At-Risk Screened Children with Celiac Disease are Comparable in Disease Severity and Dietary Adherence to Those Found because of Clinical Suspicion: A Large Cohort Study

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Objective To assess whether children at risk for celiac disease should be screened systematically by comparing their baseline and follow-up characteristics to patients detected because of clinical suspicion.

Study design Five hundred four children with celiac disease were divided into screen-detected (n = 145) and clinically detected cohorts (n = 359). The groups were compared for clinical, serologic, and histologic characteristics and laboratory values. Follow-up data regarding adherence and response to gluten-free diet were compared. Subgroup analyses were made between asymptomatic and symptomatic screen-detected patients.

Results Of screen-detected patients, 51.8% had symptoms at diagnosis, although these were milder than in clinically detected children ($P < .001$). Anemia (7.1% vs 22.9%, $P < .001$) and poor growth (15.7% vs 36.9%, $P < .001$) were more common, and hemoglobin (126 g/l vs 124 g/l, $P = .008$) and albumin (41.0 g/l vs 38.0 g/l, $P = .016$) were lower in clinically detected patients. There were no differences in serology or histology between the groups. Screen-detected children had better dietary adherence (91.2% vs 83.2%, $P = .047$). The groups showed equal clinical response (97.5% vs 96.2%, $P = .766$) to the gluten-free diet. In subgroup analysis among screen-detected children, asymptomatic patients were older than symptomatic (9.0 vs 5.8 years of age, $P = .007$), but the groups were comparable in other variables.

Conclusions More than one-half of the screen-detected patients with celiac disease had symptoms unrecognized at diagnosis. The severity of histologic damage, antibody levels, dietary adherence, and response to treatment in screen-detected cases is comparable with those detected on a clinical basis. The results support active screening for celiac disease among at-risk children. *(J Pediatr 2017;183:115-21).*

Celiac disease has become a major public health issue with an estimated prevalence of 1%-3% in many Western and Asian countries.[1-3] However, because of the variable gastrointestinal and extra-intestinal symptoms involved, the majority of affected children remain unrecognized.[1,2] Because screening for the disease is available by antibody tests, it has been suggested that diagnostic rates can be increased through screening either known at-risk groups[4-6] or the entire population.[7] However, although celiac disease fulfils several World Health Organization criteria for population screening, the benefits of this approach remain controversial.[8,9] In particular, it remains unclear how well mildly symptomatic or asymptomatic screen-detected patients will adhere to a demanding and socially restrictive gluten-free diet.[6,10-17] Although untreated celiac disease predisposes to severe complications with increased use of healthcare services in symptomatic patients,[9,18,19] it is not known whether this applies to screen-detected individuals, who may possible have less severe histologic damage[20] and, consequently, better long-term outcome. Then again, complications such as poor growth, dental enamel defects, and low bone mass have been observed even in otherwise asymptomatic children with celiac disease, and these maladies may remain permanent if left untreated.[21-23]

To evaluate the potential benefits and detriments of celiac disease screening, we compared clinical, serologic, and histologic features and follow-up results between children detected during the course of risk-group screening and those identified on clinical suspicion.

EmA	Endomysial antibody
Rf	Reference value
T1DM	Type 1 diabetes mellitus
TG2ab	Transglutaminase 2 antibody

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Methods

The study was conducted at the Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, and at the Department of Pediatrics, Tampere University Hospital. Patient data were collected from our research database, which contains medical information on children diagnosed with celiac disease from the late 1960s to the present. Lacking or incomplete patient information has been supplemented with personal or telephone interviews by an experienced physician or study nurse. From the year 2012 onward, most of the database patients have participated in a prospective study enrolment. To increase the integrity of the results, only children diagnosed from the year 2000 onward were included. Exclusion criteria were age ≥18 years, unclear diagnosis of celiac disease, and lack of data regarding the initial clinical presentation. Altogether, 504 children with celiac disease proven by biopsy comprised the final study cohort.

The following celiac disease-related information was collected on each child at the time of the diagnosis: clinical characteristics, severity of histologic damage, celiac disease serology, a variety of other laboratory variables, and presence of celiac disease in the family. Follow-up data regarding adherence and clinical and serologic response to the gluten-free diet were recorded. The results were compared between children detected by screening and those found on the basis of clinical suspicion. For the corresponding subgroup analysis, screen-detected children were further divided into asymptomatic and symptomatic patients.

The Pediatric Clinic of Tampere University Hospital and the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland, approved the study. Written informed consent was obtained from all subjects and/or their parents participating in the personal interviews or prospective study enrollment.

Screen-detected patients included at-risk children such as those with celiac disease in relatives (first degree or more distant), type 1 diabetes mellitus (T1DM), or autoimmune thyroidal disease as a comorbidity. Some patients were screened for celiac disease because of attendance in a follow-up study attributable to increased genetic risk for T1DM. Clinically detected children were diagnosed on the basis of gastrointestinal or extra-intestinal symptoms or findings, including diarrhea, abdominal pain, constipation, arthralgia, dermatitis herpetiformis, anemia, and poor growth. Severity of symptoms was classified as no symptoms; mild symptoms (occasionally disturbing minor symptoms); moderate symptoms (more frequent and distracting symptoms); and severe symptoms (distracting symptoms causing recurrent nighttime awakenings, school absence, etc). Anemia and poor growth were considered as findings or complications of celiac disease and were, thus, not included in the classification of symptoms. Height and weight at the diagnosis were noted and expressed in age- and sex-dependent SD units. Poor growth was defined based on abnormalities in expected height and growth velocity as described elsewhere.[23,24] Body mass index was calculated as weight/height^2 (kg/m^2).

Small-Bowel Mucosal Damage and Laboratory Variables

At least 4 distal duodenal mucosal samples were taken during gastrointestinal endoscopy in all children with suspected celiac disease. From 2012 onward, samples were also obtained from the duodenal bulb.[25] The severity of mucosal damage was assessed from several well-orientated biopsy sections[26] and further categorized as mild (Marsh IIIa), moderate (Marsh IIIb), or total villous atrophy (Marsh IIIc).

Transglutaminase 2 antibodies (TG2ab) were measured by either automatized automated enzyme fluoroimmunoassay assay (Phadia AB, Uppsala, Sweden), or before 2011 by conventional enzyme-linked immunosorbent assay (Phadia). Values 7 U/L or higher for TG2ab are considered positive; 120 U/L is the highest reported value. Serum endomysial antibodies (EmAs) were measured by indirect immunofluorescence as previously described.[20,27] A dilution of 1: ≥5 for EmA was considered positive and further diluted up to 1:4000 or until negative.

Results of the following laboratory tests were collected on each child when available: hemoglobin (g/L), erythrocyte mean corpuscular volume (reference value [Rf] 73-95 fL), plasma albumin (Rf 36-48 g/L), plasma transferrin receptor (TfR) (age- and sex-matched Rf),[28] plasma ferritin (Rf >20 μg/L), plasma alanine aminotransferase (Rf ≤30 U/L),[29] and plasma thyroid-stimulating hormone (TSH) (Rf 0.27-4.2 mU/L). Anemia was defined as a hemoglobin value below the age- and sex-matched reference.[30] For consistency, only laboratory values taken at the time of diagnostic evaluations were accepted for the baseline comparisons. Values other than hemoglobin were systematically obtained only during the latter part of the study period.

Follow-Up Investigations

All children initiated a gluten-free diet shortly after the diagnosis under the supervision of a qualified dietitian. Adherence to the diet was assessed during each follow-up visit based on self-reported gluten avoidance and results of serology, and categorized into strict diet, occasional lapses, and no diet. Clinical and serologic response to the dietary treatment was also evaluated and classified as (1) good response (disappearance of symptoms and normalized or markedly decreased celiac antibody levels); or (2) no response (persistent symptoms and/or antibody positivity). Routine follow-up visits took place approximately 3-6 and 10-12 months after the celiac disease diagnosis. Further, 120 of the children were interviewed after a median of 4 years from the diagnosis. Results of follow-up serology were analyzed by comparing the baseline TG2ab values with those measured after a median of 13 (range 6-24) months on a gluten-free diet.

Statistical Analyses

Categorized variables are reported as percentage distributions and numeric variables as medians with quartiles. Fisher exact test or χ^2 test was used to compare categorized variables and Mann-Whitney U test with numeric variables. Binary logistic regression was used to adjust age differences between the groups. A P value of <.05 was considered significant.