Factors That Contribute to Hypertransaminasemia in Patients With Celiac Disease or Functional Gastrointestinal Syndromes

Barbara Zanini,* Roberta Baschè,* Alice Ferraresi,* Marie Graciella Pigozzi,* Chiara Ricci,* Francesco Lanzarotto,* Vincenzo Villanacci,‡ and Alberto Lanzini*

*Gastroenterology Unit, ‡Histopathology Unit, University and Spedali Civili, Piazza Spedali Civili, Brescia, Italy

BACKGROUND & AIMS: **Transaminasemia develops via different pathways in patients with celiac disease; no information is available on risk factors specifically attributable to celiac disease.**

METHODS: **We analyzed data collected from consecutive patients referred from January 1997 through December 2009 to the celiac disease clinic at the Spedali Civili of Brescia, Italy. We assessed the factors affecting hypertransaminasemia in 683 patients with celiac disease (based on serologic and biopsy analysis, cohort A; 34 ± 14 years of age) and 304 with functional syndromes (cohort B; 37 ± 13 years of age).**

RESULTS: **Hypertransaminasemia was detected in 138 patients in cohort A (20%). It was associated with malabsorption (odds ratio [OR], 2.22; $P = .004$), diarrhea (OR, 1.72; $P = .005$), and increasing severity of mucosal lesion (Marsh-Oberhuber class; OR, 1.46; $P = .001$) but not with body mass index (BMI) or the serum level of tissue-transglutaminase antibodies (tTG). Hypertransaminasemia was detected in 22 patients in cohort B (7%) and was associated with the World Health Organization's BMI categories (OR, 7.9; $P < .001$). In subsets of patients studied with the same analytical method (313 of cohort A and 188 of cohort B), the level of tTG was significantly higher in cohort A at baseline (25.2 ± 16.9 U/L aspartate aminotransferase [AST]) than in cohort B (20.6 ± 9.9 U/L AST, $P < .0001$) and was related to BMI in cohort B ($P = .0012$) but not cohort A. When patients were placed on gluten-free diets, the levels of AST decreased from 25.2 ± 16.9 U/L to 19.9 ± 6.6 U/L ($P < .0001$), independently of the changes of duodenal histology and tTG and correlated with BMI ($P = .0007$); the prevalence of hypertransaminasemia decreased from 13% to 4%.**

CONCLUSIONS: **Patients with celiac disease have a higher prevalence of hypertransaminasemia than controls (patients with functional syndromes). Hypertransaminasemia is related to the severity of the duodenal lesion and malabsorption but not BMI. By contrast, there was a positive correlation between the levels of AST and BMI in controls; this relationship was restored when patients with celiac disease were placed on gluten-free diets.**

Keywords: Liver; Associated Diseases; Clinical Presentation; Gluten Allergy.

Celiac disease (CD) is an autoimmune systemic disorder triggered by gluten ingestion (a protein contained in wheat, barley, and rye) in genetically susceptible people. The clinical expression of CD is very heterogeneous and, besides the gastrointestinal tract, it may involve many organs, including the liver, and may cause cryptogenic hypertransaminasemia.[1]

In a recent meta-analysis, Sainsbury et al[2] reported a pooled prevalence of a 6% yield of serologic testing and a 4% yield of biopsy-proven CD in patients with cryptogenic hypertransaminasemia. These authors[2] also identified 5 studies on the prevalence of hypertransaminasemia in newly diagnosed CD patients with a pooled prevalence of 27% that was reduced while on a gluten-free diet (GFD), suggesting gluten dependency of the phenomenon in 63% to 90% of patients. This gluten-dependent phenomenon has been further established by Korpimaki et al[3] in a large retrospective study on stored frozen serum samples of unmatched CD patients at diagnosis and while on a GFD and with an elegant prospective arm involving a gluten rechallenge phase.

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CD, celiac disease; GFD, gluten-free diet; tTG, tissue-transglutaminase antibodies.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.10.033

The prevalence of hypertransaminasemia varies, however, between 11%[3] and 42%[3] in different reports and in all studies,[3–7] with one exception[8]: Cases with an identifiable cause of hypertransaminasemia were not excluded from analysis. The presence of heterogeneous causes of hypertransaminasemia in different studies may help to explain the wide range of prevalence reflecting geographic differences of prevalence of hepatitis virus infections and differences of dietary habits and of genetic background. Furthermore, little information is available on the factors associated with hypertransaminasemia and with the serum transaminase level in CD patients. Korpimaki et al[3] reported a higher prevalence of hypertransaminasemia in patients with moderate symptoms (23%) than in those with no or mild symptoms (9%), and an effect of malabsorption has been reported in abstract form by Lewis et al[7] that also reported, by contrast with Bardella et al,[4] an association with the severity of duodenal histologic abnormality.

The observations reported above must be taken cautiously because of the confounding factor of heterogeneous causes of hypertransaminasemia. We reasoned that cases with identifiable etiologies should be excluded in order to look at factors affecting hypertransaminasemia specifically related to CD. The aim of the study was to assess the factors associated with hypertransaminasemia and with serum level of transaminase in a large retrospective cohort of CD patients after exclusion of cases with a known etiology of hypertransaminasemia. Patients were studied according to a standardized protocol involving, among other measurements, the assessment of the serum transaminase level measured twice before and during GFD. We compared the cohort of CD patients with a cohort of patients referred to our CD clinic for suspected CD and diagnosed as having functional intestinal syndromes.

Methods

We extracted information from a prospectively maintained database of consecutive patients referred from January 1997 to December 2009 to our CD clinic at the Spedali Civili of Brescia, Italy for suspected CD. Only adult patients, older than 18 years, with information on clinical, serologic, and histologic characteristics and with a final diagnosis of CD or of functional gastrointestinal syndromes were included in the study and identified as cohort A and B, respectively.

Because over the years the laboratory methods for the measurement of transaminase levels adopted in our institution have changed, we also identified within the 2 cohorts a subgroup of patients studied with the same laboratory methods for transaminase assay. The upper limit of normal of this method is 35 U/L for aspartate aminotransferase (AST) and 50 U/L for alanine aminotransferase (ALT) as measured by the enzymatic rate method and defined by our institutional laboratory as the reference value for the local population of blood donors.

The diagnosis of CD was based on positive CD-related serology and on characteristic duodenal histologic alteration. Tissue-transglutaminase antibodies (tTG) were measured by the enzyme-linked immunosorbent assay procedure with human recombinant tTG antigen with 2 commercial kits: Eu-tTg (Eurospital, Trieste, Italy) or Celikey (Phadia, Uppsala, Sweden). Antiendomysial antibodies were detected by indirect immunofluorescence using monkey esophagus tissue as substrate (Anti-endomysium, Eurospital). According to our institutional protocol,[9] a minimum of 4 endoscopic biopsies were obtained in the duodenum, and the specimens were oriented on a cellulose filter with mucosal side facing up, as previously described. The duodenal histology was classified according to Marsh as modified by Oberhuber et al.[10] The same experienced pathologist (VV) reviewed 95% of the endoscopic biopsies.

The diagnosis of functional syndromes was based on Rome II criteria up to year 2007 and on Rome III criteria thereafter. The working definition of hypertransaminasemia was as follows: the presence of either AST or ALT serum concentrations exceeding the upper limit of normal and exclusion of hepatitis B virus and hepatitis C virus infection, autoimmune hepatitis, deranged iron metabolism, and alcoholism. The working definition of malabsorption was the presence of diarrhea and unintentional weight loss greater than 2 kg.

Serum samples for analysis of several parameters were collected at the time of endoscopic biopsy in virtually all cases at our institution. The main information extracted from the database included demographic characteristics; body mass index (BMI); clinical characteristics (general, gastrointestinal, extra intestinal manifestations); presence of associated diseases; duodenal histology; CD-related serology; HLA DQ types; and laboratory parameters at baseline including hemoglobin, ferritin, glycaemia, insulinemia, triglycerides, total cholesterol, and γ-glutamyl transpeptidase in addition to transaminases. Adherence to a GFD was assessed by the attending physician using a 4-point Likert scale classifying patients as follows: no dietary indiscretions (score 1), one serving with gluten per month (score 2), less than 4 servings per month (score 3), and 4 or more servings per month (score 4).

Expression of Results, Calculations, and Statistical Analysis

The prefix *hyper* indicates a value of transaminasemia exceeding the upper limit of normal (defined by the analytical kits). This qualitative result, independent of the analytical method used, was used to calculate the prevalence and factors affecting hypertransaminasemia in the entire cohorts A and B. Comparisons based on serum transaminase level (a quantitative result dependent on the analytical method) were based on the selected subgroup of cohorts A and B studied with the same analytical method. The BMI was calculated as weight (kilograms) per height (square meter) and was classified according to