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Alimentary Tract

Prevalence and associated factors of abnormal liver values in children with celiac disease

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ABSTRACT

Background: The prevalence and factors associated with transaminasemia in celiac disease are poorly known.
Aims: To investigate these issues in paediatric celiac patients and controls.
Methods: Alanine aminotransferase (ALT) was studied in 150 children with untreated celiac disease, 161 disease controls and 500 population-based controls. The association between ALT and clinical and histological variables and the effect of a gluten-free diet were investigated in celiac patients.
Results: ALT was >30 U/l: celiac disease 14.7%, ulcerative colitis 37.2%, Crohn's disease 16.7%, reflux disease 16.2%, functional gastrointestinal symptoms 8.9%, and controls 3.6%. Factors associated with increased ALT were poor growth (45.5% vs 24.2%, $P = 0.039$) and severe villous atrophy (median 23.0 U/l vs partial atrophy 19.0 U/l, $P = 0.008$), but not age, sex, body-mass index, type or severity of symptoms and co-morbidities. ALT had a moderate correlation with endomysial ($r = 0.334$, $P < 0.001$) and transglutaminase antibodies ($r = 0.264$, $P = 0.002$) and ferritin ($r = -0.225$, $P = 0.03$), but not with other laboratory values. On gluten-free diet median ALT decreased from 22.0 U/l to 18.0 U/l ($P = 0.002$) and 80% of the high values normalized.
Conclusion: Increased ALT is associated with more advanced serological and histological celiac disease. Adherence to a gluten-free diet appears to result in normalization or reduction of ALT levels.

1. Introduction

The estimated prevalence of celiac disease is as high as 1–2% in many Western countries and even rising [1,2]. Currently most patients remain undiagnosed, but the clinical prevalence has also increased rapidly, being now for example in the Scandinavian countries more than 0.5% [3–5]. The major reason for the improved diagnostic efficacy is recognition of the diversity of the clinical picture, including a variety of extra-intestinal symptoms [6,7]. One of the best-characterized of these is hypertransaminasemia [8–11], the prevalence of which in untreated adults has been up to 42% [12–14]. Only a limited number of studies have been conducted in children, but the percentages have been generally comparable to those reported in adults [9,15,16].

Interestingly, we recently observed only 11% of Finnish adults with celiac disease to have elevated transaminases at diagnosis [17]. A plausible explanation for such a low prevalence is early diagnosis of celiac disease due to active case-finding and increased at-risk group screenings. Supporting such a conception, even normal transaminase values improved on a gluten-free diet, indicating the presence of early gluten-dependent liver damage [17]. It is unclear whether a similar decrease in transaminasemia is under way in children, where the diagnostic approach and clinical picture have also changed markedly during the 2000s [3]. Moreover, it remains obscure what patient-related factors are associated with increased liver values in celiac disease.

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Here we further elucidated these issues by comparing the median levels and prevalence of increased alanine aminotransferase (ALT) values between children with untreated celiac disease, children with other chronic gastrointestinal diseases, and population-based controls. Further, we investigated the association between ALT levels and different clinical, laboratory and histological parameters and the effect of a gluten-free diet in celiac disease patients. We hypothesized that the prevalence of increased ALT has decreased also in children with celiac disease, and that increased values are associated with more severe disease.

2. Materials and methods

2.1. Study design and participants

The study was conducted at the Tampere Centre for Child Health Research, Tampere University Hospital and the University of Tampere, and at the Institute of Biomedicine, University of Eastern Finland. It involved well-defined cohorts of children with celiac disease and those with other gastrointestinal diseases, and healthy children from a general population. Inclusion criteria were age below 18 years and available ALT value either at diagnosis (disease groups) or at study enrolment (population controls). Exclusion criteria were unclear diagnosis of celiac disease and other gastrointestinal diseases and presence of medication (such as liver-toxic drugs, supplements or herbal products) known to affect the liver metabolism. Children with known co-existing condition (such as congenital liver disease, malignancy, viral or autoimmune hepatitis, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, Wilson's disease, other metabolic liver disease) possibly affecting liver values, were excluded from all study groups. In addition, celiac disease patients were further investigated for possible underlying liver diseases in case of persistently high liver values despite a gluten-free diet.

Children with biopsy-proven (Marsh IIIa-c) celiac disease were collected from our regularly updated database, comprising a large cohort of children diagnosed at the Department of Paediatric Gastroenterology [3]. Medical information on the patients has been collected systemically from the medical records and subsequently complemented with personal/parent interviews by an experienced study nurse or a paediatrician. The hospital is tertiary centre with catchment area of around one million inhabitants. In our settings primary screening of celiac disease is conducted mainly in primary care, but regardless of the disease severity children with a celiac disease suspicion are referred to Department of Paediatric Gastroenterology for further investigations. All disease patients for the present study were diagnosed at the same site between the years 2002–2014. From the database we retrospectively selected all consecutive celiac disease patients who had ALT value recorded at diagnosis. However, from the year 2012 onwards more than 90% of the children have been enrolled prospectively, and at the same time ALT has been included in the routine diagnostic evaluation, while before 2012 it was measured irregularly without systematic recommendations.

The disease control groups comprised 79 untreated children with inflammatory bowel disease (IBD) (36 with Crohn's disease and 43 with ulcerative colitis), 37 untreated children with gastrointestinal reflux disease (GERD) and 45 children with functional abdominal complaints. The patients were diagnosed in 2007–2014 at the same site as the celiac disease patients. The diagnoses of IBD and GERD were based on the criteria set by the European Society for Pediatric Gastroenterology Hepatology and Nutrition [18–20]. The diagnosis of functional gastrointestinal disorder was set for children who had undergone thorough clinical, laboratory and endoscopic investigations due to unspecific abdominal symptoms without established organic cause [21].

The population-based control group was obtained from the Physical Activity and Nutrition in Children (PANIC) study [22]. Altogether 736 children aged 6–8 years who started primary school in the Kuopio region in 2007–2009 were invited to participate in a physical activity and dietary intervention study. Of these 512 children participated and underwent analyses of general health, growth and metabolic laboratory values as described in detail elsewhere [22]. After exclusion criteria the final group comprised 500 children.

After collection of the study data (see below), all groups underwent comparisons of ALT levels and percentages of elevated values. Further, the association between baseline ALT values and different clinical, serological, laboratory and histological parameters was investigated in celiac patients, as well as the effect of the gluten-free diet.

The study was approved by the Ethics Committees of Pirkanmaa Hospital District and the Research Ethics Committee of the Hospital District of Northern Savo, and by the Department of Pediatrics, Tampere University Hospital. In addition, all children and/or their parents participating in prospective study enrolment or personal interviews gave written informed consent.

2.2. General assessments

The following clinical information was recorded on children in the disease groups at the time of diagnosis and on the population controls during the study visit: age, gender, presence of other diseases and medications, body mass index (BMI, kg/m^2) and BMI standard deviation score and ALT value (U/l). In addition, weight loss, baseline haemoglobin value and possible presence of anaemia were recorded in the disease groups, as well as gastrointestinal symptoms such as diarrhoea, melena/hematochezia, abdominal pain, constipation, gastroesophageal reflux, vomiting and dysphagia. Of the different liver biochemical tests only ALT was used, since it is more specific for hepatocyte injury than aspartate aminotransferase and almost exclusively used in the first-line screening test for liver damage in children [23]. In the present study ALT values higher than >30 U/l were considered increased in both genders [24–26].

2.3. Celiac disease-specific data

2.3.1. Clinical parameters

In addition to the aforesaid variables, the following clinical data were recorded on the children with celiac disease at diagnosis: type (gastrointestinal, extra-intestinal and screen-detected) and severity (asymptomatic, mild, moderate and severe) of clinical symptoms, possible presence of concomitant celiac disease-associated conditions (type 1 diabetes, autoimmune thyroidal disease, Down's syndrome), and growth parameters. Poor growth was defined as a significant deviation from the expected height or abnormal growth velocity [27].

2.3.2. Laboratory values, celiac disease serology and histology

The following blood parameters in addition to ALT and haemoglobin were collected on each celiac disease patient when available at the time of diagnosis: alkaline phosphatase (U/l), mean corpuscular volume (fl), total iron (μmol/l), transferrin receptor 1 (mg/l), ferritin (μg/l), albumin (g/l), thyroid-stimulating hormone (TSH) (mU/l) and thyroxin (pmol/l). These laboratory values were recorded in order to further estimate the overall severity of the disease.

Serum endomysial antibodies (EmA) were measured by an indirect immunofluorescence method using human umbilical cord as substrate [28]. Titres 1:5 or lower were considered positive and