

At-risk screened children with celiac disease are comparable in disease severity and dietary adherence to those found due to clinical suspicion: a large cohort study

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Abbreviations: EmA – endomysial antibody, Hb – blood hemoglobin, Rf – reference value, TG2ab – transglutaminase 2 antibody, T1DM – type 1 diabetes mellitus

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Abstract

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: Altogether 504 celiac disease children were divided into screen-detected (n=145) and clinically detected cohorts (n=359) and the groups underwent comparisons of clinical, serological and histological characteristics and laboratory values. Further, 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: Altogether 51.8% of screen-detected patients also had symptoms at diagnosis, although these were milder than in clinically detected children ($p<0.001$). Anemia (7.1% vs 22.9%, $p<0.001$) and poor growth (15.7% vs 36.9%, $p<0.001$) were more common and hemoglobin (126 g/l vs 124 g/l, $p=0.008$) and albumin (41.0 g/l vs 38.0 g/l, $p=0.016$) lower in clinically detected patients, but there were no differences in serology or histology between the groups. Screen-detected children evinced better dietary adherence (91.2% vs 83.2%, $p=0.047$), and the groups showed equal clinical response (97.5% vs 96.2%, $p=0.766$) to the gluten-free diet. In subgroup analysis among screen-detected children, asymptomatic patients were older than symptomatic (9.0 yr vs 5.8 yr, $p=0.007$), but the groups were comparable in other variables.

Conclusion: More than half of the screen-detected celiac disease patients here had symptoms unrecognized at diagnosis. Further, they had severity of histological damage, antibody levels, dietary adherence and response to treatment comparable to those detected on clinical basis. The results support active screening for celiac disease among at-risk children.

Introduction

During the past few decades, 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, due to the plethora of unspecific gastrointestinal and extra-intestinal symptoms involved, the great majority of affected children remain unrecognized.^{1,2} Since screening for the disease is simple by modern antibody tests, it has been suggested that for increased diagnostic efficiency we should screen either known at-risk groups^{4–6} or even the whole population.⁷ However, although celiac disease fulfils several WHO criteria for screening, the overall benefits of this approach remain controversial.^{8,9} In particular, it remains unclear how well often mildly symptomatic or apparently asymptomatic screen-detected patients adhere to the demanding and socially restrictive gluten-free diet.^{6,10–17} Although untreated celiac disease is known to predispose to severe complications and incur incremental use of health care services and medicines in symptomatic patients,^{9,18,19} it is obscure whether this also applies to screen-detected individuals, especially as it is possible that they have less severe histological damage²⁰ and subsequently 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}

In order to further elucidate the potential benefits and detriments of celiac disease screening, we compared clinical, serological and histological features and follow-up results between children detected in the course of risk-group screening and those found due to clinical suspicion.

Methods

Patients and study design

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 continuously updated 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 onwards most of the database patients have participated in a prospective study enrolment. In order to increase the integrity of the results, only children diagnosed from the year 2000 onwards 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 biopsy-proven celiac disease comprised the final study cohort.

The following celiac disease-related information was collected on each child at the time of the diagnosis (below in detail): clinical characteristics, severity of histological damage, celiac disease serology and a variety of other laboratory parameters, and presence of celiac disease in the family. In addition, follow-up data regarding adherence and clinical and serological response to the gluten-free diet were recorded. After data assembly, the results were compared between children detected by screening and those found on the grounds 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 data collection from medical records and supplementary patient interviews. Written informed consent was obtained from all subjects and/or their parents participating in the personal interviews or prospective study enrolment.

Data analyses

Clinical characteristics

Screen-detected patients included at-risk children such as those with celiac disease in relatives (first degree or more distant) or type 1 diabetes (T1DM) or autoimmune thyroidal disease as a comorbidity. Some patients were screened for celiac disease because of attendance in a follow-up study due 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: 1) no symptoms; 2) mild symptoms (occasionally disturbing minor symptoms); 3) moderate symptoms (more frequent and distracting symptoms); and 4) severe symptoms (distracting symptoms causing e.g. recurrent nighttime awakenings and school absence). Anemia and poor growth were considered as findings or complications of celiac disease and were thus not included to the classification of symptoms. Height and weight at the diagnosis were noted and expressed in age- and gender-dependent standard deviation (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 parameters

At least four distal duodenal mucosal samples were taken upon gastrointestinal endoscopy in all children with celiac disease suspicion. From the year 2012 onwards, the samples have also been systematically obtained from the duodenal bulb.²⁵ The biopsies were referred to the hospital

pathology unit, where the severity of mucosal damage was assessed from several well-orientated biopsy sections²⁶ and further categorized as mild (Marsh IIIa), moderate (Marsh IIIb) or total villous atrophy (Marsh IIIc).

Transglutaminase 2 antibodies (TG2ab) were measured at the local hospital laboratory by either automatized EliA assay (Phadia AB, Uppsala, Sweden), or before the year 2011 by conventional ELISA (Phadia). In our laboratory, values 7 U/l or higher for TG2ab are considered positive and 120 U/l is the highest reported value. Serum endomysial antibodies (EmA) were measured in our research center 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: blood hemoglobin (Hb) (g/l), erythrocyte mean corpuscular volume (MCV) (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 (ALT) (Rf ≤30 U/l)²⁹ and plasma thyroid-stimulating hormone (TSH) (Rf 0.27–4.2 mU/l). Anemia was defined as a Hb 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 Hb started to be taken systematically 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 serological 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 in our clinical practice took place approximately 3–6 and 10–12 months after the celiac disease diagnosis. Further, 120 of the children were supplementary interviewed after a median of 4 years from the diagnosis. Results of follow-up serology were analyzed in detail by comparing the baseline TG2ab values to those measured after a median of 13 (range 6–24) months on a gluten-free diet.

Statistics

Categorized variables are reported as percentage distributions and numeric variables as medians with quartiles. Chi-square test or Fisher's exact 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 <0.05 was considered significant. Analyses were performed with SPSS version 22 (IBM Corp., Armonk, NY).

Results

Altogether 145 (28.8%) of the children were detected by screening and 359 (71.2%) on clinical basis (Table 1). The main presentation was gastrointestinal in 68.0% and extra-intestinal in 32.0% of the patients detected due to symptoms. There were no differences between screen- and clinically detected children in age or gender, but celiac disease in first-degree relatives and concomitant T1DM were more common among the screen-detected children (Table 1) these also being the primary reasons for screening. Clinically detected patients had more anemia and poor growth, but these disorders were also seen in a substantial proportion of those found by screening (Table 1).

As many as 51.8% of the screen-detected children also reported symptoms unrecognized at diagnosis, even if less severe than in patients diagnosed in clinical practice (Fig. 1A–B; online only). In detailed analysis, diarrhea or loose stools were more common among clinically detected patients, but otherwise the groups did not differ in the distribution of symptoms (Table 2; online only). There were no significant differences between the study groups in anthropometric measurements (Table 3) or severity of histological damage (Fig. 1C; online only). In three screen-detected and in ten clinically detected children the celiac disease diagnosis was based on lesion in duodenal bulb only ($p=1.000$). The median blood Hb and serum albumin were slightly lower among clinically detected subjects (Table 3), but except for anemia, the prevalence of abnormal laboratory values did not differ between the groups (clinically vs screen-detected): low albumin 23.0% vs 10.5%, $p=0.343$; MCV 10.6% vs 13.4%, $p=0.515$; and ferritin 20.5% vs 20.0% $p=0.958$; and increased TfR 31.3% vs 22.2%, $p=0.451$; ALT 15.6% vs 16.0%, $p=1.000$; and TSH 14.2% vs 7.3%, $p=0.251$, respectively.

Adherence to a gluten-free diet was better among the screen-detected children (Fig. 1D; online only). However, there was no significant association between the presence of strict adherence and celiac disease in the family (celiac disease 81.3% vs no disease 90.4%, $p=0.060$) or concomitant type 1 diabetes in the child (T1DM 85.8% vs no T1DM 84.6%, $p=0.835$). The clinical and serologic response were equally good in both groups (97.5% vs 96.2%, $p=0.766$). Similarly, while on diet serum TG2abs decreased in all but two screen-detected and in all clinically detected patients (Fig. 2); on later follow-up the antibodies declined even in the two cases with no initial response (data not shown). The median time on a gluten-free diet before the follow-up TG2ab

measurement was comparable between the screen-detected and clinically detected children (12.0 vs 11.0 months, $p=0.090$).

Among the screen-detected patients, symptomatic children were significantly younger and had higher EmA and lower median Hb compared with those asymptomatic upon crude analysis, but the differences in EmA and Hb were no longer significant when adjusted for age (Table 4). There were no differences between the subgroups in gender, growth parameters or presence of anemia, concomitant T1DM and celiac disease in relatives (Table 4) or prevalence of abnormal laboratory values (data not shown). Further, the screen-detected groups were comparable in severity of histological damage and dietary adherence (Fig. 3; online only).

There was no association between EmA or TG2ab levels and the severity of villous atrophy in screen-detected patients (median EmA titers Marsh IIIa=1:200, IIIb=1:500, IIIc=1:500, $p=0.164$; TG2ab levels 86.0 U/l, 114.0 U/l and 113.0 U/l, respectively, $p=0.318$), whereas the association was seen when evaluated in the whole group (EmA 1:200, 1:500 and 1:1000, $p<0.001$; TG2ab 72.0 U/l, 120.0 U/l, 120.0 U/l, $p<0.001$).

Discussion

The present study demonstrated that even screen-detected children very often suffer from unrecognized clinical symptoms and signs of celiac disease before diagnosis. Further, notwithstanding the different diagnostic approach, these patients are comparable to those found on clinical basis in respect of histological and serological markers of disease severity, and show even better adherence and response to the gluten-free diet. Our findings support active screening of celiac disease among at-risk children. However, benefits of screening on health outcomes in unselected population remain obscure.

Over half of the screen-detected children here reported gluten-responsive symptoms, which had neither led to a doctor visit nor been recognized as celiac disease in clinical practice. In line with this, other recent studies conducted among screened children and adults have shown up to 34–84% of such patients to suffer from symptoms unrecognized at the time of the celiac disease diagnosis.^{11,15,31,32} These findings demonstrate that symptom-based case finding is too inefficient to detect a large part of even children with classical gastrointestinal presentation, let alone those who present with atypical or subtle symptoms. What is more, most of the above mentioned pediatric screening studies have been conducted in Finland and other Nordic countries, where the disease is fairly well-known among pediatricians and primary care physicians,^{15,32} and in many other countries the situation might be even poorer. For example, in the USA only 17% of all celiac

disease patients were aware of their disorder before population screening,³³ and such underdiagnosing has also been observed in New Zealand and Australia.³⁴

Besides unrecognized symptoms, many of the screen-detected children here suffered from poor growth and anemia, which were not recognized as a sign of celiac disease before the screening. There has been debate as to whether the risk of long-term complications is similar among screen- and clinically detected patients,^{9,18} but data actually comparing these two groups are limited. Previously Korponay-Szabó and colleagues reported a high prevalence of 22% for anemia and 31% for poor growth in a population-based cohort of screen-detected schoolchildren in Hungary.³⁵ We have also shown these prominent complications to be present in otherwise asymptomatic patients,^{23,36} and there is some evidence that the introduction of a gluten-free diet can improve poor growth and hemoglobin values also in screen-detected children.³⁷ Other possible complications which have been observed regardless of the clinical presentation of celiac disease are for instance low bone mineral density, dental enamel defects and elevated transaminases.^{21,22,29,38}

Further supporting the presence of advanced disease and risk of complications, the screen-detected children here had levels of celiac disease autoantibodies and severity of villous atrophy similar to those detected on clinical basis. It is possible that, despite equal severity of histological injury, the clinically detected group had longer length of small intestinal injury, which may explain their apparent gastrointestinal symptoms.³⁹ However, the current evidence in adults does not support this hypothesis.⁴⁰ Earlier studies have yielded inconsistent results on the correlation between clinical picture and histological findings in celiac disease.^{20,41–43} Apart from differences in study designs these discrepancies might be at least partly explained by differences in clinical presentation of the disease between countries. During recent decades, studies from many developed countries have reported that the severity of celiac disease is becoming milder even in the subgroup of patients suffering from classical gastrointestinal symptoms,^{44,45} which may contribute to the increasing similarity between clinically and screen-detected children. Nevertheless, in favor of early diagnosis and treatment, more than half of the children in both groups here already had either moderate or total villous atrophy at diagnosis.

With a view to the reasonableness of screening, we consider it of prime importance that the compliance to gluten-free diet be comparable among screen- and symptom-detected children. Further verifying their excellent dietary adherence, the study groups showed equal clinical and serological response to the diet. Even if not all evinced complete normalization of antibodies during follow-up, a similar slow response in some celiac disease patients has also been noted elsewhere.^{12,37} The present study confirmed the results of our previous survey-based study, in which the diagnostic approach also had no effect on dietary adherence,¹⁵ and similar observations have

recently been reported from the Netherlands and Sweden.^{12,14} In contrast, in an earlier Italian study only 23% of screen-detected adolescents had satisfactory adherence to a gluten-free diet five years after the celiac disease diagnosis.¹⁰ It must, however, be emphasized that these patients were found by population-based mass-screening. Additional explanations for variable adherence might be differences in the availability and cost of gluten-free products, these being in many countries difficult to find in basic budget markets, and in awareness of celiac disease for example in restaurants.⁴⁶ Moreover, in Finland and some other countries governments financially support every child with confirmed celiac disease,⁴⁷ although this was the case also in the above-mentioned Italian study showing poor adherence.¹⁰ Other factors likely affecting dietary adherence could be the intensity and organization of follow-up, the possibility to meet a dietician, the presence of comorbidities, and celiac disease in other family members.^{13,16,48} However, we found no association between the adherence and presence of concomitant type 1 diabetes in the child or celiac disease in the family. In any case, our results demonstrate that excellent adherence to the gluten-free diet is also attainable in screen-detected celiac disease patients diagnosed and followed in a well-organized clinical practice.

Even if the benefits of the gluten-free diet in the present and some earlier studies favor screening and active treatment of celiac disease,^{6,15,17,31} there is reason for caution. Besides the social restrictions and economic burden,^{6,11,49} it is possible that the often nutritionally unbalanced diet predisposes some patients to suboptimal intake of vitamins and trace elements and to obesity.^{50,51} Further, despite the promising short-term results, there is a risk that dietary adherence declines later in adolescence and adulthood, when follow-up usually becomes less frequent and responsibility for daily treatment shifts from the parents to the patients themselves. This issue has been scantily studied, but a few years ago Van Koppen and colleagues reported good adherence and improved health in a majority of screen-detected children even 10 years after diagnosis.¹⁴ In contrast, in an earlier study by O'Leary and associated only 50% of the celiac disease patients diagnosed in childhood remained on a strict gluten-free diet after a median of 28 years' follow-up.⁵² In adults, dietary lapses have been a problem particularly in asymptomatic patients,¹¹ whereas this was not the case in the present study. More studies evaluating dietary adherence and the benefits of a gluten-free diet in the long term in screen-detected children are evidently required.

The main strengths of the present study were the large cohort of celiac disease patients diagnosed on uniform nationwide criteria, and the wide array of serological and histological variables available. In addition, follow-up data regarding adherence and clinical and serological response to the gluten-free diet were documented on the majority of the children. The main limitations include the mostly retrospective design, lack of systematic collection of laboratory

parameters other than serology during the whole study period and the lack of structured questionnaire for collection of symptoms and dietary adherence. Further, the median follow-up time in the study was too short to estimate long-term dietary adherence and the effects of an early-initiated gluten-free diet on the possible complications and comorbidities of celiac disease.

In conclusion, the high percentage of unrecognized clinical symptoms and excellent response and adherence to the gluten-free diet support active screening of celiac disease in at-risk children. An alternative option might be low-threshold case finding among at-risk children, but it is important to realize that even apparently asymptomatic patients may have well-advanced serological and histological disease and a subsequent risk of long-term complications.

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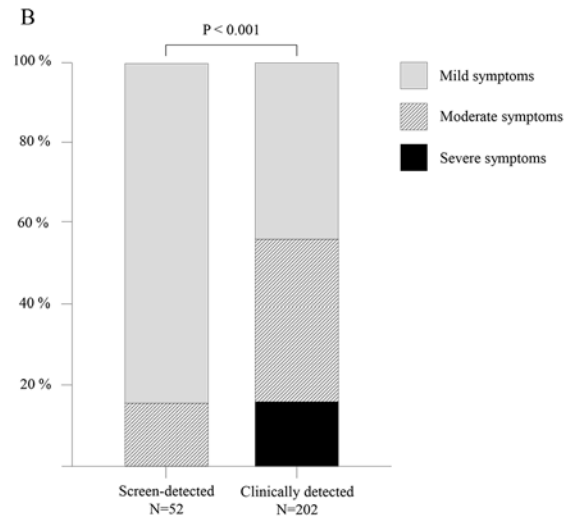
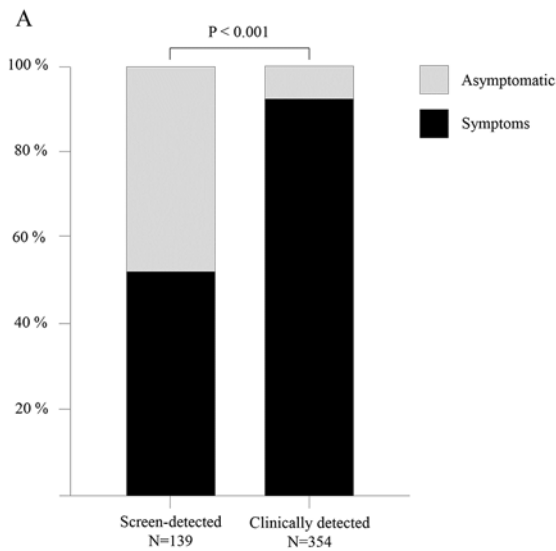


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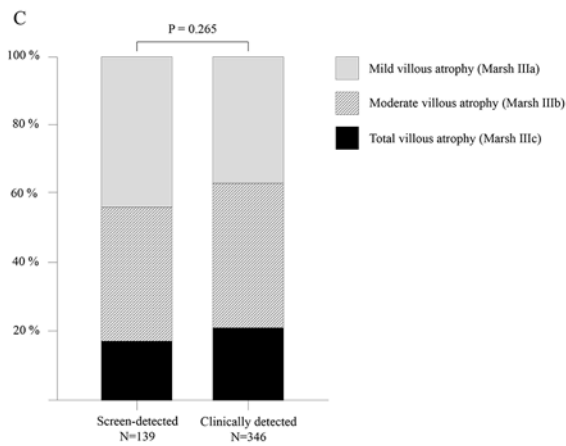


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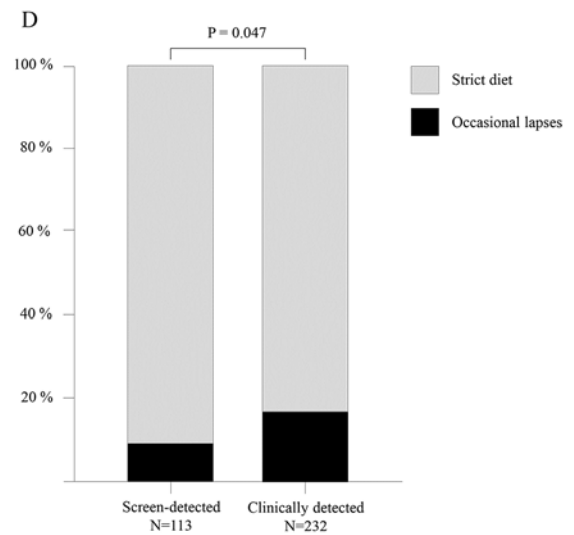


Figure 1; online only.

Figure 1; online only. Presence (A) and severity (B) of clinical symptoms, degree of small-bowel mucosal villous atrophy (C) and adherence to the gluten-free diet (D) in 504 children diagnosed with celiac disease either by screening or upon clinical suspicion. Asymptomatic patients are excluded from Supplementary Figure 1B.

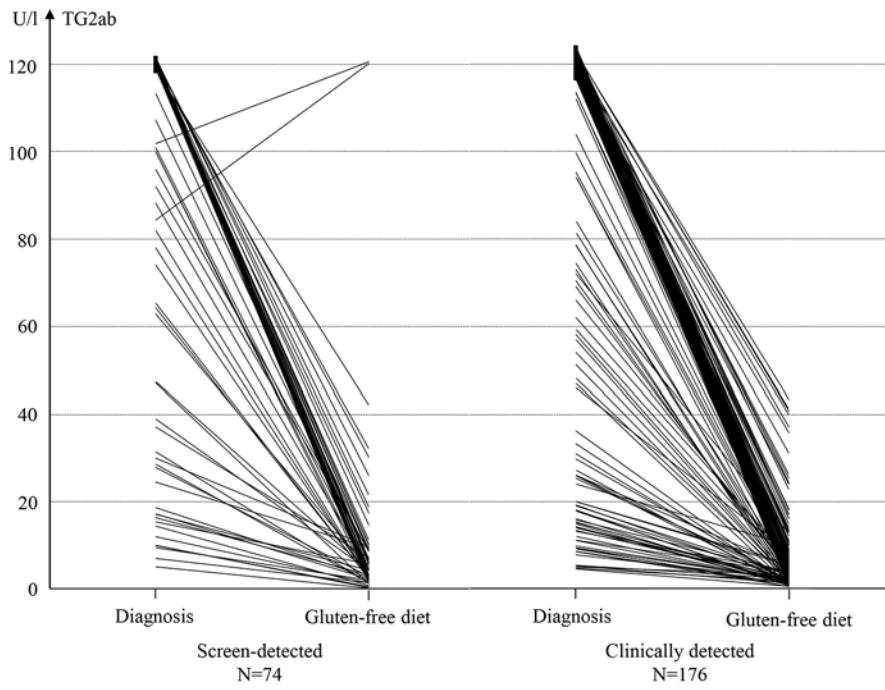


Figure 2.

Figure 2. Transglutaminase 2 antibody values at the time of diagnosis and on a gluten-free diet in 250 children diagnosed with celiac disease either by at-risk screening or based on clinical suspicion.

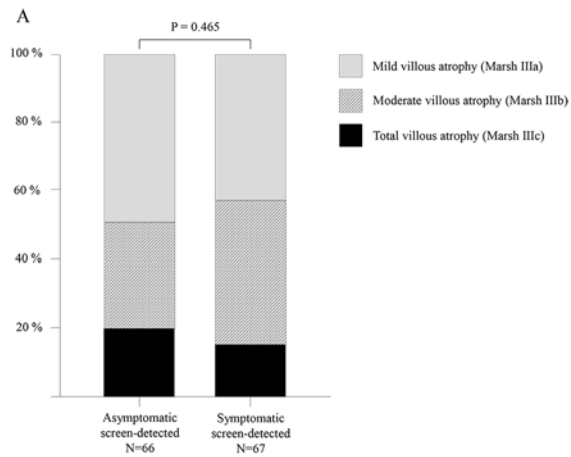


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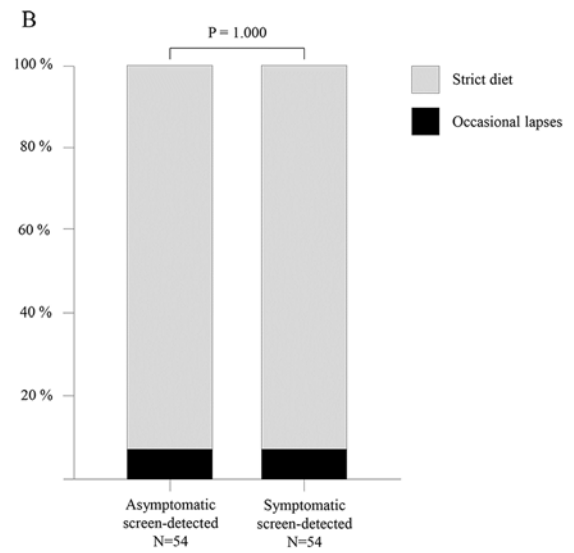


Figure 3; online only.

Figure 3; online only. Degree of small-bowel mucosal villous atrophy (A) and adherence to the gluten-free diet (B) in 139 screen-detected children with celiac disease divided into two groups based on the presence or absence of clinical symptoms at diagnosis.

Table 1. Demographic data and clinical characteristics in 504 children diagnosed with celiac disease by screening in at-risk groups or based on clinical suspicion.

	Screen-detected (N = 145)		Clinically detected (N = 359)		P value ³
	n	%	n	%	
Age at diagnosis, median (Q ₁ , Q ₃), yr	145	7.0 (4.1, 11.7)	359	8.0 (5.0, 11.7)	0.202
Girls	90	62.1	239	66.6	0.336
Celiac disease in the family	55 ¹	59.8	72 ²	33.8	<0.001
Type 1 diabetes	32	22.2	7	2.2	<0.001
Thyroidal disease	2	1.4	5	1.6	1.000
Down's syndrome	0	0.0	4	1.3	0.314
Anemia at diagnosis	10	7.1	72	22.9	<0.001
Poor growth at diagnosis	22	15.7	117	36.9	<0.001

Data available > 85% of the patients, except in ¹92 and ²213.

³Chi-square test, Fisher's exact test and Mann-Whitney U test.

Q₁ and Q₃, lower and upper quartiles.

Table 2; online only. Distribution of symptoms at diagnosis in 398 screen-detected and clinically detected children with celiac disease.

	Screen-detected (N = 72)		Clinically detected (N = 326)		P value ²
	n ¹	%	n ¹	%	
Stomach pain	61	55.7	295	65.4	0.152
Diarrhea or loose stools	63	28.6	277	42.2	0.045
Constipation	62	25.8	272	21.3	0.443
Skin symptoms	72	9.7	325	6.2	0.300
Arthralgia	72	2.8	326	7.7	0.194

¹Data available.

²Chi-square and Fisher's exact test.

Table 3. Laboratory values and growth parameters at celiac disease diagnosis in 504 children diagnosed by screening in at-risk groups or based on clinical suspicion.

	Screen-detected (N = 145)		Clinically detected (N = 359)		P value ²
	n ¹	Median (Q ₁ , Q ₃)	n ¹	Median (Q ₁ , Q ₃)	
Endomysial antibody, titer	103	1:500 (1:100, 1:2000)	247	1:500 (1:100, 1:1000)	0.576
Hemoglobin, g/l	81	126 (121, 135)	258	124 (112, 131)	0.008
Mean corpuscular volume, fl	67	81.0 (76.0, 84.0)	227	80.5 (76.0, 83.0)	0.595
Albumin, g/l	19	41.0 (38.0, 42.0)	74	38.0 (36.8, 40.0)	0.016
Transferrin receptor, mg/l	18	4.5 (3.1, 6.1)	67	4.4 (3.5, 6.5)	0.763
Ferritin, µg/l	25	10.0 (6.0, 17.0)	83	13.0 (7.0, 23.0)	0.468
Alanine aminotransferase, U/l	25	20.0 (16.0, 25.5)	122	20.0 (16.0, 26.0)	0.903
Thyroid-stimulating hormone, mU/l	41	2.0 (1.5, 3.2)	120	2.5 (1.7, 3.3)	0.212
Height, SD	87	0.3 (-0.5, 1.2)	170	0.0 (-0.8, 0.9)	0.242
Weight, SD	66	-0.4 (-1.0, 0.5)	133	-0.3 (-1.3, 0.5)	0.695
Body mass index, kg/m ²	80	16.3 (15.0, 18.0)	167	16.3 (14.9, 18.6)	0.808

¹Data available.

²Mann-Whitney U test.

Q₁ and Q₃, lower and upper quartiles; SD, standard deviation.

Table 4. Clinical characteristics, laboratory values and growth parameters in 139 children with screen-detected celiac disease divided into two groups based on the presence or absence of symptoms at diagnosis.

	Asymptomatic screen-detected (N = 67)		Symptomatic screen-detected (N = 72)		P value ⁴
	n	%	n	%	
Girls	42	62.7	45	62.5	0.982
Celiac disease in the family	23 ¹	54.8	31 ²	68.9	0.175
Type 1 diabetes	18	26.9	11	15.5	0.101
Anemia at diagnosis	3	4.7	4	5.6	1.000
Poor growth at diagnosis	11	16.9	9	12.9	0.506
	n ³	Median (Q ₁ , Q ₃)	n ³	Median (Q ₁ , Q ₃)	
Age at diagnosis, yr	67	9.0 (4.9, 12.0)	72	5.8 (3.9, 10.0)	0.007
Endomysial antibody, titer	53	1:200 (1:100, 1:1000)	45	1:1000 (1:200, 1:4000)	0.032 ⁵
Hemoglobin, g/l	36	132 (123, 136)	39	124 (117, 130)	0.010 ⁶
Height, SD	43	0.3 (-0.7, 1.2)	39	0.2 (-0.4, 1.2)	0.838
Weight, SD	33	-0.5 (-1.1, 0.9)	29	-0.3 (-1.1, 0.3)	0.651
Body mass index, kg/m ²	43	16.0 (15.1, 18.1)	33	16.4 (14.8, 17.8)	0.604

Data available > 95% of the patients, except in ¹42, ²45 and ³numbers reported in the column below.

⁴Chi-square test, Fisher's exact test and Mann-Whitney U test.

P values when adjusted for age using binary logistic regression: ⁵0.076 and ⁶0.233.

Q₁ and Q₃, lower and upper quartiles; SD, standard deviation.