Clinical Features of Celiac Disease: A Prospective Birth Cohort

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abstract

OBJECTIVES: To investigate clinical features of celiac disease (CD) and their association with risk factors for CD in a genetic risk birth cohort.

METHODS: Children from 6 clinical centers in 4 countries positive for HLA-DR3-DQ2 or DR4-DQ8 were annually screened for tissue transglutaminase antibodies (tTGA) and assessed for symptoms by questionnaires. Associations of symptoms with anthropometrics, known risk factors for CD, tTGA levels, and mucosal lesions in those biopsied were examined.

RESULTS: Of 6706 screened children, 914 developed persistent positive tTGA, 406 underwent biopsies, and 340 had CD. Compared with age-matched tTGA-negative children, those with persistent tTGA were more likely to have symptoms at 2 (34% vs 19%, $P < .001$) and 3 years of age (28% vs 19%, $P = .009$) but not at 4 years (27% vs 21%, NS). *Z*-scores for height, weight, and BMI did not differ between groups. In children with persistent tTGA, having ≥1 symptom was associated with family history of CD (odds ratio = 2.59, 95% confidence interval, 1.21–5.57) but not with age, gender, or HLA-DR3-DQ2 homozygosity. At seroconversion, tTGA levels were higher in symptomatic than asymptomatic children ($P < .001$), in those from CD families ($P < .001$), and in US participants ($P < .001$) but not associated with age, gender, or HLA genotype. tTGA levels correlated with severity of mucosal lesions both in symptomatic ($r = 0.53$, $P < .001$) and asymptomatic children ($r = 0.22$, $P = .01$).

CONCLUSIONS: A majority of children detected with persistent tTGA in screenings are asymptomatic and have normal growth by age 4 years. tTGA levels correlate more strongly with severity of mucosal lesions in symptomatic as compared with asymptomatic children.

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WHAT'S KNOWN ON THIS SUBJECT: Celiac disease (CD) may develop at any age. Young children with CD are at particular risk for malabsorption and failure to thrive. HLA-DR3-DQ2 homozygotes are at the highest genetic risk and develop CD very early in life.

WHAT THIS STUDY ADDS: Most children with CD detected in screening by 4 years of age have no symptoms and normal growth. Symptoms are unrelated to HLA genotype. Autoantibody levels correlate higher with severity of mucosal lesions in symptomatic as compared to asymptomatic children.

The clinical spectrum of celiac disease (CD) ranges from almost no signs or symptoms to clearly symptomatic forms with severe malabsorption syndrome.[1] The presentation of CD is age dependent: Signs and symptoms of malabsorption such as chronic diarrhea, failure to thrive, abdominal distention, and nutritional deficiencies including iron deficiency anemia are more prevalent in younger children. In older children the clinical picture is often not specific, with abdominal pain or extraintestinal manifestations, growth retardation, isolated anemia, and behavioral symptoms.[2–4] Because the clinical features of CD may not always be evident, a substantial proportion of patients will not be identified through symptom-based case finding.[5,6]

The cornerstones of CD diagnosis include presence of clinical signs and symptoms, seropositivity for endomysial or tissue transglutaminase autoantibodies (tTGA), carrying any of the HLA risk haplotypes DR3-DQ2 or DR4-DQ8, and showing typical histologic features in intestinal biopsies, characterized by villous atrophy and crypt hyperplasia with elevated intraepithelial lymphocytes.[1,7] None of these 4 criteria by itself is sufficient to prove diagnosis. The relationship between clinical expression, HLA, tTGA levels, and histology in symptomatic and asymptomatic patients with CD detected by screening remains elusive.

The Environmental Determinants of Diabetes in the Young (TEDDY) is a multicenter observational cohort study with the aim to identify environmental factors associated with type 1 diabetes and CD in children at HLA risk followed from birth.[8] All participants are screened with serial measurement for autoantibodies associated with these 2 disorders and by questionnaires for clinical symptoms suggestive of CD, allowing assessment of clinical symptoms in an unbiased fashion.

Recently, TEDDY study demonstrated that the risk of developing persistent tTGA, or so-called CD autoimmunity (CDA), by 5 years of the age was influenced by HLA risk genotypes, gender, family history of CD, and country.[9] The aim of the current study was to assess symptoms in children who developed CDA and CD in comparison with age-matched tTGA-negative children and to examine the associations with anthropometric measures, tTGA levels, intestinal biopsies, and identified risk factors for CD.

METHODS

Population

Participants in TEDDY are followed from birth until the age of 15 years at 1 of 6 clinical research centers located in Colorado, Georgia, and Washington in the United States and in Finland, Germany, and Sweden.[8] Between September 2004 and February 2010, 424 788 newborns were screened, of whom 21 589 infants had 1 of 9 HLA genotypes (Supplemental Table 5). Written confirmed consent for enrollment was obtained in 8676 eligible children[10] (Supplemental Table 6). The study was approved by local ethical institutional review boards and is monitored by an external advisory board formed by the National Institutes of Health.

Follow-up Procedures of Anthropometric Measures

All clinical research centers follow the same study protocol. Follow-up visits are scheduled every 3 months until the age of 4 years and every 6 months thereafter, with extensive collection of clinical data including anthropometric measures of growth (height, weight, and BMI).[11] A separate questionnaire specifically evaluates children for symptoms and clinical signs related to CD, including abdominal discomfort, anemia, chronic constipation, dental enamel defects, fatigue, frequent loose stools, irritability, neurologic symptoms, vomiting, any form of skin irritation, and poor growth reported by the parent. This questionnaire is obtained through interviews by medical staff every 6 months until the age of 2 years, annually hereafter. Symptom questionnaires at 2, 3, and 4 years of age were applied when neither the caregivers nor the study team members were aware of tTGA results.

Screening for CD

Annual screening for CD with tTGA starts at 2 years of age, as previously described.[9] In short, children tested positive for tTGA at the ages of 2 or 3 years are retested after 3 months and after 6 months if initially positive at 4 years or older. Children who were positive at 2 years of age had all previous serum samples tested with tTGA to find the first time point of antibody positivity (seroconversion). Children who were tTGA positive in 2 consecutive samples were defined as having persistent tTGA and considered to have CDA. Guardians of children with a positive test result of tTGA were informed, and if the result was confirmed on the next sample the guardians were advised to consult a pediatric gastroenterologist at the local hospital for additional evaluation of CD.

tTGA Measurements

Levels of tTGA were measured in 2 laboratories as described.[12] Serum samples from the US participants were screened for IgA-tTG at the Barbara Davis Center for Childhood Diabetes at the University of Colorado in Denver (cutoff for normal < 0.05 relative units). Serum samples from European participants were assayed at the University of Bristol in Bristol for both IgA-tTG and IgG-tTG (cutoff for normal < 1.3 relative units). All samples with IgA-tTG levels ≥ 0.01 U assessed in Denver were sent for reanalysis to Bristol, which was used as the reference laboratory.[13]

Diagnosis of CD

In children investigated for CD, it was recommended to take ≥6 biopsies from different parts of the duodenum, including the bulb. All histologic specimens were scored by the local pathologist according to the Marsh classification modified by Oberhuber[14]: normal mucosa (Marsh 0); elevated intraepithelial lymphocyte (IEL) count (ie, >25 IEL/100 enterocytes) only (Marsh 1); elevated IELs, crypt hyperplasia, and normal villous structure (Marsh 2); mild villous flattening (partial villous atrophy), elevated IELs, and crypt hyperplasia (Marsh 3a); marked villous flattening (subtotal villous atrophy), elevated IELs, and crypt hyperplasia (Marsh 3b); flat mucosa (total villous atrophy), elevated IELs, and crypt hyperplasia (Marsh 3c). Marsh score ≥2 was defined as biopsy-proven CD.[1]

Statistical Analysis

We first examined whether children with CDA reported more symptoms at initial tTGA positivity than children negative for tTGA by the same age. Symptom questionnaires at 2, 3, and 4 years of age were applied when neither the caregivers nor the study team members were aware of tTGA results. A conditional logistic regression model was used for the comparison with condition on the clinical site where the data were collected. In addition, we examined the association between reporting ≥1 symptom and risk factors for CD by using a logistic regression model. To examine the change in symptoms during the disease process, we compared symptoms reported at the initial tTGA-positive test with those reported 12 months before and with those reported at the time of persistent tTGA positivity in children with CDA. Paired *t* test was used for *z*-scores of growth measurements, and McNemar's test was used for indicating each of the symptoms. We then examined the association between tTGA level at the initial tTGA positivity and symptoms, including risk factors for CD, by using a general linear model. We analyzed correlations between tTGA level and Marsh score by using the Spearman rank correlation. When studying growth, we analyzed *z*-scores for weight, height, and BMI obtained according to the Centers for Disease Control and Prevention child growth standard charts after adjusting for clinical center (http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm). We performed all statistical analyses by using SAS version 9.3 (SAS Institute, Inc, Cary, NC), and 2-sided $P < .05$ was considered to represent a statistical significance.

RESULTS

Outcome of Screening

As of July 31, 2014, 6706 children were screened for tTGA, 914 were defined as having CDA, duodenal biopsies were performed in 406, and 340 were confirmed to have CD. At time of analysis, 458/914 (50.0%) children with CDA had completed the questionnaire at initial tTGA positivity. Of them, 115 (25%) developed CDA by 2 years of age, 142 (31%) by 3 years, 131 (29%) by 4 years, and 70 (15%) when >4 years old.

Clinical Symptoms and Anthropometric Measures on Growth

Reporting a symptom was more prevalent in younger children with CDA, except for abdominal discomfort that increased with age (Table 1). After conditioning on clinical center, the proportion of children with CDA reporting ≥1 symptom was higher than in tTGA-negative children by 2 years of age. Of note, 66% of the 2-year-old children and 73% by the age of 4 years did not report any symptom of initial positive testing. Children with CDA had a higher frequency of constipation by 2 years of age, and by 3 years of age abdominal discomfort was more prevalent than constipation in the tTGA-negative children. Poor growth was commonly reported by parents of children with CDA at the ages of 2 and 3 years but not at 4 years of age. However, anthropometric measures of growth were not substantiated by at any of the 3 different time points.

Clinical Symptoms and Risk Factors for CD

Having ≥1 symptoms at the time of initial tTGA positivity was associated with having a first-degree relative (FDR) with CD and living in the United States (Table 2). In contrast, age, gender, or carrying a high-risk HLA genotype showed no association to being symptomatic, either in children with CDA or in those with biopsy-proven CD.

Change in Clinical Parameters Over Time

A total of 205 children with CDA had completed the symptom questionnaire at 12 months before seroconversion, at initial tTGA positivity, and at the time of CDA (Table 3). There was no change in growth parameters or reported symptoms at 12 months before as compared with at seroconversion. Reporting ≥1 symptoms, abdominal discomfort, and frequent loose stools were more commonly reported by the caregivers at the time of CDA when the parents were aware of their child being positive for tTGA compared with initial tTGA positivity.

Levels of tTGA in Relation to Mucosal Lesions (Marsh Score)

Of the 458 children with CDA who had completed symptom questionnaires at seroconversion, 180 underwent intestinal biopsies. The biopsy was inconclusive in 1 child with a tTGA level of 46.6 U. Median levels of tTGA among the remaining 179 children were lower in children with Marsh score 0 to 1 (n = 24) at median 27.3 (range 1.8–96.0) units, compared with those with Marsh score 2 (n = 8) at median 84.0 (range 53.5–186.8) units (P = .003),

Marsh score 3a (n = 43) at median 73.3 (range 6.7–234.1) units ($P <$ .001), Marsh score 3b (n = 64) at median 82.1 (range 1.7–200.7) units ($P <$ .001), and Marsh score 3c (n = 40) at median 80.9 (range 3.2–208.2) units ($P <$ .001), respectively (Fig 1). Levels of tTGA increased with severity of lesions as indicated by Marsh scores, in both symptomatic (r = 0.53, $P <$ .001) and asymptomatic children (r = 0.22, P = .01).

Factors Associated With Increased Levels of tTGA

At time of initial tTGA positivity, levels were higher in the presence of ≥1 symptoms, among the US participants and those with an FDR with CD, in children with CDA or CD (Table 4). No such association was noted for age, gender, or HLA genotype. Children with CDA and CD below the 10th percentile for weight, height, and BMI tended to have higher tTGA levels at initial testing, although this difference reached significance for z-score in weight and height only at the time of persistent tTGA positivity (P = .012 and P = .033, respectively) (data not shown). In addition, at time of tTGA persistency, levels were higher in children with CDA carrying 2 copies of HLA-DR3-DQ2 (median 37.7 U) as compared with those with 1 copy of HLA-DR3-DQ2 (median 26.2 U) (P = .01) and other HLA genotypes (median 11.7 U) (P = .003).

DISCUSSION

This prospective multicenter study with annual screening for CD allowed an unbiased assessment of symptoms and anthropometric measures in children close to seroconversion and in age-matched children without CD-specific autoantibodies. One third of 2-year-old children were reported by the caregivers to have ≥1 symptoms to be associated with CD, compared with 19% in the control group. This difference decreased by 3 years of age and became insignificant by 4 years of age. The proportion of children with

TABLE 1 Clinical Presentation at Time of Seroconversion in Children Persistently Positive for tTGA in 2 Consecutive Samples (i.e., CDA) Compared With Children Negative for tTGA (No CDA)

	By 2 y of Age				By 3 y of Age				By 4 y of Age			
	CDA, n = 115	No CDA, n = 1932	OR	95% CI	CDA, n = 142	No CDA, n = 2794	OR	95% CI	CDA, n = 131	No CDA, n = 3355	OR	95% CI
Growtd, mean zscore (SD)												
Wt	0.5 (1.1)	0.2 (1.0)	1.15	0.94–1.41	0.4 (0.9)	0.5 (1.0)	0.93	0.77–1.12	0.4 (1.0)	0.5 (0.9)	0.98	0.80–1.19
Height	0.4 (0.8)	0.4 (0.9)[a]	1.03	0.82–1.29	0.4 (1.0)	0.4 (0.9)	0.95	0.79–1.15	0.6 (1.0)	0.5 (1.0)	1.04	0.87–1.26
BMI	0.3 (1.1)[b]	0.1 (1.0)[c]	1.12	0.88–1.43	0.2 (0.8)	0.2 (1.0)	0.98	0.82–1.17	0.2 (1.0)	0.2 (1.0)	0.97	0.82–1.16
Growth <10th percentile, %												
Wt	5	6	0.98	0.41–2.30	6	4	1.69	0.83–3.43	4	3	1.12	0.45–2.81
Height	3	3	0.88	0.27–2.90	6	3	1.69	0.80–3.57	4	3	1.30	0.52–3.26
BMI	7	6	1.67	0.77–3.64	4	7	0.58	0.25–1.35	6	6	0.93	0.45–1.94
Clinical presentation, %												
≥1 Symptoms	34	19	2.19†	1.45–3.3	28	19	1.66*	1.14–2.43	27	21	1.44	0.97–2.13
Abdominal pain	10	5	1.89	0.99–3.61	16	8	2.13*	1.33–3.40	15	11	1.45	0.89–2.36
Anemia	2	1	3.8	0.83–17.4	1	1	2.16	0.49–9.52	0	1	NA	NA
Constipation	11	6	1.96*	1.05–3.66	6	6	1.05	0.53–2.11	8	5	1.71	0.91–3.25
Dental enamel defects	1	1	2.94	0.37–23.4	2	1	1.74	0.53–5.76	2	2	0.8	0.19–3.31
Fatigue	1	1	1.09	0.14–8.62	2	1	1.67	0.51–5.51	0	2	NA	NA
Loose stools	13	7	1.7	0.95–3.05	6	3	1.85	0.91–3.75	4	3	1.29	0.52–3.24
Irritability	3	2	1.85	0.64–5.40	4	2	1.63	0.69–3.84	5	3	1.44	0.62–3.35
Neurologic symptoms	0	0.4	NA	NA	1	0.3	3.49	0.42–28.8	1	0.2	5.01	0.58–43.2
Poor growth	6	2	6.11†	2.44–9.15	8	2	4.61†	2.33–9.15	3	1	2.23	0.79–6.29
Skin irritation	3	2	2	0.59–6.75	1	1	0.75	0.10–5.56	2	1	2.35	0.54–10.2
Vomiting	3	1	3.41	0.94–12.3	1	1	2.66	0.60–11.7	3	27 (1)	4.07*	1.40–11.8
Other	1	0.3	2.85	0.32–25.5	1	0.1	6.36	0.69–59.0	0	2 (0.1)	NA	NA

CI, confidence interval; NA, not applicable; OR, odds ratio.
Values were available from >90% of the study subjects in each case except in [a] 1686, in [b] 81 and in [c] 1285.
* $P <$ .05.
† $P <$ .001.

TABLE 2 Association Between Identified Risk Factors for CD[11] and Having ≥1 Symptoms at Time of Seroconversion in Children With CDA Respective in CDA Children Who Were Diagnosed With CD

Variable		CDA Children				CD Children			
		n	≥1 Symptoms	OR (95% CI)	*P*	*n*	≥1 Symptoms	OR (95% CI)	*P*
Country	US	170	55 (32)	Reference		52	24 (46)	Reference	
	Finland	96	29 (30)	0.91 (0.53–1.56)	.72	28	8 (29)	0.47 (0.17–1.25)	.13
	Germany	21	4 (19)	0.49 (0.16–1.53)	.22	3	0	NA	
	Sweden	171	28 (16)	0.41 (0.24–0.69)	.001	72	10 (14)	0.19 (0.08–0.45)	<.001
Gender	Male	194	47 (24)	Reference		63	16 (25)	Reference	
	Female	264	69 (26)	1.11 (0.72–1.70)	.64	92	26 (28)	1.16 (0.56–2.39)	.69
HLA-DR3-DQ2 (*n*)	0	104	22 (21)	Reference		24	6 (25)	Reference	
	1	176	53 (30)	1.61 (0.91–2.84)	.10	60	19 (32)	1.39 (0.48–4.06)	.55
	2	178	41 (23)	1.12 (0.62–2.00)	.72	71	17 (24)	0.94 (0.32–2.76)	.92
FDR with CD	No	423	101 (24)	Reference		138	33 (24)	Reference	
	Yes	29	13 (45)	2.59 (1.21–5.57)	.02	16	8 (50)	3.18 (1.11–9.14)	.03

CI, confidence interval; OR, odds ratio.

affected growth was not different between the 2 groups at any age. Our study indicates that case finding by symptom questionnaires is insufficient to identify children with CD by 4 years of age. Instead, longitudinal screening programs similar to TEDDY enable diagnosis and treatment before symptoms and growth failure develop in children at genetic risk.

Our results are in line with a screening performed on 12-year-old Swedish school children demonstrating that clinical symptoms assessed by questionnaires at the time of blood sampling are unreliable for case finding of CD in the general population.[6] No difference in frequency or type of clinical symptoms was found between children with screening-identified CD as compared with the control group. Although children diagnosed with CD overall weighed less, were shorter, and had a lower BMI compared with those without CD, none of these parameters were reliable enough to predict CD on an individual basis.[15] However, the cross-sectional character of the Swedish study and high proportion of children diagnosed with CD before 12 years of age based on clinical symptoms does not allow the extrapolation of their findings to very young children in relation to HLA.

Given our previous results in concert with 2 recent birth cohort studies including infants from families with CD, it is clearly demonstrated that girls and HLA-DR3-DQ2 homozygotes are at a markedly higher risk for CD during childhood at a younger age compared with boys, HLA-DR3-DQ2 heterozygotes, and HLA-DR4-DQ8 carriers.[9,16,17] Although there is already credible evidence for a gene dose effect of HLA-DR3-DQ2 on the risk of CD,[18–22] the present investigation could not confirm our previous assumption that presence of symptoms in children with CDA was associated with female gender or a specific HLA genotype at

TABLE 3 Paired Comparison of the Clinical Presentation in Children With CDA Who Had Completed the Symptom Questionnaires at 3 Time Points (*n* = 205)

Clinical Presentation	(I) At 12 mo Before Initial tTGA Positivity, *n* (%)	(II) At Time of Initial tTGA Positivity, *n* (%)	(III) At Time of Persistent tTGA Positivity (CDA), *n* (%)	*P* (I vs II)	*P* (II vs III)
Wt, *z*-score (SD)	0.38 (0.90)	0.41 (0.85)	0.40 (0.83)	0.38	0.61
Height, *z*-score (SD)	0.56 (0.90)	0.57 (0.91)	0.56 (0.89)	0.42	0.99
BMI, *z*-score (SD)	0.06 (0.97)	0.12 (0.90)	0.14 (0.90)	0.70	0.93
≥1 Symptoms	41 (20)	43 (21)	88 (43)	0.89	<0.001
Abdominal discomfort	17 (8)	26 (12)	59 (29)	0.14	<0.001
Anemia	1 (0.5)	2 (1)	1 (0.5)	1.00	1.00
Constipation	12 (6)	14 (7)	22 (11)	0.80	0.08
Dental enamel defects	1 (0.5)	3 (1)	5 (2)	0.50	0.50
Fatigue	4 (2)	3 (1)	8 (4)	1.00	0.23
Frequent loose stools	12 (6)	6 (3)	23 (11)	0.21	<0.001
Irritability	4 (2)	8 (4)	15 (7)	0.22	0.09
Neurologic symptoms	2 (1)	1 (0.5)	1 (0.5)	1.00	1.00
Poor growth	1 (0.5)	2 (1)	3 (1)	1.00	1.00
Skin irritation	3 (1)	0 (0)	0 (0)	NA	N.A.
Vomiting	3 (1)	3 (1)	3 (1)	1.00	1.00
Other	1 (0.5)	0 (0)	1 (0.5)	NA	N.A.

NA, not applicable.

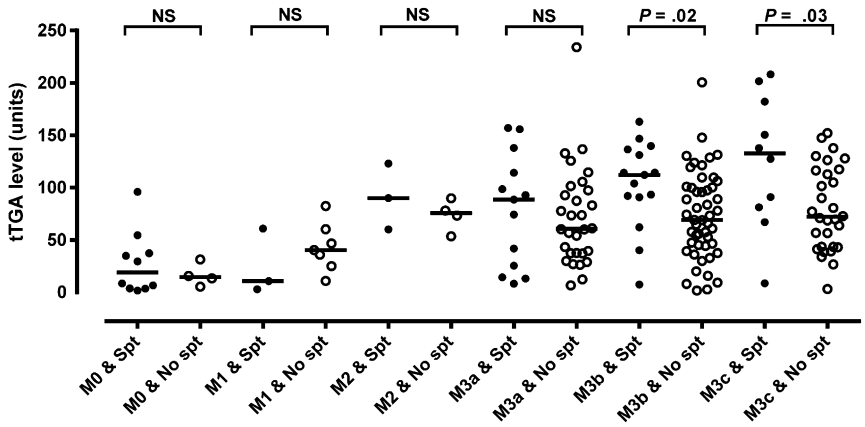

FIGURE 1

tTGA levels in 179 children undergoing intestinal biopsies and categorized according to Marsh score (M) with and without reporting clinical symptoms (spt). We obtained *P* values by using a general linear model after adjusting for country, gender, and HLA.

seroconversion. In contrast to our findings, adult patients with symptomatic CD being homozygous for HLA-DR3-DQ2 seem to be at higher risk of developing more complicated, more severe, and more refractory CD.[20,22] The fact that our screening indicated that young children from the highest HLA risk group did not differ with respect to symptoms from those in the lower HLA risk groups does not exclude the possibility that patients homozygous for HLA-DR3-DQ2 may develop more disease complications if not diagnosed and treated early after seroconversion.

Instead, we found that seropositive participants from the US centers (as compared with Swedish) and children having an FDR with CD (as compared with those without family risk) were more likely to report symptoms. Although it is possible that the threshold for awareness and reporting of symptoms differ between countries, screenings of relatives who are found to have CD are likely to report more symptoms than those from families with no known member with CD.[23] It is thus tempting to suspect that TEDDY parents who are affected by CD themselves or already have another child with CD in the family observe their children more closely for signs of CD. A biased observation of reporting symptoms is therefore the most likely explanation for the intraindividual increase of reported symptoms between the time of seroconversion when parents were unaware of the screening results and when they were informed about the outcome at follow-up.

It has been elegantly demonstrated that tTGA levels correlate with the degree of small bowel lesions, expressed as a Marsh score,[24] and symptomatic patients with CD and tTGA levels >10 times the upper limit of normal have a high likelihood of being affected by the disease.[24–26] Moreover, scores on gastrointestinal symptoms correlate with tTGA levels in adult patients,[26] and young children with severe signs of malabsorption have significantly higher tTGA levels than older children presenting with nonspecific symptoms.[24] In our cohort, symptomatic children with CDA and CD had higher tTGA levels at seroconversion. The correlations between tTGA levels and severity of histologic findings were significant in both groups, although this correlation

TABLE 4 Factors Associated With Levels of tTGA at Time of Seroconversion in Children With CDA and in Children With CDA Who Were Diagnosed With CD

Variable		Children With CDA				Children With CD			
		n	tTGA Level Median (Q1, Q3)	Parameter Estimate (SE)	*P*	*n*	tTGA Level Median (Q1, Q3)	Parameter Estimate (SE)	*P*
Wt <10th percentile	No	428	16.5 (5.1, 48.7)	Reference		146	43.6 (14.9, 91.3)	Reference	
	Yes	17	35.8 (16.5, 78.7)	13.8 (9.8)	.16	6	63.8 (20.8, 100.5)	−8.9 (20.5)	.66
Height <10th percentile	No	426	16.3 (5, 49.8)	Reference		140	45.5 (14.7, 86.7)	Reference	
	Yes	15	32.6 (20.8, 94.6)	17.1 (10.4)	.10	9	48.2 (21.4, 100.5)	5.4 (16.2)	.74
BMI <10th percentile	No	396	16.5 (4.9, 49.6)	Reference		132	45.5 (15.1, 91.7)	Reference	
	Yes	20	31.6 (17.0, 72.8)	13.9 (9.1)	.12	7	82.3 (57.5, 137.8)	21.6 (18.5)	.24
≥1 Symptoms	No	342	14.9 (4.9, 41.1)	Reference		113	39.1 (11.5, 74.2)	Reference	
	Yes	116	29.1 (6.4, 79.1)	20.0 (4.3)	<.001	42	81.5 (32.1, 135.4)	37.5 (8.4)	<.001
Country	US	170	30.0 (11.4, 70.3)	Reference		52	63.0 (31.6, 116.7)	Reference	
	Finland	96	10.1 (3.9, 31.7)	−22.4 (5.1)	<.001	28	29.4 (9.6, 81.4)	−29.3 (11.2)	.010
	Germany	21	13.6 (4.0, 29.5)	−22.4 (9.3)	.02	3	78.0 (75.2, 98.4)	7.6 (28.3)	.79
	Sweden	171	13.9 (4.3, 41.0)	−16.5 (4.4)	<.001	72	34.7 (9.7, 70.5)	−28.0 (8.7)	.002
Gender	Male	194	16.5 (5.4, 41.4)	Reference		63	38.9 (13.9, 100.5)	Reference	
	Female	264	18.9 (5.0, 57.4)	2.2 (3.9)	.58	92	51.0 (16.7, 78.6)	0.4 (8.1)	.96
HLA-DR3-DQ2 (*n*)	0	104	18.4 (4.7, 39.9)	Reference		24	70.2 (22.3, 101.3)	Reference	
	1	176	17.6 (5.2, 54.4)	3.6 (5.1)	.48	60	52.4 (20.7, 93.4)	−7.2 (11.8)	.54
	2	178	17.4 (5.3, 55.2)	2.7 (5.1)	.59	71	34.0 (7.9, 78.0)	−20.5 (11.5)	.08
FDR with CD	No	423	6.2 (5.0, 47.2)	Reference		138	42.0 (14.9, 86.1)	Reference	
	Yes	29	49.8 (20.2, 97.5)	28.7 (7.8)	<.001	16	89.1 (37.3, 118.4)	28.2 (12.9)	.030

was low in asymptomatic children. Other factors associated with high levels of tTGA in our cohort independent of age were presence of symptoms, lower weight, and lower BMI, supporting previous indications that children with high tTGA levels are phenotypically different from those with low tTGA levels.[27] The finding that tTGA levels at seroconversion were associated with having an FDR with CD was unexpected, however. Children living in families with an affected family member have lower rates of gluten consumption,[28] which in turn would reduce tTGA levels. Because of the small number of children with a family history of CD, a chance finding cannot be ruled out.

The major strength of TEDDY as compared with previous investigations is its prospective design, which enabled unbiased data collection for clinical symptoms before and shortly after the time of seroconversion, as compared with the seronegative control group. The large sample size of TEDDY allows sufficient statistical power to look at differences between subpopulations with and without known risk factors for CD. A limitation of the study is the fact that parents of children developing tTGA were informed about the autoantibody status of their child, which may have biased symptom reporting at follow-up. Furthermore, not all study participants with CDA were referred for a biopsy. Children with low tTGA levels reporting no symptoms are less likely to undergo biopsies. The differences in diagnostic procedures between the clinical centers, where a lesser proportion of US participants with CD compared with European children underwent endoscopy, might therefore have had an effect on our results when we studied CD as an outcome.

CONCLUSIONS

This prospective screening for CD showed that at least two-thirds of children have no symptoms at the time of seroconversion to tTGA positivity by 4 years of age. Among symptomatic children, constipation is as commonly reported as diarrhea. *Z*-scores for height, weight, and BMI at this young age are not different between screening-detected tTGA-positive and seronegative children. Although girls and HLA-DR3-DQ2 homozygous children are more likely to develop CDA early in life, symptoms and tTGA levels are not associated with these risk factors at time of seroconversion. Instead, tTGA levels correlate with symptoms and severity of mucosal lesions, although this finding is weaker in asymptomatic compared with symptomatic children with CD. Our findings may have implications for future screening of the general population and case-finding strategies in at-risk groups.

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