPGHAN guidelines. Twenty-seven patients (3.9%) had serum levels of ALT > 40 U/L (HTS group). Table 1 compares subjects with HTS and control group for the main characteristics collected. Median ALT and AST levels in the HTS group were 57 U/L (IQR: 49-80 U/L) and 67 U/L (IQR: 53-85 U/L), respectively. GGT levels were normal (< 20 U/L) in all but five patients (median 8.0 U/L, IQR 6.0-12.5). Of these five, two also had elevated ALT levels.

At univariate analysis, median age was significantly lower in the HTS group as compared to patients with normal ALT levels (2.58 vs 7.10 years, p<0.0001). Prevalence was highest in patients under 2 years of age (7/40, 17.5%) (figure 1). No difference in the male/female ratio was noted between the two groups. Presence of symptoms at presentation was similar between HTS and control group (88.5% vs 73.6%, p=0.26), but when only signs and symptoms of malabsorption were considered (diarrhea, failure to thrive, weight loss, anemia, or low ferritin level) a statistically significant difference was observed (15.8% in the control group vs 40.7% in the HTS group, p=0.002). Hemoglobin and ferritin levels median values were also significantly lower in the HTS group (p=0.01 and p=0.02, respectively). A trend towards higher anti-TG2 values (median 128 U/L vs 94 U/L, p=0.06) as well as towards less frequent EMA positivity (19/27, 70.4%, vs 574/673, 85.3%, p=0.051) was observed in the HTS group but did not reach statistical significance. Among patients with HTS in whom intestinal biopsy was performed, all patients had Marsh 3 changes, except two who had Marsh 2 changes. No patient in the potential CD group had elevated ALT levels. No statistically significant difference was noted between control and HTS groups in terms of associated autoimmune diseases, and familial history of CD or other autoimmune diseases.

At multivariate logistic analysis (which included age, malabsorption symptoms, anti-TG2 levels, hemoglobin levels, and ferritin levels as variables), only age ≤4.27 years still correlated with an increased risk of HTS (OR 3.73; 95% CI: 1.61 - 8.66). Statistical significance was not retained for signs or symptoms of malabsorption (OR 2.18; 95% CI: 0.91 – 5.22, p=0.08).

Follow-up. Of the 27 patients with HTS, nine were lost to follow-up because they lived far from our institute and declined to return for further evaluation. The remaining 18 patients where retested after at least 12 months from the start of GFD (median 31.5 months, range 12-82 months). All but three patients had normal ALT levels on a GFD (median value in patients who normalized ALT levels: 10 U/L, IQR 7-14). Three patients still had elevated ALT levels: in the first patient, ALT was 83 U/L at the last available follow-up visit (after 22 months of GFD), and had significantly reduced from the diagnosis (175 U/L). Good adherence to GFD was reported, but EMA was still positive, therefore significant gluten intake was considered to be present. The second patient had only slightly elevated ALT levels after four years of GFD (47 U/L), which had progressively decreased from the diagnosis (104 U/L at diagnosis, 68 U/L after 18 months of GFD). Anti-TG2 IgA and EMA were negative; a slowly resolving form of celiac hepatitis was hypothesized. Both patients were completely asymptomatic, and other liver disorders (autoimmune liver disease, viral hepatitis, fatty liver disease, Wilson disease, alpha-1 antitrypsin deficiency) were excluded. The third patient was a 12-year-old girl who had elevated liver enzymes after six months of GFD (ALT 133 U/L, AST 83 U/L) and elevated GGT (138 U/L). Notably, she was one of the few patients with elevated GGT at CD diagnosis. Abdominal ultrasonography showed inhomogeneous liver structure and splenomegaly, while magnetic resonance cholangiography showed diffuse irregular stenosis of biliary ducts. Auto-antibodies for autoimmune liver disease were negative, while a liver

biopsy was consistent with sclerosing cholangitis. Concurrent inflammatory bowel disease was excluded.

Discussion

The prevalence of HTS and autoimmune liver disease in our cohort were 3.9% and 0.14%, respectively. These figures are significantly lower than those previously reported in medical literature for liver involvement in pediatric CD. Previous studies found HTS in 15% to 57% of celiac children at the diagnosis,[20–24] with a 2013 meta-analysis estimating its prevalence 36%,[24] while prevalence of autoimmune liver disease was estimated at 1-2%.[23 25] Several factors may concur to explain this difference. First, in order to increase specificity of our findings, we choose to exclude patients with an isolated elevation of AST, since this finding may be nonspecific. Previous studies on prevalence of HTS in children with CD often included also patients with isolated AST elevation, and when only patients with elevated ALT when considered, the prevalence of abnormal findings was actually lower (14.9% - 27.7%).[20 21] Transaminases reference intervals can vary among clinical laboratories, and slightly different upper limits of normal have been used in different studies. We chose 40 U/L as the upper limit of normal for serum ALT levels since this is the upper limit of normal adopted by our laboratory, and it is consistent with the results of a recent meta-analysis on transaminases levels in healthy children.[33] The median value of ALT in the HTS group was only 1.8 times the upper limit of normal and the highest value of ALT was 175 U/L. Notably, GGT were normal in all but five patients. Of these five, two also had elevated ALT levels, and one of these two was eventually diagnosed with sclerosing cholangitis, while in the other both values normalized after GFD. This observation underscores that abnormal GGT values are not common in patients with CD at the diagnosis, and should raise suspicion of a cholestatic condition, especially when associated with abnormal ALT levels.

Data on risk factors for liver involvement are also discordant, with younger age, poor growth, severe villous atrophy, low ferritin level, elevated autoantibodies being associated to HTS in several studies. In our study malabsorption signs/symptoms were associated with liver involvement at univariate analysis, but after multivariate analysis only age remained as a significant risk factor. It is possible that different age distribution among studies influences the observed prevalence of HTS. In our cohort, median age was 6.95 years, with 41/700 patients under 2 years of age. This is in accordance with international data showing that age at CD diagnosis is now higher than in the past.[34 35] We could provide data for 700 (86.8%) patients from the whole cohort of 806 patients, while for 106 patients ALT levels were not available. Clinical characteristics among these two groups were similar except for age, which was lower in the second group (4.5 years, IQR 2.4 – 8, vs. 6.9 years, IQR 4.1 – 10.4, $p<0.0001$). While this may represent a bias, the overall prevalence of HTS is unlikely to be significantly affected. In fact, estimating prevalence of HTS in the untested group of patients using data from the 700 patients for whom ALT levels were available and applying an age-adjusted 95% confidence interval would result in 4 – 11 (mean 7) extra cases of HTS. This would lead to an overall estimated prevalence of 31 – 38 (mean 34) cases on the whole population of 806 patients (4.2%, 95% CI 3.1% - 5.8%). When compared to the observed prevalence (3.9%, 95% CI 2.6–5.5%), the difference was not statistically significant ($p=0.79$). The majority of patients (96.6%) in our study had intestinal biopsy performed, and all but 2 patients with HTS had villous atrophy (Marsh 3 changes), while no cases of HTS were found in the potential CD group. This observation is also consistent with previous reports on the association between elevated transaminases and intestinal atrophy, both in children and in adults.[17 36] In agreement with previous studies, most of our patients with HTS normalized transaminases levels on a GFD, with only one patient presenting with a slow fall of ALT levels despite a good compliance to GFD.

Overall, our results indicate a low prevalence of liver involvement in children with CD at the diagnosis. This seem to be in accordance with the results of the most recent studies. In 2014 data from the Spanish National Registry of Celiac Disease found "abnormal liver enzymes" in 13.6% of patients, even though it is not clear which enzymes were evaluated and which cut-off were chosen.[37] In 2016, Äärelä et al. reported ALT>30 U/L in 14.7% of patients, [36] while Lee et al. reported elevated transaminases (both ALT and AST) in 15.1%.[38] Remarkably, prevalence of autoimmune liver disease was also very low (0.14%) compared to historical data (1-2%).[23 25]

The reason for these changes in the epidemiology of hepatic manifestations of CD are not known. We speculate it may be related to an increased awareness of CD among the medical community leading to earlier diagnoses, and to the changing epidemiology of CD with increasing age at the diagnosis,[39 40] since HTS is more common in younger patients, also in our cohort.

In conclusion, our data show that the prevalence of liver involvement in children with untreated CD at the time of diagnosis, both as asymptomatic HTS and autoimmune liver disease, is now lower than previously reported, possibly due to changing epidemiology of CD. Younger age is confirmed to be the single most important risk factor for HTS. Transaminases levels among patients with HTS are usually mildly elevated, and spontaneous resolution following GFD is the norm. CD-associated autoimmune liver disease is rare.

References

1 Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–60.

2 Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet 2017;391:70–81.

3 Jericho H, Sansotta N, Guandalini S. Extraintestinal Manifestations of Celiac Disease: Effectiveness of the Gluten-Free Diet. J Pediatr Gastroenterol Nutr 2017;65:75–9.

4 Pinto-Sánchez MI, Bercik P, Verdu EF, et al. Extraintestinal manifestations of celiac disease. Dig Dis 2015;33:147–54.

5 Ventura A, Martelossi S. Dental enamel defects and coeliac disease. Arch Dis Child 1997;77:91.

6 Rubio-Tapia A, Murray JA. The liver in celiac disease. Hepatology 2007;46:1650–8.

7 Marciano F, Savoia M, Vajro P. Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms. Dig Liver Dis 2016;48:112–9.

8 Anania C, De Luca E, De Castro G, et al. Liver involvement in pediatric celiac disease. World J Gastroenterol 2015;21:5813–22.

9 Volta U, Rodrigo L, Granito A, et al. Celiac disease in autoimmune cholestatic liver disorders. Am J Gastroenterol 2002;97:2609–13.

10 Gillett HR, Cauch-Dudek K, Jenny E, et al. Prevalence of IgA antibodies to endomysium and tissue transglutaminase in primary biliary cirrhosis. Can J Gastroenterol 2000;14:672–5.

11 Lawson A, West J, Aithal GP, et al. Autoimmune cholestatic liver disease in people with coeliac disease: a population-based study of their association. Aliment Pharmacol Ther 2005;21:401–5.

12 Caprai S, Vajro P, Ventura A, et al. Autoimmune Liver Disease Associated With

Celiac Disease in Childhood: A Multicenter Study. Clin Gastroenterol Hepatol 2008;6:803–6.

13 Villalta D, Girolami D, Bidoli E, et al. High prevalence of celiac disease in autoimmune hepatitis detected by anti-tissue tranglutaminase autoantibodies. J Clin Lab Anal 2005;19:6–10.

14 Hagander B, Berg N, Brandt L, et al. Hepatic injury in adult coeliac disease. Lancet 1977;2:270–2.

15 Bardella MT, Fraquelli M, Quatrini M, et al. Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. Hepatology 1995;22:833–6.

16 Korpimäki S, Kaukinen K, Collin P, et al. Gluten-sensitive hypertransaminasemia in celiac disease: An infrequent and often subclinical finding. Am J Gastroenterol 2011;106:1689–96.

17 Zanini B, Baschè R, Ferraresi A, et al. Factors that contribute to hypertransaminasemia in patients with celiac disease or functional gastrointestinal syndromes. Clin Gastroenterol Hepatol 2014;12:804–810.e2.

18 Castillo NE, Vanga RR, Theethira TG, et al. Prevalence of abnormal liver function tests in celiac disease and the effect of a gluten-free diet in the US population. Am J Gastroenterol 2015;110:1216–22.

19 Sainsbury A, Sanders DS, Ford AC. Meta-analysis: Coeliac disease and hypertransaminasaemia. Aliment Pharmacol Ther 2011;34:33–40.

20 Bonamico M, Pitzalis G, Culasso F, et al. Hepatic damage in celiac disease in children. Minerva Pediatr 1986;38:959–62.

21 Farre C, Esteve M, Curcoy A, et al. Hypertransaminasemia in pediatric celiac disease patients and its prevalence as a diagnostic clue. Am J Gastroenterol 2002;97:3176–81.

22 Arslan N, Büyükgebiz B, Oztürk Y, et al. The prevalence of liver function abnormalities in pediatric celiac disease patients and its relation with intestinal biopsy findings. Acta Gastroenterol Belg 2005;68:424–7.

23 Di Biase AR, Colecchia A, Scaioli E, et al. Autoimmune liver diseases in a paediatric population with coeliac disease - a 10-year single-centre experience. Aliment Pharmacol Ther 2010;31:253–60.

24 Vajro P, Paolella G. Pediatric Celiac Disease, Cryptogenic Hypertransaminasemia, and Autoimmune Hepatitis. J Pediatr Gastroenterol Nutr 2013;56:663–7.

25 Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999;117:297–303.

26 Lippi G, Luca Salvagno G, Montagnana M, et al. Influence of hemolysis on routine clinical chemistry testing. Clin Chem Lab Med 2006;44:311–6.

27 Marsh M. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330–54.

28 Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990;65:909–11.

29 National Institute for Health and Clinical Excellence. Coeliac disease - Recognition and assessment of coeliac disease. NICE Guidel 86 Published Online First: 2009. doi:10.1136/bmj.b1684

30 Salmi TT, Collin P, Korponay-Szabó IR, et al. Endomysial antibody-negative coeliac disease: clinical characteristics and intestinal autoantibody deposits. Gut 2006;55:1746–53.

31 Salmi TT, Collin P, Jarvinen O, et al. Immunoglobulin A autoantibodies against transglutaminase 2 in the small intestinal mucosa predict forthcoming coeliac disease. Aliment Pharmacol Ther 2006;24:541–52.

32 Not T, Ziberna F, Vatta S, et al. Cryptic genetic gluten intolerance revealed by intestinal antitransglutaminase antibodies and response to gluten-free diet. Gut 2011;60:1487–93.

33 Stirnadel-Farrant HA, Galwey N, Bains C, et al. Children's liver chemistries vary with age and gender and require customized pediatric reference ranges. Regul Toxicol Pharmacol 2015;73:349–55.

34 Kivelä L, Kaukinen K, Lähdeaho M-L, et al. Presentation of Celiac Disease in Finnish Children Is No Longer Changing: A 50-Year Perspective. J Pediatr 2015;167:1109–1115.e1.

35 Tapsas D, Hollén E, Stenhammar L, et al. The clinical presentation of coeliac disease in 1030 Swedish children: Changing features over the past four decades. Dig Liver Dis 2016;48:16–22.

36 Äärelä L, Nurminen S, Kivelä L, et al. Prevalence and associated factors of abnormal liver values in children with celiac disease. Dig Liver Dis 2016;48:1023–9.

37 Cilleruelo ML, Roman-Riechmann E, Sanchez-Valverde F, et al. Spanish National Registry of Celiac Disease: Incidence and Clinical Presentation. J Pediatr Gastroenterol Nutr 2014;59:522–6.

38 Lee GJ, Boyle B, Ediger T, et al. Hypertransaminasemia in Newly Diagnosed Pediatric Patients With Celiac Disease. J Pediatr Gastroenterol Nutr 2016;63:340–3.

39 Volta U, Caio G, Stanghellini V, et al. The changing clinical profile of celiac disease: a 15-year experience (1998-2012) in an Italian referral center. BMC Gastroenterol 2014;14:194.

40 Almallouhi E, King KS, Patel B, et al. Increasing Incidence and Altered Presentation in a Population-based Study of Pediatric Celiac Disease in North America. J Pediatr Gastroenterol Nutr 2017;65:432–7.

Figure legend

Figure 1. Prevalence of elevated ALT levels among different age groups.

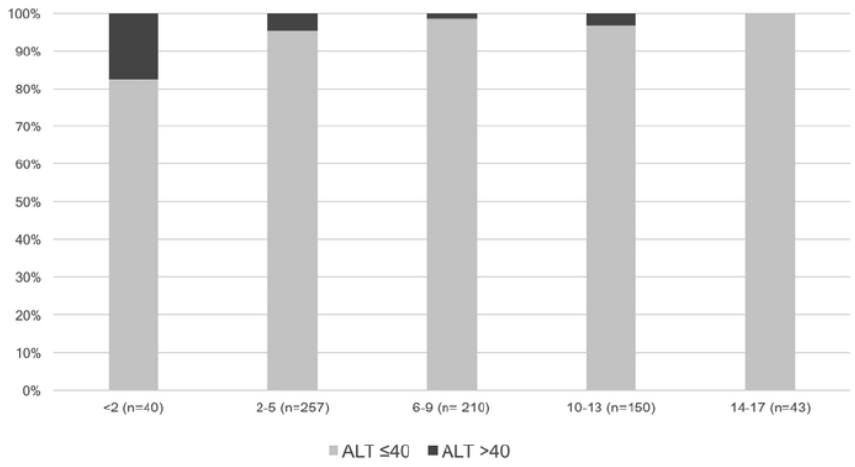

Table 1. Study population characteristics.

	Control group (673 patients)	**HTS group (27 patients)**	**P-value**
ALT (median, U/L; IQR)	16 (13 - 21)	57 (49 - 72)	
Age (median, years; IQR)	7.10 (4.19 – 10.53)	2.58 (2.05 – 6.13)	< 0.0001
Male/Female ratio	227/446	7/20	0.53
Symptoms at presentation (n; %)	495 (70.7%)	23 (85.2%)	0.26
Malabsorption symptoms (n; %)	106 (15.1%)	11 (40.7%)	0.002
Associated autoimmune diseases (n; %)	81 (11.6%)	4 (14.8%)	0.56
Familial history, CD (n; %)	186 (26.6%)	4 (14.8%)	0.18
Familial history, other autoimmune diseases (n; %)	137 (19.6%)	6 (22.2%)	0.80
Hemoglobin (median, g/dL; IQR)	11.8 (11.0 - 12.5)	11.2 (10.2 – 12.1)	0.02
Ferritin (median, ng/dL; IQR)	17.6 (9.23 – 30.0)	8.6 (3.0 -19.0)	0.01
Anti-TG2 (median, U/mL; IQR)	94.0 (21.0 – 172.0)	128.0 (71.0 – 310.0)	0.05
EMA positivity (n; %)	574 (85.3%)	19 (70.4%)	0.051
Potential CD (n; %)	56 (8.0%)	0 (0.0%)	0.15