Presentation of Celiac Disease in Finnish Children Is No Longer Changing: A 50-Year Perspective

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Objectives To chart trends in the presentation of celiac disease in a large cohort of Finnish children diagnosed over a period of 48 years.

Study design Clinical and serologic data, severity of small-bowel mucosal damage, and presence of associated conditions were gathered from 596 children diagnosed with celiac disease in 1966-2013. The children were divided into 4 groups based on the year of diagnosis (before 1980, 1980-1999, 2000-2009, and 2010-2013), and the variables were compared between the periods. The incidence of celiac disease autoimmunity in 2001-2013 was calculated based on the number of new antibody-positive cases in each year.

Results Age at diagnosis rose from median 4.3 years before 1980 to between 7.6 and 9.0 years in the later periods. The severity of clinical presentation, in general, became milder and poor growth less common during the entire study period of 50 years. Percentages of children with classical gastrointestinal presentation decreased, and those with atypical or subclinical presentation increased after the 1990s, these changes leveling off in 2000-2013. Similarly, the severity of small-bowel mucosal damage was milder after the 1990s. The incidence of celiac disease autoimmunity increased in the early 2000s but then fluctuated without a clear trend. There were no significant secular changes in sex distribution, presence of anemia, levels of celiac antibodies, or celiac disease-associated conditions.

Conclusions The clinical and histologic presentation of celiac disease in children became milder, especially in the 1980s and 1990s. However, most of these changes have reached a plateau in recent years. *(J Pediatr 2015;167:1109-15)*.

Celiac disease is a chronic condition in which an immunoreaction to gluten causes small-bowel mucosal damage and various symptoms in susceptible individuals.[1] During the past few decades, the incidence of the disease has increased significantly,[2-5] constituting a major health problem affecting up to 1%-3% of children.[6,7] Concomitant with the increasing incidence, changes in the clinical presentation have been observed since the 1980s.[8] Instead of the classical symptoms of diarrhea and failure to thrive, atypical symptoms have been increasingly encountered, as well as asymptomatic patients detected by targeted screening of at-risk groups.[2,3,9-12] In addition, the average age at diagnosis has risen from <2 years[8] up to 6-9 years in many developed countries.[2,3,9,11-14] Most of these changes are probably explained by new serologic tools,[2,9] increased awareness among physicians, and at-risk group screenings.[10] This notwithstanding, there are differences in the prevalence and presentation of celiac disease between closely located geographic areas and fluctuations even within the same country,[15,16] and the true prevalence of the disease has also increased.[3,17,18] These observations suggest that environmental factors have a role in these phenomena. Related changes have also been observed in other autoimmune diseases.[19-21] However, at least in some developed countries, these changes might already have reached a plateau.[22-24] Thus far, no similar trends in celiac disease has been reported.

In Finland, celiac disease is particularly common[6] and centralized diagnostics, together with nationwide guidelines, enable reliable long-term evaluation of the natural history of the disease. We sought to characterize trends in the clinical and histologic presentation and incidence of celiac disease in a large and unique cohort of children diagnosed over a period of almost 50 years.

CDA	Celiac disease autoimmunity
EmA	Endomysial antibody
PVA	Partial villous atrophy
SVA	Subtotal villous atrophy
TG2ab	Transglutaminase 2 antibody
TVA	Total villous atrophy

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Methods

The study was conducted in the Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital. Inclusion criteria were confirmed celiac disease and age under 18 years at diagnosis. The patients were collected from our continuously updated research database comprising information on children diagnosed with celiac disease from 1966 to the present. A considerable proportion of the information in our database has been collected prospectively. Apart from this, data were collected from the medical records and, when these proved inadequate, supplemented with personal interviews by a study nurse with expertise in celiac disease. Collection of medical records and patient interviews was approved by the Pediatric Clinic of Tampere University Hospital and the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland. All subjects and/or their parents gave written informed consent to participate in the supplementary personal interviews.

In Finland, the diagnostics of celiac disease in children is coordinated by the university hospitals (currently 5), and nationwide guidelines are systematically applied in all these tertiary centers.[25] All patients with celiac disease receive financial compensation from the government, a definitive biopsy-proven diagnosis being required. In our database, early diagnoses before the 1970s were made almost exclusively at the pediatric department in Helsinki University Hospital, and most of the later diagnoses in Tampere University Hospital. A great majority of the database diagnoses from the 1960s to the present were made either personally or under the supervision of the study authors.

Altogether 596 children with celiac disease fulfilled the inclusion criteria and comprised the study population. To analyze the clinical incidence of celiac disease from the year 2001 onward, the annual number of seropositive children referred to our hospital for gastrointestinal endoscopy because of celiac disease suspicion in 2001-2013 was calculated (see below).

The following data at the time of celiac disease diagnosis were collected on all children: age, sex, clinical presentation, presence of growth failure or overweight, presence of anemia and hemoglobin value, severity of the small-bowel mucosal damage, serum celiac disease-specific antibodies, and presence of celiac disease-associated conditions, including type 1 diabetes, autoimmune thyroidal disease, and Down syndrome.

The 596 study children were divided into 3 subgroups based on their age at celiac disease diagnosis as follows: (1) infants (<2 years of age); (2) toddlers/preschoolers (2-7 years of age); and (3) school-aged children (>7 years of age). The clinical presentation of the disease was subcategorized into 3 groups according to the main symptoms recorded at diagnosis: (1) gastrointestinal symptoms including diarrhea, vomiting, abdominal pain, and constipation; (2) extra-intestinal symptoms such as arthralgia, dental enamel defects, neurologic and musculoskeletal symptoms, short stature or failure to thrive, and elevated liver enzymes; and (3) children detected by screening in at-risk groups (eg, family history of celiac disease or presence of an associated disorder such as type 1 diabetes). The severity of clinical presentation at diagnosis was classified into 4 grades as follows: (1) no clinical symptoms (screen-detected asymptomatic subjects); (2) mild symptoms (occasionally disturbing gastrointestinal or extra-intestinal symptoms and normal growth); (3) moderate symptoms (symptoms more distracting or frequent or a combination of several symptoms); and (4) severe symptoms (symptoms seriously disturbing daily life, eg, recurrent nighttime awakenings because of pain or symptoms requiring acute inpatient care).

Poor growth was defined as a significant height or weight deceleration compared with the reference rate for age and sex or compared with expected height based on midparental height. This method has long been used in our clinical practice and has been proven to be a sensitive method to detect growth failure in untreated celiac disease.[26] Height-to-weight ratio was used to define if a child was overweight. It describes a percentual difference of child's weight compared with the median weight of those with same height. Children were considered to be overweight when the height-to-weight ratio was >10% (<7 years old) or >20% (≥7 years old) on nationally standardized growth charts.[27] Anemia at diagnosis was defined as a hemoglobin value (g/L) below the age- and sex-matched reference value.

Small-bowel mucosal biopsies before 1986 were obtained either using the Watson gastrointestinal biopsy capsule or during upper gastrointestinal endoscopy; from 1986 onward, endoscopy has been used exclusively. The degree of small-bowel mucosal damage was categorized into partial (PVA), subtotal (SVA), and total villous atrophy (TVA) because this grading has been systematically applied by pathologists during the entire study period. The corresponding Marsh-Oberhuber grades are approximately IIIa, IIIb, and IIIc.[28]

From the 1970s to the 1990s, anti-gliadin and antireticulin antibodies were used in most cases. Human umbilical cord-based measurement of endomysial antibodies (EmAs) was introduced in 1994, and serum transglutaminase 2 antibody (TG2ab) in 1997; assays for these have been used as a first-line screening method for celiac disease in our clinical practice since the end of the 1990s.[29] As a result, the median values for EmA in 2000-2009 and 2010-2013 could be calculated. This could not be done with TG2ab because the testing methods have varied over time, and the cut-off values for positivity have been set by manufacturers using different criteria.[30]

From the year 2001 onward, practically all children referred to our hospital because of celiac disease suspicion have been EmA- and/or TG2ab-positive. We defined celiac disease autoimmunity (CDA) as elevated TG2ab/EmA regardless of biopsy results,[31] and subsequently estimated the annual incidence rate of CDA in 2001-2013 by dividing the number of seropositive cases by the number of at-risk children in our catchment area (119 243-121 581 during the